Aragon Pharmaceuticals, Inc. *

Clinical Protocol
COVID-19 Appendix 1

A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer (mCRPC)

Protocol 56021927PCR3001; Phase 3
ACIS
(ARN-509 Chemo-naïve Indicated Subjects)

JNJ-56021927 (apalutamide)

*Aragon Pharmaceuticals, Inc. is a wholly-owned subsidiary of Johnson & Johnson. Janssen Research & Development, LLC is part of the Janssen Pharmaceutical Companies of Johnson & Johnson and provides various services to its affiliated company, Aragon Pharmaceuticals, Inc. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen-Cilag International NV; Janssen, Inc.

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

EudraCT NUMBER: 2014-001718-25

Status:	Approved
Date:	14 April 2020
Prepared by:	Janssen Research & Development, LLC
EDMS number:	EDMS-RIM-33929, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT AND APPROVED VERSIONS OF PROTOCOL 56021927PCR3001 (EDMS-ERI-81017110)

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

COVID-19 APPENDIX 1

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

This Appendix applies to all current versions of Protocol 56021927PCR3001.

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If, at any time, a subject's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the subject and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a subject has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

- These emergency provisions are meant to ensure subject safety on study while site capabilities are compromised by COVID-19-related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible.
- Study treatment should be continued if, in the assessment of the investigator, it does not result in risk to the subject. Remote medical consultation and alternatives to study medication dispensing, administration, and clinical safety laboratory assessments (including home health nursing) will allow continued study participation for subjects in this trial. If at any time a subject's safety is considered to be at risk due to study treatment, study intervention will be temporarily or permanently discontinued, while every effort should be made to maintain follow-up on study.
- The benefit of continuing study treatment should be considered by the investigator for each individual subject, considering the potential impact of reduced direct clinical supervision on subject safety. A temporary interruption of study drugs might be considered based on investigator´s discretion and documented.
- Dispensing of study medication:

  For subjects unable to visit the clinic/hospital, direct-to-patient (DTP) shipment or handover to a caregiver or delegate of oral study drugs may be implemented, where allowed per local regulations and if requested by the treating study physician. Where DTP shipments or handover to delegates are deemed necessary, the process must be coordinated between the site and sponsor staff following standard DTP procedures for arranging shipment and adhering to associated approvals and documentation requirements.

  For subjects able to visit the clinic/hospital, but who request to reduce visit frequency or for who limited access to the site is expected, an additional supply of oral study drugs can be provided.
- Dispensing and administration of NIMP:

  For subjects unable to visit the clinic/hospital, alternatives to NIMP dispensing and administration (including specifically GnRH-analogues), home health nursing and application by a qualified person at subject´s home may be implemented, where allowed per local regulations and if requested by the treating study physician. Where DTP shipments of NIMP are deemed necessary, the process must be coordinated between the site and sponsor staff following standard DTP procedures for arranging shipment and adhering to associated approvals and documentation requirements.
- Delay of study procedures:

  If study procedures cannot be performed per study protocol and are delayed, subjects should stay on the assigned treatment until these procedures can be performed, which may result in a prolongation of study treatment exposure. Investigators should inform the sponsor as soon as they become aware of any delays.
- Central laboratory testing should be performed according to the current time and events schedule as outlined in the protocol under which the site is currently operating. If central laboratory tests cannot be performed, the use of a local laboratory is allowed for study

evaluations. A copy of the local laboratory report should be reviewed by the investigator and retained, along with reference ranges, for source documentation and captured in the CRF.

- To safely maintain subjects on study treatment while site capabilities are compromised by COVID-19-related restrictions, subjects for whom there is no safety concern may have tele-health visits (conducted via phone or video conversation as per local regulation) until such time that on-site visits can be resumed. Normal study procedures should be followed for the applicable visit as closely as possible. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement. If required per protocol, ePRO information should be collected via phone or video conversation or by use of the provided electronic device (as applicable for the study and per local regulations).
- If imaging cannot be performed at the site due to COVID-19 related restrictions, the use of local facilities close to the subject's home is permitted, but provision of scans to the investigative site and central readers should be arranged by the investigator and documented if required according to the current time and events schedule. If imaging is not possible as outlined in time and events tables, missed imaging should be documented as a deviation related to COVID-19 and be made up as soon as possible.
- If a subject develops SARS-CoV-2 infection or related disease, the investigator should contact the sponsor to discuss plans for study intervention and follow-up. An interruption of study treatment should be considered by the investigator, depending on symptoms and concomitant medication used for the treatment of COVID-19. Treatment must be interrupted if prohibited medication is used. Standard Adverse Event/Serious Adverse Event reporting requirements apply.
- When a subject, for whom study treatment has been interrupted, recovers from suspected or confirmed SARS-CoV-2 infection or related disease and all toxicities improve to Grade ≤1, the investigator should discuss with sponsor about resuming study treatment.
- Consenting and re-consenting of subjects will be performed as applicable for the measures taken (including also remote consenting by phone or video consultation) and according to local guidance for informed consent applicable during the COVID-19 pandemic.

INVESTIGATOR AGREEMENT

COVID-19 Appendix 1
JNJ-56021927 (apalutamide) Clinical Protocol 56021927PCR3001

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): Spyros Triantos, MD

Institution: Janssen Research & Development

Signature: PPD Date: 14 APRIL 2020
(Day Month Year)

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

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 5
Status: Approved, Date: 14 April 2020

Aragon Pharmaceuticals, Inc.*

Clinical Protocol

A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer (mCRPC)

Protocol 56021927PCR3001; Phase 3
ACIS
(ARN-509 Chemo-naïve Indicated Subjects)

AMENDMENT 4

JNJ-56021927 (apalutamide)

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

EudraCT NUMBER: 2014-001718-25

Status: Approved
Date: 18 February 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-81017110; 7.0

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

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LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	29 August 2014
Amendment 1	17 November 2014
Amendment 2	04 August 2016
Amendment 3	30 January 2017
Amendment 4	18 February 2020

Amendments are listed beginning with the most recent amendment.

Amendment 4 (18 February 2020)

The overall reason for the amendment: The overall reason for the amendment is to allow for an Open-Label Extension Phase or Long-Term Extension Phase after unblinding the study at the planned final analysis.

- If cross-over is offered, subjects randomized to placebo and AAP will be offered the option to cross-over to open-label apalutamide and AAP, and subjects randomized to apalutamide and AAP will have the option to continue on apalutamide and AAP as open-label treatment.
- If cross-over is not recommended, subjects will enter the Long-Term Extension Phase with limited data collection. Subjects randomized to apalutamide and AAP will be offered the option to receive open-label AAP alone or to receive open-label apalutamide and AAP; subjects randomized to placebo and AAP will have the option to continue on open-label AAP alone.

In conjunction with the start of the Open-Label Extension Phase or Long-Term Extension Phase, and given the well-characterized and over-time consistent safety profiles of apalutamide and AAP, data collection will be limited, to lower the burden to subjects.

Applicable Section(s)	Description of Change(s)
Rationale: To provide detailed information for the Open-Label Extension Phase and the Long-Term Extension Phase.	
Synopsis (Overview of Study Design); 3.1 Overview of Study Design; 9.1.1 Overview	Added text to include the Open-Label Extension Phase or Long-Term Extension Phase in the study design. Referred to the new Attachment 9 and Attachment 10 for details of the Open-Label Extension Phase and Long-Term Extension Phase, respectively. Revised the heading for Figure 2 to "Schematic Overview of the Study **Until the Start of the Extension Phase (Open-Label Extension or Long-Term Extension)**"
9.1.6 After Study Unblinding (new subheading)	Provided information on options available after the study is unblinded.
9.1.6.1 Open-Label Extension (new subheading)	Provided information on the Open-Label Extension Phase; details are provided in Attachment 9.
9.1.6.2 Long-Term Extension With Limited Data Collection (new subheading)	Provided information on the Long-Term Extension Phase with limited data collection; details are provided in Attachment 10.
Section 9.1.7 Data Collection Following IDMC Recommendation to Unblind	Deleted the existing details for data to be collected after the study is unblinded, and referred to Attachment 9 and Attachment 10 for details.

Applicable Section(s)	Description of Change(s)
Attachment 9: Open-Label Extension in the Event of Subjects Being Offered Cross-over to Open-label Apalutamide in Combination With AAP After Study Unblinding (new attachment)	This attachment includes detailed information, including a Time and Events Schedule, for the Open-Label Extension Phase after study unblinding.
Attachment 10: Long-Term Extension in the Event of Limited Data Collection After Study Unblinding (new attachment)	This attachment includes detailed information, including a Time and Events Schedule, for the Long-Term Extension Phase with limited data collection after study unblinding.
Rationale: Revisions, updates, and clarifications were provided.	
Section 8.3 Restricted Concomitant Medications	To provide updated information on restricted concomitant medications based on current knowledge, revisions were made to the list of restricted concomitant medications to reflect the most current information in the Investigator's Brochure.
Section 11.1 Analysis Populations	Specified that for patient-reported outcomes (PROs), all time-to-event analyses will be based on the intent-to-treat (ITT) population.
Section 11.5 Biomarker Analyses	Revisions were made to text describing statistical power relating to biomarker analyses.
Attachment 8 (Anticipated Events)	Events that are included in efficacy endpoints for the study should not be included in the anticipated events list. Therefore, events that pertain to the endpoint of "Time to symptomatic skeletal-related event" (cauda equina syndrome, pathological fracture, and spinal cord compression) were deleted. The review and reporting requirements for anticipated events were clarified. Specified that Japan will not identify anticipated events for the Health Authorities. Revised "Anticipated Event Review Committee" (ARC) to "Safety Assessment Committee" (SAC).
Rationale: Minor errors and inconsistencies were noted.	
Throughout the protocol	Minor errors and inconsistencies were revised, and grammatical, formatting, or spelling changes were made. Abbreviations and references were updated as needed.

Amendment 3 (30 January 2017)

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: Fracture was identified as a new adverse drug reaction for apalutamide, limited to the CRPC patient population. As such, the main reason for this amendment is to allow use of bone modifying agents (for preserving bone mineral density during cancer treatment as well as skeletal integrity in patients with bone metastasis) without restrictions (Investigator Brochure updated as well with this information and additional details).

The rationale for and description of the changes are listed below, when revisions are provided verbatim, bold font denotes new text, and strikethrough denotes deleted text.

Applicable Section(s)	Description of Change(s)
Rationale: Remove requirement for a subject to use a bone modifying agent only if he had been on a stable dose for at least 4 weeks prior to randomization. Of note, this change was made only in Section 8.1 (which governs use of medications during the treatment phase), but not to the Inclusion/Exclusion criteria, Section 4 (which applies to pre-treatment/screening phase) because at the time of this amendment, the study is fully enrolled.	
Section 8.1, Permitted Supportive Care Medications	Deleted text: ~~Bisphosphonates and denosumab for management of bone-related metastasis should be used according to their market authorized approved label and only if the subjects are on a stable dose for at least 4 weeks prior to randomization~~ Replaced with: **Bone modifying agents, including bisphosphonates and denosumab, should be used in accordance with label indications to help preserve bone mineral density during cancer treatment (including ADT) and skeletal integrity in subjects with bone metastasis.**
Rationale: Included bullet regarding apalutamide's potential to induce CYP3A4 (for consistency with the information provided in the IB).	
Section 8.3, Restricted Concomitant Medications	Added: **Apalutamide may induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have a narrow therapeutic index**

Applicable Section(s)	Description of Change(s)
Rationale: Correction to the disease evaluation on study as outlined in Attachment 7 from 2 cm in diameter to ≥2 cm in greatest diameter	
Attachment 7, Guidance Document for PCWG2 Criteria and RECIST 1.1	Disease Evaluation on Study • Soft tissue lesions (nodal and non-nodal: Use RECIST 1.1 with caveats) • Only report changes in lymph nodes that were **≥2 cm in greatest** diameter at baseline
Rationale: Progression-free survival after first subsequent therapy (PFS2) was described in the statistical analysis plan but not in the protocol.	
Synopsis, Efficacy Evalutations/Endpoints; Time & Events Schedule; Section 9.1.5 Follow-up Phase; Section 9.2.2. Endpoints	Added a line to the T&E for collection of progression data on first subsequent therapy, added a statement to collect progression data on first subsequent therapy to Section 9.1.5, and added PFS2 as another endpoint in the efficacy evaluations section.
Rationale: Update JNJ-56021927 with apalutamide	
Throughout synopsis and protocol	Replaced 'JNJ-56021927' (except in the title and in some aspects of the description of the drug) with 'apalutamide.'

Amendment 2 (4 August 2016)

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 3 main reasons for this amendment are the following: 1) to incorporate a non-binding futility analysis based on radiographic progression-free survival (rPFS) per recommendation of the Independent Data Monitoring Committee (IDMC); 2) to provide flexibility regarding the timing of the primary analysis of rPFS relative to the timing of the analysis for overall survival (OS); and 3) to provide greater clarity for disease evaluations based on the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 and the Prostate Cancer Working Group 2 (PCWG2) criteria.

The rationale for and description of the changes are listed below, when revisions are provided verbatim, bold font denotes new text, and strikethrough denotes deleted text.

Applicable Section(s)	Description of Change(s)
Rationale: Per recommendation from the IDMC a non-binding futility analysis based on rPFS is being incorporated.	
Synopsis, Futility Analyses; 11.10 Futility Analyses	Added the following statement: **In addition, a non-binding futility analysis on rPFS will be implemented after observing approximately C % (CC events) of the total number of required CC events.** Additional statement in Section 11.10: **Details for each futility analysis will be provided in the statistical analysis plan.**

Applicable Section(s)	Description of Change(s)
Rationale: To provide more flexibility for the timing of the primary rPFS analysis relative to the analysis of OS	
11.3 Efficacy Analyses	Revised the current protocol wording: ~~The primary analysis of rPFS will be performed at the same time as the first interim analysis of OS.~~ Replaced with the following: **The final rPFS analysis will take place after approximately CC events are observed. The timing of the first interim analysis of OS may occur at the same time as the final analysis of rPFS. Alternatively, the analyses may be performed at a different time if the number of death events needed for a valid interim analysis of OS would require a long delay in the analysis of the rPFS endpoint. The alpha-spending for the interim analysis of OS will be adjusted accordingly (see Section 11.9).**
Rationale: In response to questions from investigators, a guidance document outlining the PCWG2 and RECIST v1.1 criteria for evaluation of disease progression, is being provided.	
Attachment 1	Added reference to Scher 2008 publication (PCWG2 criteria)
Added Attachment 7	Attachment 7 includes detailed guidance on the PCWG2 criteria
9.2.1.2 Efficacy Criteria	Minor revisions were made for improved clarity.
Rationale: Hepatotoxicity is an important identified risk while using abiraterone acetate; therefore additional monitoring (eg, LFT measurements) and drug modifications (eg, discontinuation) were added in the event of clinical signs or symptoms suggestive of hepatotoxicity.	
6.3.2 Toxicity Attributed to Abiraterone Acetate	**Added the following: If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, in particular serum ALT, should be measured immediately. If subjects develop severe hepatotoxicity (ALT 20 x ULN) anytime while on abiraterone acetate, subjects should be discontinued and not be re-treated with abiraterone acetate.** **Subjects who develop a concurrent elevation of ALT >3 X ULN and a total bilirubin >2 X ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation should be permanently discontinued from treatment with abiraterone acetate.**
Rationale: Error corrected in Table 3	
Table 3	Footnote a: Missing "total" (should be total bilirubin) when describing Grade 3 liver function test abnormalities.
Rationale: The measurement of TSH should be performed at the End-of-Treatment (EOT) visit	
Time and Events Schedule; Table 7	A tickbox for TSH was added under the column EOT. Updated footnote b of Table 7 to include the EOT Visit.
Rationale: The volumes in Table 7 were updated. The chemistry and PSA evaluations are measured from the same sample.	
Table 7; 9.1.1 Overview; 16.1 Study-Specific Design Considerations; References	Updated the table and revised blood volumes accordingly. Revised the description of blood volumes in Section 9.1.1. Removed the repeat of blood volumes in Section 16.1 and added the American Red Cross Reference.

Applicable Section(s)	Description of Change(s)
Rationale: Subjects who discontinue study drug before radiographic progression will continue with imaging assessments during the Follow-up Phase according to the local standard of care. If available, collect information on imaging assessments until documentation of radiographic progression.	
9.1.5 Follow-up Phase	Added the following: **Subjects who discontinue study drug before radiographic progression will continue with imaging assessments during the Follow-up Phase according to the local standard of care. If available, collect information on imaging assessments until documentation of radiographic progression.**
Time and Events Schedule	Added the following note**: If available, collect information on imaging assessments until documentation of radiographic progression (see Sections 9.1.5 and 10.2)**
Rationale: To provide additional guidance on discontinuation of treatment and collection of the reason for discontinuation.	
10.2 Discontinuation of Study Treatment	Revised text in this section as follows: **Subjects should be encouraged to continue treatment until radiographic progression or unequivocal clinical progression. If the subject has radiographic progression without evidence of unequivocal clinical progression and alternate therapy is not initiated, treatment may continue at the discretion of the investigator. Subjects should not discontinue treatment for PSA progression in the absence of radiographic progression or unequivocal clinical progression. If a subject discontinues study treatment before evidence of radiographic progression, data on subsequent imaging assessments performed per the local standard of care will be collected if available (see Section 9.1.5). Radiographic progression is defined by PCWG2 (see Attachment 7). Bone scan worksheets may be used as source documentation for tracking progression or response (see Section 17.5).** **The primary reason for discontinuation of study treatment is to be recorded in the eCRF. A study treatment discontinuation form should be emailed to the sponsor's medical monitor prior to discontinuation in IWRS (see the SIPPM for details).**
Rationale: With the last amendment the duration of the Screening Phase was increased from 35 days to 42 days. This change was not captured throughout the protocol.	
Figure 2, Time and Events Schedule, footnote f, and 9.1.2 Screening Phase	Corrected 35 days to 42 days.
Rationale: Clarification that the computed tomography (CT)/magnetic resonance imaging exams must include the chest, abdomen, and pelvis.	
Time and Events Schedule	CT/MRI exams of chest, abdomen and pelvis must be performed
Rationale: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) grades are part of the safety evaluation and was not described in the Safety Evaluations Section	
Synopsis Efficacy Evaluations/Endpoints; Time and Events Schedule; 9.2.1 Evaluations; 9.7 Safety Evaluations; 9.7.1 Safety Assessments	Moved ECOG timing to safety from efficacy. Added a section for ECOG PS to Safety Evaluations section.

Applicable Section(s)	Description of Change(s)
Rationale: A pain assessment was included in the eCRF but was not previously mentioned in the Time and Events Schedule of the protocol.	
Time and Events Schedule	Added a row for this assessment and the following note: Subjects should also complete "How would you rate your pain over the past 7 days?" (0 to 10 scale). Site personnel should record response in the eCRF and in the clinic visit record. During non-visit cycles the information will be collected by telephone contact.
Rationale: In Japan, an enhanced medical monitoring and IDMC review of the safety was performed for Cycle 1 data of the first 20 subjects randomized to the study. As this action has been completed, the Japanese protocol can align with the global protocol.	
Synopsis Safety Evaluations, 9.7 Safety Evaluations, Attachment 7 of the country-specific amendment.	The wording in these sections of the Japan country-specific amendment pertaining to the enhanced monitoring and IDMC review is not applicable to the global protocol. Attachment 7 in the country-specific amendment is not applicable to the global protocol.
Rationale: In Japan, sparse PK samples are being collected from all randomized subjects.	
Synopsis Population Pharmacokinetic Evaluations; Time and Events Schedule; 9.3.1 Evaluations	Added the following statement to the Time and Events Schedule: **In Japan, samples will be collected from all randomized subjects.** Added the following statement to the synopsis and Section 9.3.1: **In Japan, blood samples for PK assessment will be collected from all randomized subjects.**
Rationale: Modified compliance wording for consistency with other apalutamide Phase 3 protocols.	
7 Treatment Compliance	Replaced the current wording: ~~If dosing compliance is not 100% in the absence of toxicity, then investigators should re-instruct subjects regarding proper dosing procedures before continuation with the study. Subsequent dosing compliance procedure will be conducted at each study visit. Subjects who have study drug dosing compliance of 75% or lower for 2 consecutive cycles (independent of an AE) should be discontinued from the study (see Section 10.2).~~ With current wording: **In the absence of toxicity, if the dosing compliance is not 100%, then investigators or designated study site personnel should re-instruct subjects regarding proper dosing procedures and the subject may continue study treatment.**
10.2 Discontinuation of Study Treatment	Removed the following bullet: ~~Dosing noncompliance (≤75% compliance for 2 consecutive cycles)~~
Rationale: Phase 3 protocols are to include an attachment with a listing of anticipated events. The text and attachment were taken from the latest protocol template.	
12.3.1 All Adverse Events; Attachment 8	Added the following statements to Section 12.3.1: **Anticipated events will be recorded and reported as described in Attachment 8. For anticipated events reported as individual serious adverse events, the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the institute where required).**

Applicable Section(s)	Description of Change(s)
Rationale: The generic name for JNJ-56021927, apalutamide, is replacing the compound number as protocols are amended.	
Synopsis, 1 Introduction	The following revised sentence is included in the synopsis and introduction: JNJ-56021927 (ARN-509; apalutamide, hereafter referred to as apalutamide) is an orally available, small molecule, non-steroidal potent and selective antagonist of the androgen receptor (AR) receptor (anti-androgen).
Title page	The generic name apalutamide has replaced ARN-509
Throughout the protocol	Replaced "JNJ-56021927" with apalutamide throughout the protocol.
4.2 Exclusion Criteria	Changed JNJ-56021927 to apalutamide in Exclusion Criterion #12
Rationale: Central laboratories send laboratory data that are not required per protocol but are done per standard practice in the central laboratory.	
9.7 Safety Evaluations	Added the following note: **Note: Any abnormal WBC evaluations will also be reported by the central laboratory.**
Rationale: Removed redundant information in Attachment 3. Updated with new drug-drug interaction information for apalutamide.	
Attachment 3	Removed redundant or outdated information. Provided website for more information of CYP450 drug interactions.
8.3 Restricted Concomitant Medications	This section was updated with new information.
Rationale: Additional minor revisions were made to the Time and Events Schedule to reduce redundancy and for clarification.	
Time and Events Schedule, Footnotes i and j	The original footnotes i and j were removed and the information was incorporated into the notes in the body of the table. Remaining footnotes were revised accordingly. Removed the proposed sample sizes for the biomarker samples as this information was included in the biomarker section of the protocol.
Rationale: Dose modification guidance for seizures is incorporated in Table 6 and did not need to be repeated in text. .	
6.3.3 Toxicity Attributed to Apalutamide/Placebo	Removed redundant text.

Applicable Section(s)	Description of Change(s)
Rationale: Updated safety and efficacy information for apalutamide and apalutamide plus abiraterone acetate	
1.1.2 Apalutamide; References	Revised and updated the information on the ARN-509-001 study and added the clinical study report reference. Removed reference to Rathkopf study as data in CSR are more up to date. Incorporated updated information from Studies ARN-509-004 and 56021927PCR1010. Updated with information on new Phase 3 studies. Added references to reference section.
Rationale: The sponsor continually reviews the protocol template for potential improvements. Major revisions to the protocol based on the updated template are noted in the following sections. Minor revisions, not noted here, have also been made throughout the document.	
4.3 Prohibitions and Restrictions	Added the following: **Refer to Sections 8.2 and 8.3 for details regarding prohibited and restricted therapy during the study**
12.2 Special Reporting Situations (bullet #3)	Inadvertent exposure to study drug changed to accidental or occupational exposure.
12.3.1 All Adverse Events	Revised wording regarding SUSARs.
16.2.2 Independent Ethics Committee or institutional Review Board	The requirement to document the yearly approval of the protocol by the IEC/IRB was changed from a requirement to where required.
16.2.5 Country Selection	Clarification that drug will be launched in countries **if the need for the product persists**.
17.4 Source Documentation	Clarifications to requirements for source documents and the authors of the data entry, and the electronic source system utilized for data.
17.5 Case Report Form Completion	Clarifications to case report form completion requirements.
17.6 Data Quality Assurance	Added direct transmission of clinical laboratory data from a central laboratory into the sponsor's database
17.8 Monitoring	Clarification of monitoring requirements.
17.10 On-Site Audits	Revised the following sentence: These audits will require access to all study records, including source documents, for inspection ~~and comparison with the eCRFs~~.
Rationale: Program-wide decision to no longer refer to apalutamide as a second-generation anti-androgen, rather it should be referred to as a "next" generation anti-androgen. Statements comparing apalutamide with enzalutamide were removed.	
1.1.2 Apalutamide; References	Revised text and references accordingly.
Rationale: Minor errors were corrected, minor revisions were made.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Minor organizational changes were made.
1.1.2 Apalutamide	For consistency, changed from AR antagonist to anti-androgen.

Applicable Section(s)	Description of Change(s)
Synopsis Biomarker Evaluations; 3.2 Study Design Rationale; 9.4 Biomarkers; 11.5 Biomarker Analyses	For consistency, the wording "up to" 220 or 500 subjects was revised to "approximately" 220 or 500 subjects.
9.7 Safety Evaluations	Removed this statement, details provided in Time and Events Schedule. ~~Required laboratory tests must be performed within 48 hours of the scheduled visit.~~
16.2.4; Privacy of Personal Data; 17.10 On-site Audits	Removed "or she" and "or her" wording, only men are enrolled in this study.
15 Study-Specific Materials	Added a link to the NCI-CTCAE version 4.03 criteria.

Amendment 1 (17 November 2014)

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 include The Committee for Medicinal Products for Human Use/European Medicines Agency (CHMP/EMA) health-technology-assessment (HTA) regulatory feedback and some added clarifications to existing text.

Applicable Section(s)	Description of Change(s)
Rationale: To give the most robustness to the study, CHMP/HTA suggested that giving a longer washout period for first generation anti-androgens would diminish the effect of prior treatment to the current study.	
4.1. Inclusion Criteria, Criterion 5.1	For Criterion #5, the washout period for subjects receiving a first generation anti-androgen was changed from 4 weeks to 6 weeks.
Rationale: Feedback from Safety Management Team (SMT) for an ongoing JNJ-56021927 study at Janssen suggested that the exclusion criterion for subjects with seizures be revised.	
4.2. Exclusion Criteria, Criterion 10.1	Modified Criterion #10 to specify seizures or known conditions that may pre-dispose a subject to a seizure making them ineligible to enroll in the study.
Rationale: The FDA requested scans at 8 week intervals over the first 24 weeks of the study to more accurately determine treatment effects based on PFS.	
Time and Events Schedule, CT or MRI, Bone Scan (^{99m}Tc)	Added extra scans at Cycle 3 Day 1 and Cycle 5 Day 1; q3 cycle scans will begin at Cycle 7
Rationale: The sponsorship statement was revised to delete information that does not apply to this study.	
Title Page	The sentence "For this study, Janssen-Cilag International NV (JCI) is the sponsor for sites in the European Union." was deleted.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification to describe that clinical benefit is defined by radiographic progression-free survival (rPFS).	
Synopsis, Objectives and Hypothesis; 2.1. Objectives 2.2. Hypothesis	In the primary objective and hypothesis statement, replaced "clinical benefit" by "radiographic progression-free survival (rPFS)".
Rationale: Clarification to more accurately define the secondary and other objectives.	
Synopsis, Objectives and Hypothesis; 2.1. Objectives	Pharmacodynamic objective removed from "Secondary Objectives" containing pharmacokinetics and made into a separate objective under "Other Objectives".
Rationale: At screening, the need for parenteral or oral opioid analgesics is excluded from the study, so any initiation of opioid analgesic lasting for ≥3 weeks for oral, or ≥7 days for non-oral formulation will meet the time to pain progression definition.	
Synopsis, Efficacy Evaluations/Endpoints 9.2.1.1. Other Efficacy Evaluations 10.2. Discontinuation of Study Treatment	Deleted “or increase in dose or frequency of the existing opioid analgesics” from the sentence describing the BPI-SF and chronic opioid use used to measure the secondary endpoint of time to pain progression
Rationale: Clarification to explain that 2 separate blood samples will be collected at each sampling time point.	
Synopsis, Population Pharmacokinetic Evaluations; Time and Events Schedule, footnote l; 9.3.1 Evaluations	Modified wording to state that 2 separate blood samples will be collected at approximately the same time for each sampling time point (1 for abiraterone and 1for JNJ-56021927).
Rationale: Consistency within protocol. Screening period changed to 42 days to account for the increased washout period for patients who received a first generation anti-androgen.	
Time and Events Schedule, Screening 9.1.2. Screening Phase	Screening period changed from 35 days to 42 days so that the washout period for Inclusion Criterion #5 can be achieved.
Rationale: Specified that 72 hours and 3 calendar days are not equivalent.	
Time and Events Schedule, footnote d; 5. Treatment Allocation and Blinding	Modified wording by adding "or” to sentence to state that all subjects must commence treatment within 72 hours or 3 calendar days of randomization
9.1.3. Treatment Phase	Added “or 3 calendar days” to describe that sujects must start study drugs within 72 hours or 3 calendar days after randomization.
Rationale: Clarification. Subjects should complete the BPI-SF ePROs for 7 consecutive days when collecting data.	
Time and Events Schedule, footnote i 9.5. Patient-Reported Outcomes	Added "consecutive" to clarify the number of days information should be entered when subjects provide data before Day 1 of each cycle, EOT visit, or druing the Follow-up Phase.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification to simplify the instructions on the ePRO device. Subjects should complete the baseline ePROs for FACT-P and EQ-5D-5L on Cycle 1 Day 1.	
Time and Events Schedule, footnote j 9.5. Patient-Reported Outcomes	Clarified this footnote to indicate that ePRO timing for FACT-P and EQ-5D-5L collection should be completed on Cycle 1 Day 1.
Rationale: Clarification to highlight modified fasting and dosing schedule on days of PK sampling.	
Time and Events Schedule, footnote l; 6.2.1. Special Dosing and Meal Instructions for PK Visits	Revised wording in footnote to delete special dosing instructions for "2 days prior and on the day before" PK sampling. Deleted text in first paragraph that referred to a modified dosing schedule being required on "the 2 days before" PK sampling and included that JNJ-56021927 and AA must be administered in the clinic "after initial PK samples are collected". Revised Table 2 to delete colums indicating fasting and dosing times for 2 days prior and on the day before PK sampling. Revised other days in Table 2 to show modified fasting and drug administration times relative to PK sample collection times.
Rationale: Clarification. Modified criterion to specify 3 ways of documenting prostate cancer progression.	
4.1. Inclusion Criteria, Criterion 6.1	Modified Criterion #6 to include "soft tissue" for radiographic progression evaluations according to Response Evaluation Criteria in Solid Tumors (RECIST), clarified that RECIST is modified based on Prostate Cancer Clinical Trials Working Group (PCWG2), and added radiographic progression of bone evaluationsaccording to PCWG2. Kept prostate cancer progression documented by prostate-specific antigen (PSA) according to the PCWG2.
Rationale: Clarification. (Initial calculation of testerone level of 1.7 nM was incorrect).	
4.1. Inclusion Criteria, Criterion 7.1; 6.1. ADT Administration	For Criterion #7, deleted 1.7 nM. Testosterone levels is now cited only as <50 ng/dL.
Rationale: Clarification. Modified Inclusion criterion to specify time frame for subjects using a condom during sexual activity. Deleted a criterion from Prohibitions and Restrictions that was redundant with an Inclusion criterion.	
4.1. Inclusion Criteria, Criterion 13.1	Modified Criterion #13 to include that subjects agree to use a condom during sexual activity "while on study drug and for 3 months following the last dose of study drug".
4.3. Prohibitions and Restrictions, Criterion 1	Deleted Criterion #1 from Prohibitions and Restrictions regarding subjects agreeing to use a condom during sexual activity because it is already stated in Inclusion Criterion #13.
Rationale: Clarification. More accurately define time frame of "study entry".	
4.2. Exclusion Criteria, Criterion 6.1	For Criterion #6, "study entry" was changed to "screening" to more acccurately define the time for parenteral or oral opioid analgesics (eg, codeine, dextropropoxyphene) to be stopped before a subject can be eligible for entering the study.
Rationale: To give the most robustness to the study, CHMP/HTA suggested that by prohibiting subjects treated with 5-α reductase inhibitors within 4 weeks of enrollment would diminish the effect of prior treatment to the current study.	
4.2. Exclusion Criteria, Criterion 14	Added Criterion #14 "Treatment with 5-α reductase inhibitors (finasteride, dutasteride), estrogens, cyproterone within 4 weeks of enrollment".

Applicable Section(s)	Description of Change(s)
Rationale: Clarification. Add more information for Adverse Event terminology grading.	
6.3.2.1. Abnormal Liver Function Test(s)	Modified footnote "a" to Table 3 to include reference for NCI-CTCAE, Version 4.03 as source for Adverse Event terminology grading. Added footnote "b" to Table 3 to clarify that the dose modifications for liver function test (LFT) abnormalities are from the ZYTIGA label and not and do not follow Version 4 of CTCAE.
Rationale: Clarification of timing of at home study drug adminsitration relative to PK sampling for subjects participating in PK sampling.	
9.1.3. Treatment Phase	Modified wording in paragraph regarding study drugs taken at home for subjects participarting in PK sampling.
Rationale: Clarified that PSA measurements, lymph node, and ^{99m}Tc bone scan will be evaluated according to an adaptation of the PCWG2 criteria.	
9.2.1.2 Efficacy Criteria	Added "lymph node" will also be evaluated as an efficay criteria.
Rationale: Consistency within the protocol.	
14.4. Preparation, Handling, and Storage	Added a sentence that subjects should use a condom while on study drug and for 3 months following the last dose of study drug so that instructions for use of the study drug are consistent with Inclusion Criterion #13.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer (mCRPC)

JNJ-56021927 (ARN-509; apalutamide, hereafter referred to as apalutamide) is an orally available, small molecule, non-steroidal potent and selective antagonist of the androgen receptor (AR) (anti-androgen). It is currently being developed for the treatment of prostate cancer.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective is to compare the radiographic progression-free survival (rPFS) of apalutamide in combination with abiraterone acetate (AA) plus prednisone or prednisolone (AAP) and AAP in subjects with chemotherapy-naïve mCRPC.

Major Secondary Objectives

The major secondary objectives are:

- To characterize the safety profile of apalutamide in combination with AAP
- To characterize the pharmacokinetics (PK) of apalutamide and abiraterone

Other Objectives

The other objectives are:

- To explore the relationship between PK and pharmacodynamics (PD) of apalutamide and abiraterone
- To evaluate exploratory biomarkers predictive of response and resistance in subjects when treated with apalutamide in combination with AAP compared with AAP
- To assess the effect on patient-reported outcomes (PROs) in this study population when treated with apalutamide in combination with AAP compared with AAP
- To evaluate other endpoints of clinical relevance including additional assessments of pain, objective response, time to symptomatic skeletal-related event (SSRE), and PSA response
- To evaluate medical resource utilization (MRU) information

Hypothesis

The primary hypothesis of the study is that apalutamide in combination with AAP compared with AAP will demonstrate improved rPFS and an acceptable safety profile in subjects with chemotherapy-naïve mCRPC.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind placebo-controlled, multinational, multicenter Phase 3 study to determine if subjects with chemotherapy-naïve mCRPC will benefit from the addition of apalutamide to AAP compared with AAP. Subjects will continue receiving gonadotropin releasing hormone analogs (GnRHa) if not surgically castrated. Approximately 960 subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to receive apalutamide and AAP or matching placebo and AAP. Subjects will be stratified by the presence or absence of visceral metastases,

Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) grade of 0 or 1, and region (European Union [EU], North America [United States/Canada], and Rest of World [ROW]). The study will consist of a Screening Phase; a Treatment Phase, and a Follow-up Phase. The study is anticipated to end approximately 84 months after the first subject has been randomized into the study.

A treatment cycle is defined as 28 days. Treatment will continue until disease progression, unacceptable toxicity, death or the sponsor terminates the study. Subjects must discontinue study drugs with documented unequivocal clinical progression as defined in the protocol. If the subject has radiographic progression, but not unequivocal clinical progression, and alternate treatment is not initiated, the subject may continue on study treatment at the investigator's discretion.

After discontinuing study drug, subjects will be contacted for survival every 3 months until death, withdrawal of consent, lost to follow up or termination of the study. In addition to survival follow up, analgesic use, SSREs, ECOG PS, and subsequent therapy for prostate cancer up to and including chemotherapy will be collected. Patient-reported outcomes (PROs) questionnaires will also be completed every 3 months up to 12 months after discontinuation of study treatment.

Subjects will be monitored for safety during the Screening and Treatment Phases and up to 30 days after the last dose of study drug. Adverse events (AEs) including laboratory AEs, will be graded and summarized using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Dose modification guidelines will be provided.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. The committee will perform periodic safety review throughout the study and review the safety of the first 60 subjects randomized to the study after treatment for at least 1 cycle. In addition, the IDMC will review the planned efficacy/futility analysis.

Following the decision to unblind the study, the Extension Phase will begin when both the Amendment 4 is approved at the site and the sponsor has notified the site of the start of the Open-Label Extension Phase or Long-Term Extension Phase.

SUBJECT POPULATION

The study population includes men with mCRPC documented by positive bone scan or metastatic lesions on CT or MRI, ≥18 years of age, with ECOG PS grade of 0 or 1. A score of 3 or less on item 3 (worst pain in the last 24 hours) of the Brief Pain Inventory-Short Form (BPI-SF) is required. Subjects are excluded if they received prior chemotherapy for mCRPC (adjuvant/neoadjuvant chemotherapy is allowed) and inhibitors of CYP17 or androgen axis signaling.

DOSAGE AND ADMINISTRATION

All subjects will receive AAP as standard of care (SOC) therapy. Abiraterone acetate 1,000 mg (4 × 250 mg tablets) will be taken orally once daily. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of AA is taken and for at least 1 hour after the dose of AA is taken. Tablets should be swallowed whole with water. The daily dose of prednisone will be 10 mg (5-mg tablet taken orally twice daily).

Although not considered study drug, subjects who have not undergone surgical castration will continue to receive regularly prescribed GnRHa.

JNJ-56021927 (apalutamide) 240 mg (4 x 60 mg tablets) or Placebo (4 tablets) will be taken orally once daily. The tablets can be taken with or without food.

EFFICACY EVALUATIONS/ENDPOINTS

Efficacy evaluations will be conducted as specified in the Time & Events Schedule. The efficacy evaluations include the following:

- Tumor measurements (computed tomography [CT] or magnetic resonance imaging [MRI], bone scans, other imaging procedures)
- Survival status, analgesic use, SSREs, and first cytotoxic chemotherapy for prostate cancer
- Serum PSA evaluation (measurements at a central laboratory)

The same imaging modality used for tumor assessments should be used throughout the evaluation of an individual subject. Unscheduled tumor assessment and appropriate imaging should be considered if signs or symptoms suggestive of disease progression, including escalating pain not referable to another cause, worsening ECOG PS grade, or physical examination findings consistent with disease progression, are recorded.

The BPI-SF (item 3) and chronic opioid use (defined as administration of additional opioid analgesics lasting for ≥3 weeks for oral, or ≥7 days for non-oral formulation) will be used to measure the secondary endpoint of time to pain progression. Analgesic usage (for time to analgesic progression endpoint) will be scored according to the World Health Organization (WHO) analgesic ladder: 0 for no analgesic, 1 for non-opioid analgesics (including non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol/acetaminophen, antidepressants, and agents intended to treat neuropathic pain), 2 for opioids for moderate pain, and 3 for opioids for severe pain.

Efficacy Endpoints

Primary: Radiographic progression-free survival is defined as the time from date of randomization to the date of radiographic progression or death, whichever occurs first. Radiographic progression will be assessed by the investigator based on soft tissue lesion by CT/MRI per modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) or by bone lesion progression on bone scans per an adaptation of the Prostate Clinical Trials Cancer Working Group 2 (PCWG2).

Secondary: Overall survival (OS), time to chronic opioid use, time to initiation of cytotoxic chemotherapy, and time to pain progression.

Other: Time to deterioration of ECOG PS, time to SSRE; objective response rate and duration of response in subjects with measurable disease; PROs as assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P), BPI-SF, and EQ-5D-5L; time to PSA progression based on PCWG2 criteria; time to analgesic progression, progression-free survival on first subsequent therapy (PFS2), and biomarker research to explore AR gene anomalies and other markers responsible for resistance to apalutamide.

POPULATION PHARMACOKINETIC EVALUATIONS

Pharmacokinetic assessment will be conducted on as many subjects as feasible (and where regulations permit). In Japan, blood samples for PK assessment will be collected from all randomized subjects. Two separate blood samples will be collected at approximately the same time for each sampling time point; 1 for abiraterone and 1 for apalutamide. On Day 1 of Cycle 1, blood samples will be collected at 2 hours and 4 hours post the first dose for each subject. On Day 1 of Cycle 3, a predose sample (up to 1 hour prior to on-site study drugs administration) and postdose samples between 0.5 and 4 hours will be collected. For the other PK visits (Cycles 2, 4, 5, and 6), blood samples will be collected predose (up to 1 hour prior to on-site study drugs administration).

BIOMARKER EVALUATIONS

Archived tumor samples (formalin-fixed paraffin-embedded [FFPE] blocks or slides) and serum samples will be collected, where country regulations permit, for biomarker evaluations. Plasma samples will be collected from approximately 220 subjects during treatment and approximately 500 subjects at the end-of-treatment or progression; whole blood and serum will be collected from approximately 220 subjects at the time points indicated in the Time & Events Schedule. Plasma-based circulating DNA will be used to assess the presence of the AR^{F876L} mutation and whole blood or plasma DNA to assess other markers that may be associated with resistance to AA alone and in combination with apalutamide. Serum samples will be collected to compare the effect of testosterone and steroid metabolites when subjects are treated with AAP alone and in combination with apalutamide. Archival FFPE tumor blocks or tumor slides will be collected from at least 300 subjects in this study to investigate whether genomic classifiers can be used to identify a more homogeneous population of high-risk subjects. This will potentially allow selection of the appropriate high-risk patient population for future studies of apalutamide and AAP.

PATIENT-REPORTED OUTCOMES EVALUATIONS

Three PRO instruments, the Functional Assessment of Cancer Therapy-Prostate (FACT-P), BPI-SF, and EQ-5D-5L will be administered in this study.

MEDICAL RESOURCE UTILIZATION EVALUATIONS

Medical resource utilization data associated with medical encounters will be collected in this study.

SAFETY EVALUATIONS

Safety evaluations include AEs, vital signs measurements, physical examinations, and clinical laboratory tests.

STATISTICAL METHODS

The primary analysis population will use the intent-to-treat (ITT) population, which includes all randomized subjects. The ITT population will be used for the analysis of subject disposition and efficacy. The safety population includes all subjects who received at least 1 dose of study drug.

This study is sized (approximately [redacted]% power) to detect a hazard ratio (HR) of [redacted] in the secondary endpoint of OS based on an assumed median OS of [redacted] for the control group (AAP). Under the assumption that the failure distribution of OS follows an exponential distribution with a constant hazard rate, approximately [redacted] death events will be required to detect the assumed HR of [redacted] at a maximum two-sided significance level of 0.05, with enrollment duration of approximately [redacted] (approximately 960 subjects) and an additional follow up of approximately [redacted] to reach the total number of death events.

It is estimated that approximately [redacted] rPFS events would be required to provide at least [redacted]% power in detecting an HR of [redacted] (median rPFS of [redacted] for the control group [AAP alone] versus [redacted] for the treatment group of apalutamide plus AAP) at a two-tailed level of significance of 0.05 under the assumption of a positive correlation between rPFS and OS;

Efficacy Analysis

Kaplan-Meier product limit method and stratified Cox model will be used to estimate the survival distribution of the time-to-event variables and to obtain the HR and corresponding confidence interval (CI) respectively. The testing of the time-to-event endpoints will be based on the stratified log-rank test. Response rate variable will be evaluated using the Chi-square statistic.

Population PK and Pharmacodynamic Analyses

Population PK analysis of plasma concentration-time data of apalutamide and abiraterone may be performed using nonlinear mixed-effects modeling. If sufficient data are available, the relationship of exposure to apalutamide and active metabolite JNJ-56142060, and abiraterone to measures of efficacy and AEs may also be analyzed. The population PK/PD analysis results will be presented in a separate report.

Biomarkers Analyses

The associations of the biomarkers with clinical response or time-to-event endpoints may be assessed using appropriate statistical methods (such as analysis of variance [ANOVA], categorical, or survival models), depending on the endpoint. A detailed statistical analysis plan will be prepared for these exploratory studies.

Patient-Reported Outcomes Analysis

Scales from BPI-SF and FACT-P: Descriptive statistics of each scale score at baseline and follow up assessments will be summarized by treatment groups; time to degradation in each scale will be analyzed using Kaplan-Meier method and stratified Cox proportional-hazard model. Additional analysis may be carried out, if appropriate. Analysis details will be included in the statistical analysis plan.

The EQ-5D-5L data will be summarized descriptively by treatment group and study visit. Each level of every dimension will be summarized using count and percent. EQ-5D-5L Visual Analog Scale (VAS) will be described using summary statistics (n, mean, median, etc.).

Medical Resource Utilization Analysis

Medical resource utilization will be descriptively summarized by treatment group. The results will be presented in a separate report.

Safety Analyses

The safety parameters to be evaluated are the incidence and intensity of AEs, clinically significant changes in the subject's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

Interim Analyses

For the OS endpoint, 2 interim analyses are planned in this study after observing approximately [redacted]% ([redacted] events) and [redacted]% ([redacted] of the total number of required ([redacted] events. The final analysis of OS will be performed when approximately [redacted] death events are observed. The testing of the OS endpoint will be carried out based on the group sequential design according to the [redacted]. Assuming a maximum overall 2-tailed significance level of 0.05, the estimated cumulative alpha spend are [redacted] and [redacted] at the first and second interim analyses, respectively. The exact significance levels will be determined according to the observed number of events at the time of analysis.

Futility Analyses

A non-binding futility analysis is planned using PSA90 decline rate defined as the proportion of subjects with a decline of PSA of 90% or more from baseline. In the case that a PSA90 decline rate of 30% in the control group is observed, it is assumed that an absolute increase of [redacted]% over the control group would be clinically meaningful. This futility analysis will occur when approximately [redacted] subjects have been treated for at least [redacted] cycles. This sample size should control the type II error rate of approximately [redacted]% under the assumed decline rates. The purpose of this analysis is to provide an early look to ensure the treatment

group of apalutamide plus AAP has sufficient antitumor activity compared with AAP alone. This futility analysis will not be used to substantiate an efficacy claim. Non-binding futility analyses will be implemented at the planned interim analyses for OS.

In addition, a non-binding futility analysis on rPFS will be implemented after observing approximately [redacted]% ([redacted] events) of the total number of required [redacted] events.

TIME AND EVENTS SCHEDULE

PHASE	Notes	Screening Phase	Treatment Phase[a]								Follow-up Phase[c]
CYCLE (defined as 28 days):		Within 42 days of randomization unless otherwise specified	Cycle 1		Cycle 2		Cycle 3		Cycle 4 until EOT	EOT Visit (within 30 days of last dose)[b]	Every 3 months
CYCLE DAY:	Unless otherwise specified, study visits/procedures have a ±2-day time window		1	15	1	15	1	15	1		
Screening											
Informed consent (must be performed before any study-specific procedures)		X									
Inclusion/exclusion criteria		X									
Prestudy anti-cancer therapy, palliative radiation, or surgical therapy for metastatic disease		X									
Medical history and demographics		X									
Randomization[d]		X									
Study Drug Administration											
Dispense study drug			X		X		X		Every cycle up to Cycle 24 then q3 cycles		
Dosing compliance[e]					X		X		Every cycle up to Cycle 24 then q3 cycles		
Safety											
Electrocardiogram, 12-lead[f]		X									
Physical examination[g]		X	X		X		X		Every cycle up to Cycle 24 then q3 cycles	X	
Vital signs	Blood pressure, heart rate, respiratory rate, and body temperature at screening; afterwards only blood pressure	X	X		X		X		Every cycle up to Cycle 24 then q3 cycles	X	
ECOG PS		X	X		X		X		Every cycle up to Cycle 24 then q3 cycles	X	X

PHASE	Notes	Screening Phase	Treatment Phase[a]							Follow-up Phase[c]
CYCLE (defined as 28 days):		Within 42 days of randomization unless otherwise specified	Cycle 1		Cycle 2		Cycle 3		Cycle 4 until EOT	EOT Visit (within 30 days of last dose)[b]	Every 3 months
CYCLE DAY:	Unless otherwise specified, study visits/procedures have a ±2-day time window		1	15	1	15	1	15	1		
Efficacy											
CT or MRI	The same modality (CT or MRI) should be used throughout the study. Imaging visits may occur up to 8 days before cycles requiring images. Unscheduled assessments may be performed if signs of disease progression are observed. CT/MRI exams of chest, abdomen and pelvis must be performed. If available, collect information on imaging assessments until radiographic progression is documented (see Sections 9.1.5 and 10.2)	X					X		Cycle 5 then q3 cycles beginning at Cycle 7	X[h]	
Bone Scan (^{99m}Tc)	Scan visits may occur up to 8 days before cycles requiring images. Unscheduled assessments may be performed if signs of disease progression are observed.	X Within 6 weeks of randomization					X		Cycle 5 then q3 cycles beginning at Cycle 7	X[h]	
ePROs	During the Screening Phase, BPI-SF is collected from Day-6 prior to randomization until C1D1 with the last day being completed on C1D1 before any other procedures. During the Treatment Phase, 7-day assessments for each cycle are done with the last day being completed D1 before any other procedures at on-site visits. During the Follow-up Phase, the 7-day assessments will be done remotely. The consecutive 7-day assessments will also be completed for the EOT Visit.	Start on Day -6 prior to randomization	X		X		X		Every cycle	X	q3 months for up to 12 months after treatment discontinuation

PHASE	Notes	Screening Phase	Treatment Phase[a]							Follow-up Phase[c]
CYCLE (defined as 28 days):		Within 42 days of randomization unless otherwise specified	Cycle 1		Cycle 2		Cycle 3		Cycle 4 until EOT	EOT Visit (within 30 days of last dose)[b]	Every 3 months
CYCLE DAY:	Unless otherwise specified, study visits/procedures have a ±2-day time window		1	15	1	15	1	15	1		
ePROs (continued)	Baseline questionnaires for FACT-P and EQ-5D-5L should be completed on C1D1. At all clinic visits the questionnaires should be completed before any other visit procedure. During Follow-up Phase, the questionnaires will be completed remotely.		X[i]		X		X		Cycles 4, 5, 6 then q3 cycles	X	q3 months for up to 12 months after treatment discontinuation
Additional pain assessment	Subjects should also complete "How would you rate your pain over the past 7 days?" (0 to 10 scale). Site personnel should record response in the eCRF and in clinic visit record. On non-visit cycles, the responses will be collected by telephone contact.		X		X		X		Every cycle	X	
Medical Resource Utilization			Continuous							X	
Survival status and subsequent anti-cancer therapy (up to and including chemotherapy), analgesic use, and SSREs (see Section 9.2)	See also Section 9.1.5									X	X
Progression on first subsequent therapy											X
Clinical Laboratory											
Hematology	Hemoglobin, WBCs including absolute neutrophil count, platelet count.	X	X[i]		X		X		Cycles 4,5,6 then q2 cycles from Cycle 8 to Cycle 24 then q3 cycles	X	
Serum chemistry	Potassium, sodium, total protein, calcium, creatinine, lactate dehydrogenase, albumin (Screening only)	X	X[i]		X		X		Cycles 4,5,6 then q2 cycles from Cycle 8 to Cycle 24 then q3 cycles	X	
Liver function tests	ALP, ALT, AST, total bilirubin; direct and indirect bilirubin if Gilbert's is suspected at Screening only	X	X[i]	X	X	X	X	X	Cycles 4,5,6 then q2 cycles from Cycle 8 to Cycle 24 then q3 cycles	X	

PHASE	Notes	Screening Phase	Treatment Phase[a]								Follow-up Phase[c]
CYCLE (defined as 28 days):		Within 42 days of randomization unless otherwise specified	Cycle 1		Cycle 2		Cycle 3		Cycle 4 until EOT	EOT Visit (within 30 days of last dose)[b]	Every 3 months
CYCLE DAY:	Unless otherwise specified, study visits/procedures have a ±2-day time window		1	15	1	15	1	15	1		
PSA		X	X[i]		X		X		Every cycle to Cycle 12 then q2 cycles up to Cycle 24 then q3 cycles	X	
Fasting glucose and lipids	Lipid panel includes HDL, LDL, triglycerides	X	X[i]						Cycle 12, then q12 cycles		
Serum testosterone		X									
TSH	T3 and T4 only to be done if TSH is abnormal	X	X[i]						Cycle 4 then q2 cycles to Cycle 24, then q3 cycles	X	
Ongoing Subject Review											
Concomitant therapy	*Continuous from time of signing of ICF until 30 days after the last study drug dose*										
Adverse events[b]	*Continuous from time of signing of ICF until 30 days after the last study drug dose*										
Pharmacokinetics											
PK sparse sampling[j]	Samples will be collected from as many subjects as feasible (and where regulations permit). In Japan, samples will be collected from all randomized subjects.		X		X		X		Cycles 4, 5, and 6 only		
Biomarkers (See also Section 9.4).											
FFPE tumor blocks or slides for biomarker assessments	Samples obtained at time of original diagnosis. The tumor blocks or slides can be provided anytime on or after C1D1.		X								
Plasma sample collection	Plasma samples (10 mL at each draw) at C1D1 (baseline) and C12D1, and EOT or progression.		X						Cycle 12 only	X	
Whole blood sample collection	Whole blood samples (2.5 mL at each draw) at C1D1 (baseline), C12D1, and EOT or progression		X						Cycle 12 only	X	
Serum sample collection	Serum samples (8.5 mL at each draw) at C1D1 (baseline), C3D1, C12D1, and EOT or progression		X				X		Cycle 12 only	X	

AE=adverse event; ALP=alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPI-SF = Brief Pain Inventory - Short Form; C1D1=Cycle 1 Day 1; C12D1=Cycle 12 Day 1; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=end-of-treatment; ePRO=electronic device for patient-reported outcomes; EQ-5D-5L=Euro-QoL; FACT-P=Functional Assessment of Cancer Therapy-Prostate; FFPE=formalin-fixed paraffin-embedded; ICF=informed consent form; LFT=liver function test; MRI=magnetic resonance imaging; MRU=medical resource utilization; PK=pharmacokinetic; PROs=patient-reported outcomes; PSA=prostate-specific antigen; q=every; SOC=standard of care; SSRE=symptomatic skeletal-related event; ^{99m}Tc=technetium-99m; TSH=thyroid stimulating hormone WBCs=white blood cells

[a] Subjects should visit the clinic on Day 1 of each cycle for assessments and on Day 15 of each cycle for LFT assessments for the first 3 cycles. From Cycle 4 to EOT, visits are monthly up to Cycle 24 (q3 cycles); the assessments may differ from cycle to cycle as shown in the table.

[b] Subjects who discontinued from treatment due to disease progression, AE or other reasons and enter the Follow-up Phase must have the EOT Visit completed before starting any subsequent anti-cancer treatment for prostate cancer. If a subject is unable to return to the site for the EOT Visit, the subject should be contacted to collect AEs that occur within 30 days after the last dose of study drug.

[c] Follow up for survival will continue until death, withdrawal of consent, lost to follow up or until study termination. Deaths regardless of causality will be reported in the eCRF. Serious adverse events that occur after 30 days following the last drug administration thought to be related to study drug will be collected and reported via the SAE form within 24 hours of discovery or notification of the event and documented (see Section 12.3.2).

[d] Subjects must meet all inclusion and none of the exclusion criteria before randomization can occur. Subjects must start study drug on C1D1; C1D1 may occur anytime within 72 hours or 3 calendar days of randomization.

[e] Includes a tablet count (see Section 7).

[f] Serum chemistry results must be available before ECG can be obtained. ECGs obtained within 42 days of randomization should be rechecked if prior ECG was obtained when potassium level was <3.5mmol/L or unknown. Serum potassium <3.5 mmol/L should be corrected before ECG recording. Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.

[g] Weight should be obtained with subjects wearing light clothing and no shoes. The Screening physical examination will include, at a minimum, the general appearance of the subject, height and weight, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Weight and symptom-directed physical examinations should be obtained during the Treatment Phase and at the EOT Visit.

[h] Bone scans, CT, or MRI scans at EOT Visit are not required if scans were done within the previous 6 weeks.

[i] Screening laboratory evaluations can be used for C1D1 assessments if performed within 14 days of C1D1, otherwise the laboratory assessments must be repeated on C1D1.

[j] See Section 6.2.1 for special dosing instructions on the day of PK sampling. Two separate blood samples will be collected at approximately the same time for each sampling time point; 1 for abiraterone and 1 for apalutamide. On Day 1 of Cycle 1, blood samples will be collected at 2 hours and 4 hours post the first dose. On Day 1 of Cycle 3, predose samples (up to 1 hour prior to on-site study drug administration) and postdose samples between 0.5 and 4 hours will be collected. For the other PK visits (Cycles 2, 4, 5, and 6), blood samples will be collected predose (up to 1 hour prior to on-site study drugs administration). See also Section 9.3.

ABBREVIATIONS

AA	abiraterone acetate
AAP	abiraterone acetate plus prednisone or prednisolone
ACTH	adrenocorticotropic hormone
ADT	androgen deprivation therapy
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
BPI-SF	Brief Pain Inventory-Short Form
BCRP	breast cancer resistance protein
CRF	case report form (paper or electronic as appropriate for this study)
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EBRT	external beam radiation therapy
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eDC	electronic data capture
ePRO	electronic device for patient-reported outcomes
EQ-5D-5L	Euro-QoL
EOT	End-of-Treatment
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDHT	16β-[^{18}F] fluoro-α-dihydrotestosterone
FFPE	formalin-fixed paraffin-embedded
$GABA_A$	gamma aminobutyric acid chloride channel
GCP	Good Clinical Practice
GnRHa	gonadotropin releasing hormone analog
HR	hazard ratio
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	interactive web response system
IUD	intrauterine device
IUS	intrauterine system
LFT	liver function test
LTE	Long-Term Extension
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MRU	medical resource utilization
NCI	National Cancer Institute
NM-CRPC	non-metastatic castration-resistant prostate cancer
OATP1B1	organic anion transporter 1B1
OLE	Open-Label Extension
OS	overall survival
PCWG2	Prostate Cancer Clinical Trials Working Group 2
P-gp	P-glycoprotein
PK	Pharmacokinetics
PQC	product quality complaint
PRO	patient-reported outcome(s)
PSA	prostate-specific antigen
ROW	rest of world
rPFS	radiographic progression-free survival

SAC	Safety Assessment Committee
SAE	serious adverse event
SIPPM	study-site investigational product procedures manual
SSRE	symptomatic skeletal-related event
SUSAR	suspected unexpected serious adverse reaction
^{99m}Tc	technetium-99m
TSH	thyroid stimulating hormone
WBC	white blood cell
UGT	uridine diphosphate glucuronosyl transferase
ULN	upper limit of normal

1. INTRODUCTION

JNJ-56021927 (ARN-509; apalutamide, hereafter referred to apalutamide) is an orally available, small molecule, non-steroidal potent and selective antagonist of the androgen receptor (AR) (anti-androgen). It is currently being developed for the treatment of prostate cancer.

For the most comprehensive nonclinical and clinical information regarding apalutamide, refer to the latest version of the Investigator's Brochure and Addenda for JNJ-56021927 (apalutamide).[18]

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

1.1. Background

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males worldwide.[19] Treatment aimed at eradicating the primary tumor, typically with surgery or radiation, is unsuccessful in ~30% of men, who develop recurrent disease that usually manifests first as a rise in plasma prostate-specific antigen (PSA) followed by metastasis to distant sites. Prostate cancers are dependent for their growth and survival on androgen-mediated signaling.[31,34] In patients with locally advanced or metastatic disease, the depletion of androgens through either medical[9] or surgical[15] castration, decreases androgen receptor (AR) signaling and leads to tumor regression. Unfortunately, these regressions in patients with metastatic prostate cancer are universally transient, with a median duration of disease control between 13 and 22 months and median overall survival (OS) of 28 to 36 months.[32]

Treatment results with androgen deprivation therapy (ADT; gonadotropin releasing hormone analogs [GnRHa] or surgical castration) with or without anti-androgens are generally predictable: a decline in PSA followed by tumor regression, a period of stability in which the tumor does not proliferate and PSA remains stable, followed by rising PSA and regrowth as a castration-resistant disease. Nearly all men with progressive prostate cancer eventually develop castration-resistant disease. Prostate cancer progression despite castrate levels of testosterone represents a transition to a lethal disease stage.

1.1.1. Inhibition of CYP17 and Abiraterone Acetate

Testosterone synthesis occurs in several locations. Peripheral conversion of adrenal androgens to testosterone may result in circulating testosterone concentrations approaching 10% of pre-castrate concentrations. Prostate cancer tissue can be a source of androgen production that stimulates growth in an autocrine or paracrine manner, independent of circulating androgens.[24]

ZYTIGA® (Abiraterone acetate [JNJ-212082]) is a pro-drug of abiraterone (JNJ-589485) 17-(3-pyridyl) androsta-5,16-dien-3β-ol], an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme CYP17. This enzyme is found in testes, adrenals, and in prostate tissues and tumors.[1,24,25]

The clinical benefits of abiraterone acetate (AA) in combination with prednisone or prednisolone (hereafter referred to as AAP) were demonstrated in 2 large randomized, double-blind, placebo-controlled Phase 3 studies (COU-AA-301 and COU-AA-302). These studies included subjects with mCRPC post-chemotherapy (COU-AA-301) and chemotherapy-naïve (COU-AA-302).[10,27,29]

As of 01 March 2014, AAP is approved in more than 86 countries for patients with mCRPC. The combination of AAP has now been adopted as standard front-line therapy for mCRPC and will be combined with the experimental compound apalutamide, and will also be the treatment in the control arm for this study.

1.1.2. Apalutamide

Additional clinical benefit beyond suppression of testosterone production might also be obtained by the use of next generation anti-androgens in patients with mCRPC. This is supported by molecular profiling studies of CRPC, which commonly show increased AR gene expression.[4] The increased AR levels are sufficient to confer resistance to anti-androgen therapy in mouse models, shorten tumor latency and confer agonist properties to first generation anti-androgens, such as bicalutamide or flutamide.[5] The potential for agonist activity by these approved anti-androgens in the setting of increased AR expression is a potential liability, best illustrated by the observation of tumor regression and declines in PSA following discontinuation of either of these anti-androgens, the so-called anti-androgen withdrawal syndrome.[21] Collectively, these findings implicate increased AR levels as one mechanism of drug resistance. They also suggest that drugs retaining antagonism and not displaying agonism in cells over-expressing AR levels might be useful therapeutically.

Apalutamide has been developed to overcome the potential therapeutic deficiencies of first generation anti-androgens. Apalutamide is a potent and selective anti-androgen that acts by inhibiting the action of androgen, nuclear translocation of the AR and DNA binding to androgen response elements and unlike bicalutamide, it exhibits no significant agonist activity in AR-over-expressing prostate cancer cells.[5]

Clinical Studies

Apalutamide is being evaluated in Phase 1, Phase 1/2, and Phase 3 studies in patients with CRPC (non-metastatic and metastatic), high-risk localized or locally advanced prostate cancer, and biochemically relapsed hormone-sensitive prostate cancer.

Study ARN-509-001 is an ongoing Phase 1/2 study in patients with progressive advanced CRPC. A clinical study report was completed based on a clinical cutoff of 31 December 2014. At the time of this cutoff, 26 (27%) subjects were continuing to receive treatment.[6] In the Phase I portion of the study, 30 patients with mCRPC received at least 1 dose of apalutamide at escalating dose levels: 3 patients each at 30, 60, 90, 120, 180, 240, 390, 480-mg/day, and 6 patients at 300-mg/day. Ninety-seven subjects divided into 3 subgroups are being evaluated in the Phase 2 portion (Cohort 1: NM-CRPC n=51; Cohort 2: mCRPC without previous ketoconazole, abiraterone acetate/prednisone, enzalutamide or chemotherapy [for mCRPC]

n=25; and Cohort 3: mCRPC post abiraterone acetate/prednisone, no previous chemotherapy [for mCRPC] n=21).

The results of the Phase 1 portion of the study from 30 patients with mCRPC demonstrated that treatment with apalutamide resulted in PSA declines at all dose levels tested. Apalutamide was well tolerated, with only 1 dose-limiting toxicity (DLT) at the 300 mg dose level (Grade 3 treatment-related abdominal pain). The event lasted 6 days and resolved with dose interruption and subsequent dose reduction to 240 mg (120 mg twice daily). Three additional subjects were treated at the 300 mg dose level with no reported DLTs. Eligibility criteria for Phase 1 and 2 excluded subjects with a history of seizure or a condition that may predispose to seizure and concurrent therapy with medications known to have seizure potential were also prohibited. No seizures were reported at any dose level. The pharmacokinetic (PK) profile was determined to be linear and dose-proportional. The maximum tolerated dose (MTD) was not determined. The determination of the recommended Phase 2 dose of 240 mg daily was based on an integrated approach: comparing the dose required for maximum tumor regression in mouse xenograft models with clinical PK and pharmacodynamics, and assessing the safety and tolerability at doses up to 480 mg.

Treatment-related adverse events observed across the 3 cohorts in >10% of patients were fatigue (47%), diarrhea (28%), nausea (27%), abdominal pain (13%); and hot flush, hypothyroidism, and dysgeusia (each 11%). Treatment -related adverse events of blood TSH increased were reported for 8 patients (8%). Decreased appetite and weight decreased were reported as treatment-related adverse events for 8 patients (8%) and 5 subjects (5%), respectively. Nineteen (20%) patients had reported treatment-related adverse events under the system organ class (SOC) of skin and subcutaneous tissue disorders, which included pruritus (7 [7%] patients), rash (7 [7%] patients), rash erythematous (3 [3%] patients), dry skin (3 [3%] patients), and rash macular (3 [3%] patients).

The efficacy of apalutamide was also evaluated in the Phase 2 portion of Study ARN-509-001. The percentage of patients with PSA reductions of 50% at 12 weeks was 89% for Cohort 1, 88% for Cohort 2, and 22% for Cohort 3. Similar data were observed after 24 weeks. The data available to date indicate that apalutamide shows durable PSA responses in NM-CRPC and early mCRPC (before treatment with abiraterone acetate or chemotherapy). Apalutamide also has activity in a subgroup of patients with mCRPC that have progressed on abiraterone actetate. With a median follow up of 28.0 months, the median time to PSA progression for Cohort 1 was 24.0 months (95% CI: 16.3; NE). With a median follow-up of 22.1 months for Cohort 2, the median time to PSA progression was 18.2 months (95% CI: 8.3; NE). The median follow-up for Cohort 3 was 5.6 months with a median time to PSA progression of 3.7 months (95% CI: 2.8; 5.6).

Study ARN-509-004 is an ongoing Phase 1b to assess the safety, PK and preliminary antitumor activity of ascending doses of apalutamide and AAP in subjects with mCRPC. Six subjects were enrolled in this study.[8] All 6 subjects received AA (1,000 mg orally once daily) and prednisone (5 mg orally once daily) starting on Cycle 1 Day 1. Daily administration of apalutamide as softgel capsules was initiated on Cycle 1 Day 8. Three subjects enrolled in Cohort 1 received

120-mg apalutamide orally once daily. Three subjects enrolled in Cohort 2 received 240-mg apalutamide orally once daily. The pharmacokinetic (PK) samples were collected on Cycle 1 Day 7 (AAP alone) and Cycle 1 Day 36 (AAP+apalutamide). The PK results suggested that apalutamide does not appear to have a major effect on abiraterone exposure. As subjects are continuing treatment, safety and preliminary antitumor activity are not yet available.

A Phase 1b study was initiated (Study 56021927PCR1010) to assess the PK of abiraterone and its metabolites when dosed alone or in combination with apalutamide in up to 26 subjects with mCRPC. Safety data from 29 subjects after a median treatment duration of 12.1 weeks (range: 4 to 24 weeks) was reported.[7] The safety profile of combination treatment with apalutamide plus AAP is as expected, based on the known side effects observed to date with apalutamide or AAP, individually. No new safety signals were noted with the combination therapy. Most commonly reported drug-related AEs (≥10% of subjects) were fatigue (41%), dysgeusia (21%), diarrhea (17%), hypokalemia (17%), vomiting (14%), decreased appetite (14%), upper abdominal pain (10%), nausea (10%) and dyspepsia (10%). The majority of these drug-related AEs were Grade 1 and Grade 2 in severity. Drug-related AEs of Grade ≥3 toxicity were reported in 3 (10%) subjects and included fatigue, hepatic function abnormal (ALT increase), hypokalemia, and hyponatremia. One subject experienced an SAE of Grade 4 hypokalemia. One death was reported in this study due to progressive disease. Serious adverse events were reported in 4 subjects (14%) including influenza, viral infection, hypokalemia and hyponatremia/atrial fibrillation. No AEs leading to discontinuation of treatment were reported during the study. There were approximately 34%, 25%, and 11% decreases in the geometric mean abiraterone C_{max}, $AUC_{0\text{-}24h}$, and C_{min}, respectively when AAP was co-administered with apalutamide. These decreases were not considered to be clinically relevant. Refer to Investigator's Brochure (Section 4.3.3.3) for further details.[18]

Study ARN-509-003 is a Phase 3 study of apalutamide compared with placebo in patients with high-risk (defined as a PSA doubling time ≤10 months) NM-CRPC, which is also ongoing. Study 56021927PCR3002 is an ongoing Phase 3 study of apalutamide compared with placebo in patients with hormone-sensitive mCRPC, and Study 56021927PCR3003 is an ongoing study of apalutamide compared with placebo in subjects with high-risk, localized or locally advanced prostate cancer receiving treatment with primary radiation therapy.

1.2. Control

ZYTIGA® (abiraterone acetate; JNJ-212082)

Abiraterone acetate in combination with prednisone or prednisolone is the currently accepted standard regimen for front-line treatment of patients with mCRPC, will be used as the active control.

In clinical studies in subjects with mCRPC, the most common AEs related to AA have included fatigue most likely attributable to the underlying disease, and hypertension, hypokalemia, fluid retention/edema, due to mineralocorticoid excess caused by compensatory adrenocorticotropic hormone (ACTH) drive. In this study, low-dose prednisone is expected to mitigate these effects through abrogation of the ACTH drive.

Abiraterone acetate should be used with caution in subjects with a history of cardiovascular disease. Caution should be exercised when treating subjects whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention. For further information regarding AA, prednisone or prednisolone refer to the local prescribing information.

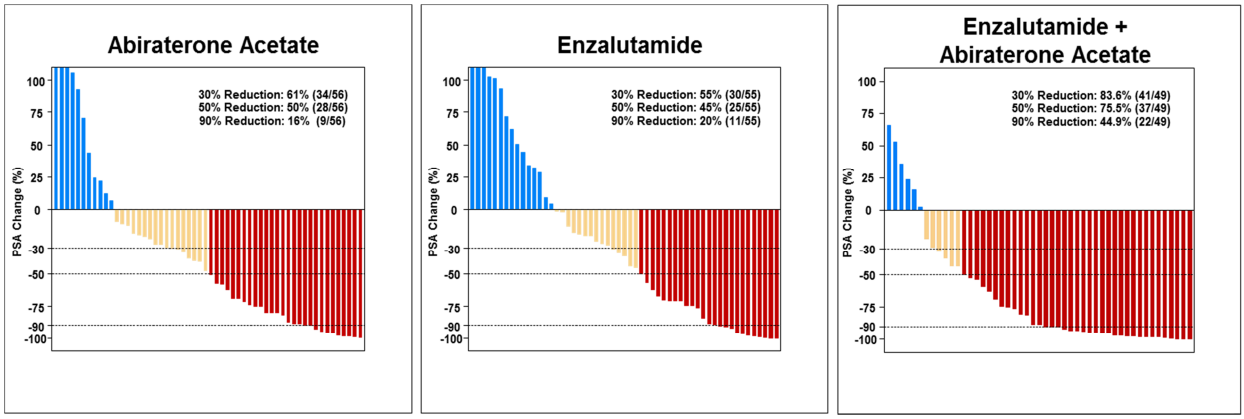
1.3. Overall Rationale for the Study

Abiraterone acetate and apalutamide are both directed at the androgen axis with very distinct mechanisms to inhibit AR activation. AA exerts its effect through inhibition of androgen biosynthesis while apalutamide targets the AR. Moreover, they do not appear to have overlapping clinical toxicity in patients.

There is also early evidence that the combination of both drugs could theoretically delay the emergence of clinical resistance to either drug. Despite the survival benefit associated with AA treatment of mCRPC, both primary and secondary resistance to AA has been observed. In xenograft models of CRPC, treatment with AA inhibits tumor growth, production of serum PSA, and intratumoral androgens, thereby indicating that the anti-tumor activity of AA is primarily through effects on tissue androgens. Accompanying the marked suppression of tumor androgen levels are increased expression of the AR, ligand-independent AR splice variants, and induction of steroidogenic genes including CYP17A1.[14] The increased expression of several of these genes showed strong correlation with dihydrotestosterone (DHT) levels in recurrent tumors. These data suggest that resistance can potentially be targeted by using combinations with potent AR antagonists such as apalutamide.

The availability of 2 highly active agents from different classes with complementary mechanisms raises the important scientific and clinical question of whether the benefit of the combination is superior to that of individual agents and can overcome mechanisms of resistance developed to either drug alone. Three separate studies conducted at a single institution with AAP, enzalutamide, and the combination of AAP and enzalutamide showed improved PSA response with AR combination therapy compared with either agent alone (Figure 1).[11,12,13,14] In the waterfall plot below (far right), the single arm study with the combination of AAP and enzalutamide in patients with mCRPC (data from 41 patients) showed a PSA response rate (12-weeks, ≥ 50% reduction) of 76% (higher than either single agent) and a favorable safety profile.[12]

Figure 1: PSA Response With AR Combination Therapy in mCRPC



Source: Efstathiou et al ESMO Oral presentation Sept 2013.[12]

Taken together, these data suggest that the combination of apalutamide and AAP may have activity superior than either drug alone or may help avoid the adaptive responses resulting in resistance.[11,12,13,14]

A randomized, double-blind, placebo-controlled study is needed to obtain definitive data on the clinical benefit and safety of combining a potent anti-androgen (apalutamide) and AAP. Study 56021927PCR3001 is designed to assess the efficacy and safety of apalutamide in combination with AAP compared with AAP in subjects with chemotherapy-naïve mCRPC and will explore mechanisms of resistance that may develop with treatment.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to compare the radiographic progression-free survival (rPFS) of apalutamide in combination with AA plus prednisone or prednisolone (AAP) and AAP in subjects with chemotherapy-naïve mCRPC.

Major Secondary Objectives

The major secondary objectives are:

- To characterize the safety profile of apalutamide in combination with AAP
- To characterize the pharmacokinetics (PK) of apalutamide and abiraterone

Other Objectives

The other objectives are:

- To explore the relationship between PK and pharmacodynamics (PD) of apalutamide and abiraterone

- To evaluate exploratory biomarkers predictive of response and resistance in subjects when treated with apalutamide in combination with AAP compared with AAP
- To assess the effect on patient-reported outcomes (PROs) in this study population when treated with apalutamide in combination with AAP compared with AAP
- To evaluate other endpoints of clinical relevance including additional assessments of pain, objective response, time to symptomatic skeletal-related event (SSRE), and PSA response
- To evaluate medical resource utilization (MRU) information

2.2. Hypothesis

The primary hypothesis of the study is that apalutamide in combination with AAP compared with AAP will demonstrate improved rPFS and an acceptable safety profile in subjects with chemotherapy-naïve mCRPC.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind placebo-controlled, multinational, multicenter Phase 3 study to determine if subjects with chemotherapy-naïve mCRPC will benefit from the addition of apalutamide to AAP compared with AAP. Subjects will continue ADT (in this study, GnRHa or surgical castration). Approximately 960 subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to receive apalutamide and AAP or matching placebo and AAP. Subjects will be stratified by the presence or absence of visceral metastases, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) grade of 0 or 1, and region (European Union [EU], North America [United States/Canada], and Rest of World [ROW]). The study will consist of a Screening Phase; a Treatment Phase, and a Follow-up Phase. The study is anticipated to end approximately 84 months after the first subject is randomized. A study design scheme is provided in Figure 2.

A treatment cycle is defined as 28 days. Treatment will continue until disease progression, unacceptable toxicity, death or the sponsor terminates the study. Subjects must discontinue study drugs with documented unequivocal clinical progression (see Section 10.2). If the subject has radiographic progression, but not unequivocal clinical progression, and alternate treatment is not initiated, the subject may continue on study treatment at the investigator's discretion.

After discontinuing study drug, subjects will be contacted every 3 months (see Section 9.1.5) until death or termination of the study. In addition to survival follow up, analgesic use, SSREs, ECOG PS, and subsequent therapy for prostate cancer up to and including chemotherapy will be collected. Patient-reported outcomes (PROs) questionnaires will also be administered every 3 months for up to 12 months after treatment discontinuation.

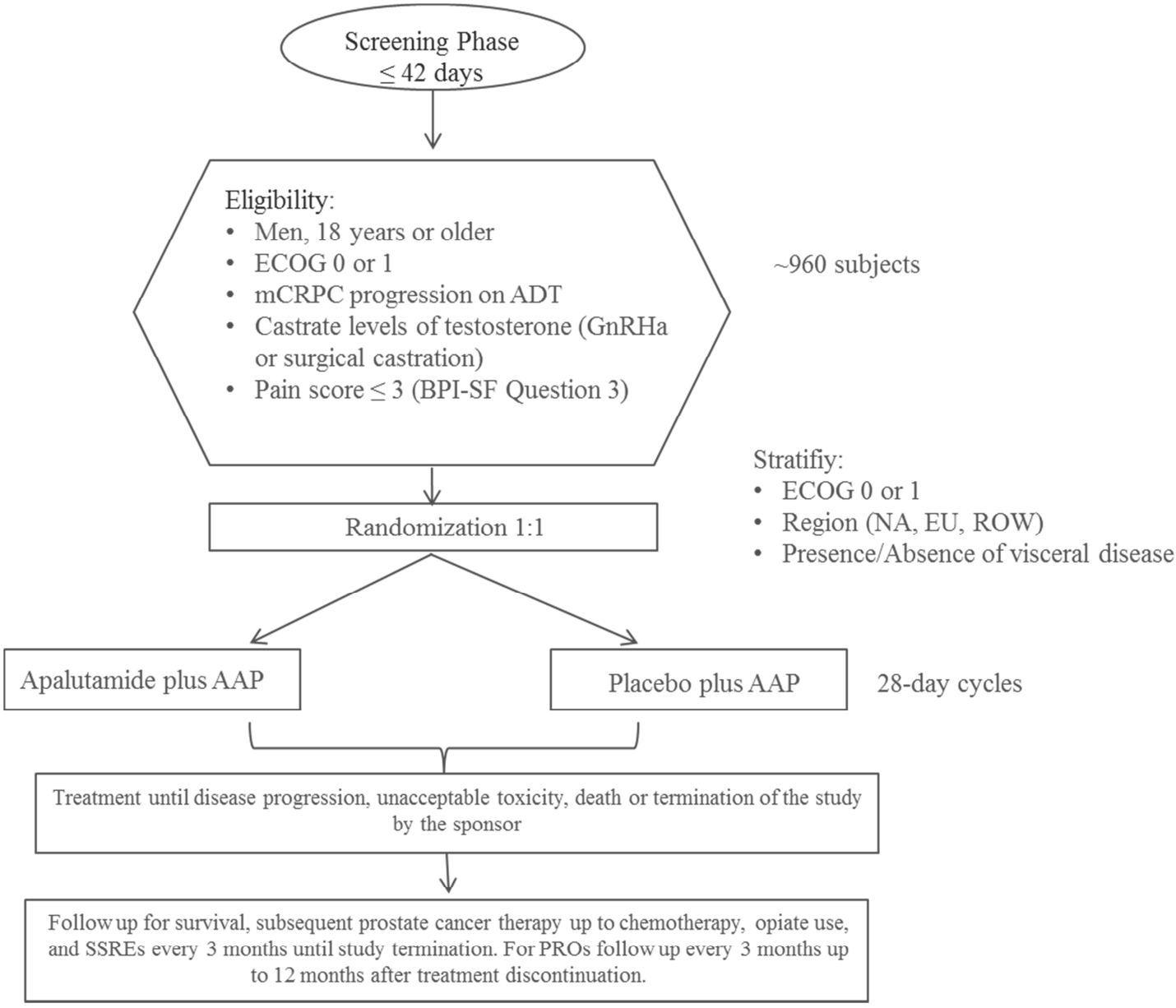
Subjects will be monitored for safety during the Screening and Treatment Phases and up to 30 days after the last dose of study drug. Adverse events, including clinically significant laboratory abnormalities reported as AEs, will be graded and summarized using National Cancer

Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Dose modification guidelines will be provided.

An Independent Data Monitoring Committee (IDMC) will be commissioned for the study to perform regular safety review and the planned interim analyses. Refer to Section 11.11, Independent Data Monitoring Committee, for details.

A diagram of the study design is provided below in Figure 2.

Figure 2: Schematic Overview of the Study Until the Start of the Extension Phase (Open-Label Extension or Long-Term Extension)



AAP=abiraterone acetate plus prednisone/prednisolone; ADT=androgen deprivation therapy, BPI-SF=Brief Pain Inventory-Short Form; ECOG=Eastern Cooperative Oncology Group; GnRHa=gonadotropin releasing hormone analog; mCRPC=metastatic castration-resistant prostate cancer; NA=North America (United States, Canada) PRO=patient-reported outcomes; SSRE=symptomatic skeletal-related event; ROW=Rest of World.

Following the decision to unblind the study, the Extension Phase will begin when both the Amendment 4 is approved at the site and the sponsor has notified the site of the start of the Open-Label Extension Phase or Long-Term Extension Phase. Details are provided in Attachment 9 (Open-Label Extension: to be followed in case of subjects being offered cross-over to open-label apalutamide in combination with AAP) and Attachment 10 (Long-Term Extension: to be followed in case of limited data collection after unblinding when cross-over is not recommended).

3.2. Study Design Rationale

Abiraterone acetate in combination with prednisone has been approved for the treatment of men with mCRPC before and after chemotherapy. The efficacy and safety of AAP therapy in patients with mCRPC are established by the results of the Phase 3 multinational, randomized, double-blind, placebo-controlled studies Study COU-AA-301 (post-chemotherapy) and Study COU-AA-302 (chemotherapy-naïve).[10,27,29]

The dose of 1,000 mg AA daily and 5 mg twice daily prednisone is the prescribed dose for patients with mCRPC. The rationale for the combination and choice of active comparator is discussed in Section 1.3. The dose of 240 mg daily of apalutamide is the dose determined from the Study ARN-509-001 PK/pharmacodynamic study and is the therapeutic dose (see Section 1.1.2).

Blinding, Control, Study Phase/Periods, Treatment Groups

This is a randomized, double-blind, placebo-controlled study. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinding will also enhance the validity of PRO data.

Population Pharmacokinetics

The assessment of PK is important in understanding the exposure levels of apalutamide and abiraterone in this patient population when apalutamide and AA are administered concurrently. The study includes a sparse pharmacokinetic sampling strategy for population PK purposes, which can serve as a means to derive the individual subject's exposure to apalutamide and abiraterone. In addition to determination of covariates that influence the PK of the drug, the data may provide supportive evidence for the efficacy and safety analyses and identify at-risk subjects who require a dose-adaptation.

Biomarker Collection

The goal of the biomarker study is to obtain additional information on resistance mechanisms. Archived tumor samples (formalin-fixed paraffin-embedded [FFPE] blocks or slides) and serum samples will be collected, where country regulations permit, for biomarker evaluations. Results from Study ARN-509-001 in patients with CRPC provide evidence that an acquired mutation in AR (AR^{F876L}) may be associated with resistance to apalutamide.[20] Multiple other biomarkers have been shown to be associated with resistance to abiraterone, enzalutamide or apalutamide.

These include AR gene anomalies (eg,: AR amplification, ARv3/7, and ARv567), and expression of AR axis genes such as TMPRSS-ERG, AGR2, HSD3B1, HSD3B2, HSD17B, PGR, AKR1C3, SRD5A1, CYB5A, CYP17A1, DUSP5, HNF1A, NR0B1, POR, ANLN, NUSAP, etc.[2,3,23,33] Circulating tumor DNA and RNA can be detected in blood samples but in limited quantities, therefore, corresponding candidate biomarkers representing resistance classes will be analyzed in plasma (DNA) or whole blood (PAXgene RNA).[26,28] Plasma-based circulating DNA will be used to assess the presence of the AR^{F876L} mutation and copy number variations, while ribonucleic acid (RNA) extracted from whole blood will be used to assess other markers that may be associated with resistance to abiraterone acetate alone and in combination with apalutamide. Understanding the frequency of patients developing the AR^{F876L} mutation and the timing for development of the AR^{F876L} mutation may inform both how many and when patients may need alternative treatments. Understanding the frequency of patients developing other resistance mechanisms will inform future combination treatments with apalutamide. Previous data show that treatment with AAP decreases testosterone while treatment with enzalutamide can increase serum testosterone concentration.[11] Serum samples will be collected to test the effect of AAP alone and in combination with apalutamide, on testosterone and steroid metabolites.

Plasma samples will be collected from approximately 220 subjects during treatment and approximately 500 subjects at EOT and whole blood will be collected from approximately 220 subjects at the time points indicated in the Time & Events Schedule. Samples are being collected at baseline, Cycle 12, and at time of progression. The samples collected at Cycle 12 are intended to evaluate emergence of acquired resistance such as AR mutation.[20] Serum samples will be collected from approximately 220 subjects at time points indicated in the Time and Events Schedule. Intermediate time points were selected to capture changes in hormone levels.[11]

Recently, studies have identified molecular classifiers that are superior to existing measures of stratifying high-risk disease.[17,22] Archival FFPE tumor samples are also being collected to determine if genomic classifiers can be used to identify a more homogeneous population of high-risk patients. This will potentially allow selection of the appropriate high-risk patient population for future studies of apalutamide and AA in early disease settings.

Patient-reported Outcomes

The goal of collecting PRO data is to explore patient benefits in pain, fatigue, and functional status. In both Studies COU-AA-301 and COU-AA-302, significant delay in pain progression and improvements in functional status were found for AAP compared with prednisone plus placebo. Patient-reported outcomes will be measured utilizing the EQ-5D-5L, BPI-SF, and FACT-P questionnaires. The FACT-P questionnaire will provide an assessment of the subject's self-reported functional status, well-being, and prostate cancer symptoms over time. It is important to establish that addition of apalutamide to AAP does not result in a deterioration of functional status compared with AAP. The EQ-5D-5L assessment will provide estimates of utility to include in future cost-effectiveness models. Data will be collected throughout the study as well as during the Follow-up Period (up to 12 months after study treatment discontinuation) as specified in the Time and Events Schedule.

Medical Resource Utilization Data Collection

Medical resource utilization data, associated with medical encounters, will be collected in the electronic case report form (eCRF) by the investigator and staff for all subjects throughout the study. For each AE that occurs, MRU information associated with that AE should be recorded when possible. Protocol-mandated procedures, tests, and encounters are excluded. Data may be used to conduct exploratory economic analyses.

4. SUBJECT POPULATION

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

4.1. Inclusion Criteria

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

1. Subject must be a man age ≥18 years of age inclusive
2. Adenocarcinoma of the prostate
3. Metastatic disease as documented by technetium-99m (^{99m}Tc) bone scan or metastatic lesions by computed tomography (CT) or magnetic resonance imaging (MRI) scans (visceral or lymph node disease). If lymph node metastasis is the only evidence of metastasis, it must be ≥2 cm in the longest diameter.
4. Castration-resistant prostate cancer demonstrated during continuous ADT, defined as 3 rises of PSA, at least 1 week apart with the last PSA ≥2 ng/mL
5. Criterion modified per Amendment 1

5.1. Patients who received a first generation anti-androgen (eg, bicalutamide, flutamide, nilutamide) must have at least a 6-week washout prior to randomization AND must show continuing disease (PSA) progression (an increase in PSA) after the washout period.

6. Criterion modified per Amendment 1

6.1. Prostate cancer progression documented by PSA according to the Prostate Cancer Clinical Trials Working Group (PCWG2); radiographic progression of soft tissues according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST) (Attachment 1) modified based on PCWG2, or radiographic progression of bone according to PCWG2.

7. Criterion modified per Amendment 1

7.1. Surgically or medically castrated, with testosterone levels of <50 ng/dL. If the subject is being treated with GnRH analogs (subject who has not undergone bilateral orchiectomy), this therapy must have been initiated at least 4 weeks prior to randomization and must be continued throughout the study

8. ECOG PS grade of 0 or 1 (Attachment 2)

9. A score of ≤3 on the Brief Pain Inventory-Short Form (BPI-SF) Question #3 (worst pain in last 24 hours)

10. Bisphosphonates or denosumab usage is allowed only if subjects are on a stable dose for at least 4 weeks prior to randomization

11. Clinical laboratory values at Screening:

- Hemoglobin ≥9.0 g/dL, independent of transfusion and/or growth factors within 3 months prior to randomization
- Platelet count ≥100,000 x 10^9/μL independent of transfusion and/or growth factors within 3 months prior to randomization
- Serum albumin ≥3.0 g/dL
- Serum creatinine <2.0 × upper limit of normal (ULN)
- Serum potassium ≥3.5 mmol/L
- Serum total bilirubin ≤1.5 × ULN (Note: In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, subject may be eligible)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2.5 × ULN

12. Able to swallow the study drug tablets whole

13. Criterion modified per Amendment 1

13.1. Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.

14. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol (refer to Section 4.3)

15. Each subject must sign an informed consent form (ICF) indicating that he understands the purpose of and procedures required for the study and are willing to participate in the study

4.2. Exclusion Criteria

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

1. Small cell or neuroendocrine carcinoma of the prostate
2. Known brain metastases
3. Prior chemotherapy for prostate cancer, except if administered in the adjuvant/neoadjuvant setting
4. Previously treated with ketoconazole for prostate cancer for greater than 7 days
5. Therapies that must be discontinued or substituted at least 4 weeks prior to randomization include the following:
   - Medications known to lower the seizure threshold (see Attachment 3)
   - Herbal and non-herbal products that may decrease PSA levels (eg, saw palmetto, pomegranate)
   - Any investigational agent
6. Criterion modified per Amendment 1

6.1. At screening, need for parenteral or oral opioid analgesics (eg, codeine, dextropropoxyphene)

7. Subjects currently treated with spironolactone
8. Previously treated with abiraterone acetate or other CYP17 inhibitor
9. Previously treated with enzalutamide or other androgen signaling inhibitors
10. Criterion modified per Amendment 1

10.1. History of any of the following:
   - Seizure or known condition that may pre-dispose to seizure (including but not limited to prior stroke, transient ischemic attack, loss of consciousness within 1 year prior to randomization, brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect)
   - Any prior malignancy (other than adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) within 5 years prior to randomization
   - Severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias within 6 months prior to randomization or New York Heart Association (NYHA) Class II to IV heart disease
   - Any condition that in the opinion of the investigator, would preclude participation in this study

11. Current evidence of any of the following:
    - Uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥90 mmHg)
    - Gastrointestinal disorder affecting absorption
    - Active infection (eg, human immunodeficiency virus [HIV] or viral hepatitis) or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated
    - Any chronic medical condition requiring a higher dose of corticosteroid than 10 mg prednisone/prednisolone once daily
    - Any condition that in the opinion of the investigator, would preclude participation in this study
12. Subject has known allergies, hypersensitivity, or intolerance to abiraterone acetate or apalutamide or its excipients (refer to Investigator's Brochure)[18]
13. Subject plans to father a child while enrolled in this study or within 3 months after the last dose of study drug
14. Treatment with 5-α reductase inhibitors (finasteride, dutasteride), estrogens, cyproterone within 4 weeks of enrollment

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 participation:

1. Refer to Sections 8.2 and 8.3 for details regarding prohibited and restricted therapy during the study
2. If the subject is engaged in sexual activity with a woman of childbearing potential, a condom is required along with another effective contraceptive method consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies and their partners. Highly effective forms of contraception include:
    - established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS);
    - barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
    - vasectomy
3. Two highly effective forms of contraception are required during the study and for 3 months after the last dose of study drug.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Subjects will be randomly assigned to the AAP plus apalutamide group or AAP alone group in a 1:1 ratio. Randomization will take place across all study-sites using a centralized Interactive Web Response System (IWRS). A randomization scheme will be performed using permuted block randomization. Subjects will be stratified by presence or absence of visceral metastasis, ECOG PS grade (0 or 1), and region (NA, EU, ROW).

At randomization, the IWRS will assign a unique subject identification number to each subject. The subject's identification number will be used on all study-related documents including eCRFs. A treatment number will also be assigned to each subject. This treatment number is the link between a subject's eCRF and blinded treatment group assignment. Subject identification numbers will not be reused. Subjects withdrawn from the study will not be replaced. All subjects must commence treatment within 72 hours or 3 calendar days of randomization.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject in the case of an emergency.

Data that may potentially unblind the treatment assignment (ie, study drug serum concentrations, study drug preparation/accountability data, treatment allocation, biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until completion of the study or the IDMC recommendation for unblinding is accepted by the sponsor and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the IWRS, in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should be discontinued from the Treatment Phase and entered in the Follow-up Phase.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.

6. DOSAGE AND ADMINISTRATION

All subjects will receive AAP as standard of care (SOC) therapy. Investigators should refer to the Investigator's Brochure and package inserts for the storage and handling, and detailed instructions on the administration of AA and prednisone/prednisolone. Where prednisone is not commercially available, prednisolone will be substituted.

Subjects will be randomized on 1:1 ratio to receive either JNJ-56201927 (apalutamide) or matching placebo.

6.1. ADT Administration

Continuous treatment with a GnRHa or surgical castration is mandatory for all subjects in order to maintain castrate concentrations of testosterone (<50 ng/dL). The choice of GnRHa is at the discretion of the investigator. Dose and dose schedule (without interruption) will be consistent with the prescribing information and should only be adjusted if clinically indicated to maintain castrate concentrations of testosterone. For subjects who did not undergo surgical castration, concurrent treatment with a GnRHa must be documented in the eCRF.

6.2. Study Treatment Administration

Study treatment is administered orally on an outpatient basis and a treatment cycle is defined as 28 days (Table 1). Sufficient study drug for each treatment cycle will be distributed on the first day of each cycle up to Cycle 24, then every 3 cycles (see Time and Events Schedule). Subjects will begin taking study drug on Day 1 of Cycle 1. Dose modifications for toxicity are provided in Section 6.3.

Table 1: Study Treatment Administration

Study Treatments	Daily Dose	Schedule
apalutamide/placebo	240 mg (4 x 60 mg tablets)	qd with or without food (except during PK sampling, see Section 6.2.1)
AA	1,000 (4 x 250 mg tablets)	qd on empty stomach. No food should be consumed for at least 2 hours before the dose of AA is taken and at least 1 hour after the dose of AA is taken. Swallow tablets whole with water.
Prednisone	10 mg (2 x 5 mg tablets)	5 mg twice daily (recommended to be taken with food)

AA=abiraterone acetate; qd=once daily

If a dose of apalutamide (or placebo) alone, AAP alone or both is missed, it should be omitted and will not be made up or taken with the next dose the following day. If a subject forgets to take a dose of either apalutamide (or placebo) or AAP, the dose should only be replaced if the subject remembers and takes the dose within a 12-hour window.

6.2.1. Special Dosing and Meal Instructions for PK Visits

Table 2 provides a summary of the schedule and dosing instructions for PK sample collection (see also Section 9.3.1). A modified dosing schedule will be required on PK sampling days. On the days when PK samples are collected (Day 1 of Cycles 1, 2, 3, 4, 5, and 6), apalutamide and AA must be administered in the clinic after initial PK samples are collected.

Table 2: Schedule and Dosing Instructions for PK Sample Collection

C1D1	C2D1	C3D1	C4D1, C5D1, C6D1
No food for at least 2 hrs before dosing and at least 1 hr after dosing No predose PK sample apalutamide and AA administered **at same time in the clinic** PK samples collected at 2 hrs and 4 hrs postdose	No food for at least 2 hrs before dosing and at least 1 hr after dosing Predose PK sample taken up to 1 hr prior to study drug administration apalutamide and AA administered **at same time in the clinic**	No food for at least 2 hrs before dosing and at least 1 hr after dosing Predose PK sample taken up to 1 hr prior to study drug administration apalutamide and AA administered **at same time in the clinic** PK samples collected between 0.5 hr and 4 hrs postdose	Same as C2D1

AA=abiraterone acetate; PK=pharmacokinetics; C=cycle; D=day

In addition, the following information should be recorded in the eCRF:

1. Actual times of AA and apalutamide/placebo dosing one day before and during the day of all PK visits
2. Actual time of last meal time prior to dosing on Day 1 of Cycle 1 and Cycle 3
3. Actual time of first meal time after dosing on Day 1 of Cycle 1 and Cycle 3

6.3. Dose Modification and Management of Toxicity

General principles on dose modifications:

- Grade 1 or Grade 2 toxicities should be managed symptomatically without dose adjustments. Appropriate medical treatment should be used.

- In the event of a Grade 3 or higher toxicity, which cannot definitively be attributed to AA or apalutamide/placebo, both AA and apalutamide/placebo should be held until toxicity has resolved to Grade 1 or baseline.
- If Grade 3 or higher toxicity does not resolve to Grade 1 or baseline within 2 cycles, the subject should be discontinued from treatment or the investigator's rationale to continue treatment must be discussed with the sponsor.
- Dose reduction guidelines and management of toxicities provided in Sections 6.3.1, 6.3.2, and 6.3.3. A subject may have up to 2 dose adjustments for the same toxicity and if the same toxicity recurs at Grade 3 or higher after 2 dose adjustments, the subject should discontinue study treatment(s); any exceptions are noted in the individual sections.
- Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.
- The dose of prednisone can remain unchanged with dose modifications of AA or apalutamide/placebo.
- The investigator's rationale to re-escalate treatment must be discussed with the sponsor's medical monitor on an individual basis prior to implementation.

6.3.1. Toxicity Attributed to Prednisone

Prednisone may be associated with fatigue, increased appetite, insomnia, weakness, hyperglycemia, ecchymosis, and symptoms related to gastroesophageal reflux. With long-term glucocorticoid therapy, subjects may develop Cushing's syndrome, characterized by central obesity, thin skin, easy bruising, bone loss, avascular necrosis of the hip, cataract and proximal myopathy. Withdrawal of the corticosteroid may result in symptoms that include fever, myalgia, fatigue, arthralgia, and malaise. This may occur even without evidence of adrenal insufficiency. The dose of prednisone may be gradually reduced (to 5 mg) if clinically indicated and must not be discontinued while the subject receives AA.

6.3.2. Toxicity Attributed to Abiraterone Acetate

6.3.2.1. Abnormal Liver Function Test(s)

Table 3 provides dose modification recommendations for subjects who develop liver function test (LFT) abnormalities during treatment. For subjects being re-treated, serum transaminases should be monitored at a minimum of every 2 weeks for 3 months and monthly thereafter.

Table 3: Dose Modifications for LFT Abnormalities Attributed to Abiraterone Acetate			
Toxicity	**Dose of AA[b]**	**Dose of apalutamide/placebo**	**Dose of prednisone**
Grade 1 or 2[a]	No change	No change	No change
Grade 3[a]	Hold until return to baseline or to AST or ALT ≤2.5 x ULN and total bilirubin ≤1.5 x ULN, resume at 750 mg (3 tablets) only after discussion and agreement with medical monitor	Hold until return to baseline	No change
Recurrence Grade 3	Hold until return to baseline or to AST or ALT ≤2.5 x ULN and total bilirubin ≤1.5 x ULN, resume at 500 mg (2 tablets) only after discussion and agreement with medical monitor	Hold until return to baseline	No change
Grade 4[a]	Discontinue AA treatment	Hold until return to baseline	No change or consider tapering if AA discontinued

AA=abiraterone acetate; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LFT=liver function tests; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ULN=upper limit of normal

[a] NCI-CTCAE, Version 4.03: Grade 1=AST or ALT from ULN to 3 x ULN, increase in total bilirubin from ULN to 1.5 x ULN; Grade 2=AST or ALT from >3 x ULN to 5 x ULN, increase in total bilirubin from >1.5 x ULN to 3 x ULN; Grade 3=AST or ALT from >5 x ULN to 20 x ULN, increase in total bilirubin to >3 x ULN to 10 x ULN; Grade 4=AST or ALT>20 x ULN, increase in total bilirubin >10 x ULN.

[b] Abiraterone acetate dose modifications for LFT abnormalities are from the ZYTIGA label and do not follow Version 4 of CTCAE.

If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, in particular serum ALT, should be measured immediately. If subjects develop severe hepatotoxicity (ALT 20 x ULN) anytime while on abiraterone acetate, subjects should be discontinued and not be re-treated with abiraterone acetate.

Subjects who develop a concurrent elevation of ALT >3 X ULN and a total bilirubin >2 X ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation should be permanently discontinued from treatment with abiraterone acetate.

6.3.2.2. Hypertension, Hypokalemia, and Fluid Retention/Edema Due to Mineralocorticoid Excess

In subjects who develop hypokalemia on study treatment, consider maintaining the subject's potassium level at 4.0 mM or higher. If hypokalemia persists despite optimal potassium supplementation and adequate oral intake, discuss with the sponsor. Table 4 provides dose modification recommendations for drug-related hypokalemia.

Table 4: Dose Modifications for Hypokalemia Attributed to Abiraterone Acetate			
Toxicity	**Dose of AA**	**Dose of apalutamide/placebo**	**Dose of prednisone**
Grade 1 or 2	Initiate oral potassium supplementation, titrate to ≥3.5 to ≤5.0 mmol/L, maintenance at ≥4.0 mmol/L recommended	No change	No change
≥Grade 3	Hold and initiate IV potassium and cardiac monitoring, resume only after discussion and approval by the medical monitor	No change	No change or consider tapering if AA is discontinued
AA=abiraterone acetate			

For subjects who develop drug-related Grade 3 or higher hypertension, AA must be withheld and adjustment of anti-hypertensive medication should be considered (see also Table 5 below).

Table 5: Dose Modifications for Hypertension and Edema/Fluid Retention Attributed to Abiraterone Acetate			
Toxicity	**Dose of AA**	**Dose of apalutamide/placebo**	**Dose of prednisone**
Grade 1 or 2	No change	No change	No change
≥Grade 3	Hold until Grade 1 or baseline, resume at full dose	No change	No change
First Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 750 mg (3 tablets)	No change	No change
Second Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 500 mg (2 tablets)	No change	No change
Third Recurrence ≥Grade 3	Discontinue	No change	No change or consider tapering if AA is discontinued
AA=abiraterone acetate			

6.3.3. Toxicity Attributed to Apalutamide/Placebo

Table 6 provides dose modifications for apalutamide/placebo.

Table 6: Dose Modifications for Toxicity Attributed to Apalutamide/Placebo			
Toxicity	**Dose of AA**	**Dose of apalutamide/placebo**	**Dose of prednisone**
Grade 1 or 2	No change	No change	No change
≥Grade 3 or higher	No change	Hold until Grade 1 or baseline, resume at full dose	No change
First Recurrence ≥Grade 3	No change	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)	No change
Second Recurrence ≥Grade 3	No change	Hold until Grade 1 or baseline, resume at 120 mg (2 tablets)	No change
Third Recurrence ≥Grade 3	No change	Discontinue	No change
First occurrence of seizure of any grade or Grade 4 neurotoxicity	No change	Discontinue	No change
AA=abiraterone acetate			

7. TREATMENT COMPLIANCE

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

In the absence of toxicity, if the dosing compliance is not 100%, then investigators or designated study-site personnel should re-instruct subjects regarding proper dosing procedures and the subject may continue study treatment.

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

8. PRESTUDY AND CONCOMITANT THERAPY

Concomitant therapies must be recorded throughout the study beginning with signing of informed consent to 30 days after the last dose of study drug. Therapies (prescription or over the counter medications for systemic conditions and treatment of AEs) different from the study drug

must be recorded in the eCRF. Recorded information will include a description of the type of the drug, treatment period, dose and dosing regimen, route of administration, and indication. Concurrent enrollment in another investigational drug or device study is prohibited. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1. Permitted Supportive Care Medications

Supportive care medications are permitted with their use following institutional guidelines. The following supportive care medications are considered permissible during the study:

- Intermittent short course of opioid analgesics would be allowed for pain control (see also Section 10.2 regarding the use of chronic opioid analgesics for pain)
- Bone modifying agents, including bisphosphonates and denosumab, should be used in accordance with label indications to help preserve bone mineral density during cancer treatment (including ADT) and skeletal integrity in subjects with bone metastasis.
- Conventional multivitamins, selenium and soy supplements
- Eplerenone can be used to manage mineralocorticoid-related toxicities
- Additional systemic glucocorticoid administration such as “stress dose” glucocorticoid is permitted when clinically indicated for a life-threatening medical condition, and in such cases, the use of steroids will be documented as concomitant drug
- Transfusions and hematopoietic growth factors per institutional practice guidelines

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

8.2. Prohibited Concomitant Medications

As a class effect, AR antagonists (anti-androgens) have been associated with seizures due to an off-target mechanism of action (gamma aminobutyric acid chloride channel [$GABA_A$] inhibition). Therefore, drugs known to lower the seizure threshold or cause seizures are prohibited. A list of these prohibited therapies is provided in Attachment 3 of the protocol.

Other prohibited concomitant medications include:

- Investigational agents other than apalutamide
- Other anti-cancer therapy
- Other agents that target the androgen axis (eg, anti-androgens, CYP17 inhibitors)
- Radiotherapy
- 5-α-reductase inhibitors
- Chemotherapy
- Immunotherapy
- Systemic ketoconazole (or other azole drugs such as fluconazole or itraconazole)
- Diethylstilbestrol (DES) or similar

- Other preparations such as pomegranates or pomegranate juice or saw palmetto thought to have endocrine effects on prostate cancer
- Spironolactone
- Radiopharmaceuticals such as strontium (^{89}Sr) or samarium (^{153}Sm) or similar analogs such as radium-223 (^{223}Ra)

The concurrent administration of hormonal therapy (except GnRHa as described above), other anti-cancer therapy, including cytotoxic, biological, and immunotherapy is prohibited while subjects are being treated with study drug.

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

8.3. Restricted Concomitant Medications

Highlights of drug interaction with apalutamide and abiraterone are summarized below. Refer to the Investigator's Brochure (Sections 4.3.4 and 5.10) and associated addenda for complete details on the drug interaction potential of apalutamide.[18]

- Strong inhibitors of CYP2C8 or CYP3A4: Caution should be used with co-administration of a strong CYP2C8 or CYP3A4 inhibitor with apalutamide as it may increase the exposures of apalutamide and its active metabolite. No initial dose adjustment is necessary; however, consider reducing the apalutamide dose based on individual tolerability (see Section 6.3).
- Apalutamide is a moderate to strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Caution should be used with co-administration of medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 as apalutamide can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of efficacy if medication is continued. Concomitant administration of apalutamide with medications that are substrates of uridine diphosphate glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with apalutamide and evaluate for loss of efficacy.
- Effect of apalutamide on drug transporters: Apalutamide was clinically shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporter 1B1 (OATP1B1). Concomitant use of apalutamide with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with apalutamide and evaluate for loss of efficacy if medication is continued.
- Abiraterone is a strong inhibitor of CYP2D6 in humans. Caution is advised when AA is administered with medicinal products activated by or metabolized by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolized by CYP2D6 should be considered. Examples of medicinal products metabolized by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter 3 products requiring CYP2D6 to form their active analgesic metabolites).
- Abiraterone is a weak inhibitor of CYP2C8 in humans. When AA is combined with drugs that are predominantly eliminated by CYP2C8, subjects should be monitored for signs of

toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with AA.

For more information see Attachment 3.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, PK, pharmacodynamic, biomarker, PROs, MRU, and safety measurements applicable to this study. For the Open-Label Extension Phase and the Long-Term Extension Phase, this information is included in Attachment 9 and Attachment 10, respectively.

All visit-specific PRO assessments should be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. The PRO assessments will be captured electronically and preprogrammed in the appropriate sequence.

Medical resource utilization data will be collected. Refer to Section 9.6 for details.

Adverse event information will be collected using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

For subjects not participating in the biomarker study, blood volumes drawn during treatment and EOT may range from 2.5 mL to 7 mL per visit. Subjects participating in the biomarker study will have additional blood volumes drawn that range from 8.5 mL (Cycle 3 Day 1) to 21 mL per visit (Day 1 of Cycles 1 and 12 and at EOT). For subjects participating in the PK sampling and biomarker study, the total blood volume (including laboratory evaluations) on Cycle 1 Day 1 and Cycle 3 Day 1 will be 36 mL and 21 mL, respectively. See Table 7 below and the Time and Events Schedule for details.

Table 7: Summary of Blood Volumes (mL) Per Visit												
	SCR	**C1D1[a]**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C3D15**	**C4D1**	**C5D1**	**C6D1**	**CnD1**	**EOT**
Serum chemistry (including LFTs, fasting lipids and glucose)/PSA[a]	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Hematology[a]	2	2	--	2	--	2	--	2	2	2	2	2
-TSH Testosterone[a,b]	3.5	2.5	--	~~2.5~~	--	~~2.5~~	--	2.5	~~2.5~~	2.5	2.5	2.5
Total laboratory per visit	**8**	**7**	**2.5**	**4.5**	**2.5**	**4.5**	**2.5**	**7**	**4.5**	**7**	**7**	**7**
PK samples (AA)[c]	--	4	--	2	--	4	--	2	2	2	--	--
PK samples (apalutamide)[c]	--	4	--	2	--	4	--	2	2	2	--	--
Total PK per visit	--	**8**	--	**4**	--	**8**	--	**4**	**4**	**4**	--	--
Total laboratory + PK per visit	--	**15**	--	**8.5**	--	**12.5**	--	**11**	**8.5**	**11**	--	--
BM (plasma)[d]	--	10	--	--	--	--	--	--	--	--	10 (C12)	10
BM (whole blood)[d]	--	2.5	--	--	--	--	--	--	--	--	2.5 (C12)	2.5
BM (serum)[e]	--	8.5	--	--	--	8.5	--	--	--	--	8.5 (C12)	8.5
Total BM per visit	--	**21**	--	--	--	**8.5**	--	--	--	--	**21 (C12)**	**21**
Total laboratory + BM per visit	--	**28**	**–**	**–**	**–**	**13**	**–**	**–**	**–**	**–**	**28 (C12)**	**28**
Total laboratory + PK + BM per visit	--	**36**	**–**	**–**	**–**	**21**	**–**	**–**	**–**	**–**	**–**	**–**

AA=abiraterone acetate, BM=biomarker; C1D1=Cycle 1 Day 1, C1D15=Cycle 1 Day 15, etc. EOT=End-of-Treatment Visit; PK=pharmacokinetics; PSA=prostate-specific antigen; SCR=screening; TSH=thyroid stimulating hormone

Note: unit for blood volume is mL

[a] Screening laboratory evaluations can be used for C1D1 assessments if performed within 14 days of C1D1, otherwise the laboratory assessments must be repeated on C1D1. During the Treatment Phase serum chemistry and hematology samples are collected on D1 of C1 to C6 then on Day 1 of every 2 cycles from C8 to C24, then on D1 of every 3 cycles; fasting lipids and glucose samples are collected on C1D1 then every 12 cycles starting on C12D1. PSA is collected on D1 of every cycle up to C12 then on D1 of every 2 cycles up to C24, then on D1 of every 3 cycles and at the EOT Visit.

[b] Testosterone is only collected at screening. Screening laboratory evaluations for TSH and PSA can be used for C1D1 assessments if performed within 14 days of C1D1, otherwise the laboratory assessments must be repeated on C1D1. During the Treatment Phase, TSH is collected on C1D1, C4D1 then Day 1 of every 2 cycles up to C24, then D1 of every 3 cycles and at the EOT Visit.

[c] PK samples collected on D1 of C1 to C6.

[d] BM plasma and whole blood samples collected during the Treatment Phase on D1 of C1, and C12

[e] BM serum samples collected during the Treatment Phase on D1 of C1, C3, and C12

9.1.2. Screening Phase

All subjects must sign an ICF prior to the conduct of any study-related procedures. During this phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Event Schedule. Screening procedures will be performed up to 42 days before randomization unless otherwise specified. Laboratory tests noted in the inclusion criteria must be within the limits specified prior to randomization. Testing may be repeated for this purpose. The last result obtained prior to start of study treatment will be used to determine eligibility. Assessments performed as part of the subject's routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to randomization.

Subjects who do not meet all inclusion criteria or who meet an exclusion criterion may be rescreened once. Rescreening is at the discretion of the investigator and requires sponsor approval and agreement. The original reason for non-eligibility may be related to duration of an event that led to ineligibility or those events that can be managed by appropriate clinical measures leading to study eligibility (eg, resolution of a medical condition that required treatment with a contraindicated medication, treatment of cause of abnormal laboratory values, vital signs).

Subjects who are to be rescreened must sign a new informed consent before rescreening. Subjects rescreened within 42 days of planned randomization may use the initial screening laboratory results, CT/MRI and bone scans to determine eligibility. Rescreening and subsequent randomization activities (with the exception of use of original screening labs and CT/MRI and bone scans) must be conducted in accordance with all protocol defined windows and timelines.

9.1.3. Treatment Phase

The Treatment Phase will begin at Cycle 1 Day 1 of treatment and will continue until study drugs are discontinued. Subjects must start study drugs within 72 hours or 3 calendar days after randomization. Visits for each cycle will have a ±2 day window. Study visits will be calculated from the Cycle 1 Day 1 date. Subjects may have imaging visits up to 8 days before cycles requiring images. Please refer to the Time and Events Schedule for treatment visits and assessments during the Treatment Phase. The last measurements taken on Day 1 of Cycle 1 before administration of study drugs or at screening (whichever value was last) will be defined as the baseline values.

Investigators will review all clinical, laboratory and imaging data, and will use this information to make decisions about the necessity of dose modification or discontinuation during the Treatment Phase (see Section 6.3 and Section 10.2).

For subjects participating in the PK sampling, the subject must not take study drugs at home on the morning of study visits designated for PK sampling. Study drugs will be taken at the site after initial PK sampling.

Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. A subject should ordinarily be maintained on study treatment until confirmed radiographic progression is documented. If the subject has radiographic progression without clinical progression and alternate therapy is not initiated, treatment may continue at the discretion of the investigator. Subjects must discontinue treatment if unequivocal clinical progression is documented (see Section 10.2). Discontinuation of study drug (apalutamide) will not result in automatic withdrawal from the study. Once the subject discontinues study drug, the subject must complete the End-of-Treatment (EOT) Visit within 30 days after the last dose of study drug, and enter the Follow-up Phase.

9.1.4. EOT Visit

An EOT Visit must be scheduled within 30 days after the last dose of study drug for all subjects, except those lost to follow up, the subject died, or withdrawal of consent to study participation. Subjects who discontinued from treatment due to disease progression, AE or other reasons and enter the Follow-up Phase must have the EOT Visit completed before starting any subsequent anti-cancer treatment for prostate cancer. If a subject is unable to return to the site for the EOT Visit, the subject should be contacted to collect adverse events that occurred within 30 days after the last dose of study drug.

9.1.5. Follow-up Phase

Once a subject has completed the Treatment Phase, survival follow up will be performed every 3 months until death, withdrawal of consent, lost to follow up or the termination of the study. In addition to survival, analgesic use, ECOG PS, time to progression on first subsequent anti-cancer therapy, and subsequent anti-cancer therapy (up to and including chemotherapy) will also be collected. Visits to the clinic are not required; sites may collect the information by telephone interview, chart review, or other convenient methods. If the follow up information is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents.

The BPI-SF (7-day), FACT-P, and EQ-5D-5L instruments will be completed remotely every 3 months up to 12 months after treatment discontinuation. Refer to the Time and Events Schedule and Section 9.5, for specific details on PRO instruments and timing.

During the Follow-up Phase, deaths regardless of causality and serious adverse events (SAEs) thought to be related to study drugs will be collected and reported within 24 hours of discovery or notification of the event. Subjects who discontinue study drug before radiographic progression will continue with imaging assessments during the Follow-up Phase according to the local standard of care. If available, collect information on imaging assessments until documentation of radiographic progression.

9.1.6. After Study Unblinding

At the final analysis, the study will be unblinded. After the IDMC's review and the sponsor's subsequent decision and notification to the sites, either the Open-Label Extension Phase or the Long-Term Extension Phase will be initiated.

9.1.6.1. Open-Label Extension Phase

After unblinding at the final analysis, the IDMC's review, and the sponsor's subsequent decision and notification to offer cross-over, all subjects still in the double-blind phase of the study will be offered the option to enter the Open-Label Extension Phase of the study. All subjects must sign the ICF for the Open-Label Extension Phase before entering it. Details for the Open-Label Extension Phase are provided in Attachment 9.

If a dedicated Extension study becomes available, then all subjects who comply with the entry criteria for that study and consent to that study should be transferred to that study.

9.1.6.2. Long-Term Extension Phase With Limited Data Collection

After unblinding at the final analysis, the IDMC's review, and the sponsor's subsequent decision and notification not to offer cross-over, all subjects still in the double-blind phase of the study will be offered the option to enter the Long-Term Extension Phase of the study. All subjects must sign the ICF for the Long-Term Extension Phase before entering it. Details for the Long-Term Extension Phase are provided in Attachment 10.

If a dedicated Extension study becomes available, then all subjects who comply with the entry criteria for that study and consent to that study should be transferred to that study.

9.1.7. Data Collection Following IDMC Recommendation to Unblind

After unblinding and notification by the sponsor, sites will collect only the data specified in Attachment 9 or Attachment 10.

9.2. Efficacy

9.2.1. Evaluations

Efficacy evaluations will be conducted as specified in the Time & Events Schedule. The efficacy evaluations include the following:

- Tumor measurements (CT or MRI, bone scans, other imaging procedures)
- Survival status, analgesic use, SSREs, and first cytotoxic chemotherapy for prostate cancer
- Serum PSA evaluation (measurements at a central laboratory)

The same imaging modality used for tumor assessments should be used throughout the evaluation of an individual subject. Unscheduled tumor assessment and appropriate imaging should be considered if signs or symptoms suggestive of disease progression, including escalating pain not referable to another cause, worsening ECOG PS grade, or physical examination findings consistent with disease progression, are recorded.

9.2.1.1. Other Efficacy Evaluations

The BPI-SF (item 3) and chronic opioid use (defined as administration of additional opioid analgesics lasting for ≥3 weeks for oral, or ≥7 days for non-oral formulation) will be used to measure time to pain progression. Analgesic usage (for the time to analgesic progression

endpoint) will be scored according to the World Health Organization (WHO) analgesic ladder: 0 for no analgesic, 1 for non-opioid analgesics (including non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol/acetaminophen, antidepressants, and agents intended to treat neuropathic pain), 2 for opioids for moderate pain, and 3 for opioids for severe pain.

9.2.1.2. Efficacy Criteria

Tumor response will be assessed utilizing imaging measurements, as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1 Attachment 1).[16] In this study, RECIST 1.1 has been modified based on PCWG2 criteria, which are specific for this patient population. Lymph node and ^{99m}Tc bone scan will be evaluated according to an adaptation of the PCWG2 criteria (see also Attachment 1 and Scher et al.[30]). Prostate-specific antigen measurements will also be evaluated according to PCWG2 criteria. Additional details are provided in Attachment 7.

Evaluation of rPFS will be assessed by the investigator as detailed in the Imaging Manual (see Section 9.2.2 for definitions). All subject scans (CT/MRI bone scans), however will be submitted to a third-party core imaging laboratory for quality assessment and for audit purposes. It is important to the integrity of the study that all imaging studies are forwarded to the core imaging laboratory throughout the study. Further details regarding materials to be forwarded for central quality assessment can be found in the Imaging Manual and/or Investigator Site File.

9.2.2. Endpoints

The primary objective of the study is clinical benefit, which is described by the endpoints described below.

Primary Endpoint

The primary endpoint is rPFS.

Radiographic progression-free survival, as assessed by the investigator, is defined as the time from the date of randomization to the date of radiographic progression or death, whichever occurs first. Radiographic progression is defined as the time from randomization to the occurrence of one of the following:

- A subject is considered to have progressed by bone scan if:
  - The first bone scan with ≥2 new lesions compared with baseline is observed <12 weeks from randomization and is confirmed by a second bone scan taken ≥6 weeks later showing ≥2 additional new lesions (a total of ≥4 new lesions compared with baseline);
  - The first bone scan with ≥ 2 new lesions compared with baseline is observed ≥12 weeks from randomization and the ≥2 new lesions are verified on the next bone scan ≥6 weeks later (a total of ≥ 2 new lesions compared with baseline).
- Progression of soft tissue lesions measured by CT or MRI as defined in modified RECIST 1.1 criteria (Attachment 1).

Secondary Endpoints

- Overall survival (OS) is defined as the time from date of randomization to date of death from any cause
- Time to chronic opioid use (oral opioid use for ≥3 weeks; parenteral opioid use for ≥7 days) is defined as the time from date of randomization to the first date of opioid use
- Time to initiation of cytotoxic chemotherapy is defined as the time from date of randomization to the date of initiation of cytotoxic chemotherapy
- Time to pain progression defined as the time from date of randomization to the first date a subject experience an increase by 2 points from baseline in the BPI-SF worst pain intensity item 3 observed at 2 consecutive evaluations ≥4 weeks apart or initiation of chronic opioids (see Section 9.2.1.1), whichever occurs first

Other Endpoints

- Time to symptomatic skeletal-related event (SSRE) defined as the time from randomization to first occurrence of 1 of the following:
  - Use of external beam radiation therapy (EBRT) to relieve skeletal symptoms
  - The occurrence of new symptomatic bone fractures (cancer-related: vertebral or non-vertebral)
  - The occurrence of tumor-related spinal cord compression
  - Need for tumor-related orthopedic surgical intervention
- Time to deterioration of ECOG PS grade is defined as the time from randomization to the date of deterioration in ECOG PS grade (increase by at least 1 grade from baseline with confirmation)
- Objective response rate defined as the proportion of subjects with measurable disease achieving a complete or partial response according to (modified RECIST 1.1; Attachment 1)
- Duration of response in subjects with measurable disease
- PRO as assessed by FACT-P, BPI-SF, and EQ-5D-5L (see Section 9.5)
- Time to PSA progression based on PCWG2 criteria[30]
- Time to analgesic progression defined as the time interval from randomization to first date of increase in analgesic usage score ≥30% from baseline observed at 2 consecutive evaluation ≥4 weeks apart (see Section 9.2.1.1)
- PFS2 is defined as time from randomization to the date of first progression (radiographic, clinical, or PSA progression) on the first subsequent therapy or death from any cause, whichever occurs first
- Biomarker research to explore AR gene anomalies and other markers previously shown to be responsible for resistance to apalutamide

9.3. Population Pharmacokinetics

9.3.1. Evaluations

Pharmacokinetic assessments will be conducted on as many subjects as feasible (and where regulations permit). In Japan, blood samples for PK assessment will be collected from all randomized subjects. Two separate blood samples will be collected at approximately the same time for each sampling time point; 1 for abiraterone and 1 for apalutamide. On Day 1 of Cycle 1, blood samples will be collected at 2 hours and 4 hours post the first dose for each subject. On Day 1 of Cycle 3, predose samples (up to 1 hour prior to on-site study drugs administration) and postdose samples between 0.5 and 4 hours will be collected. For the other PK visits (Cycles 2, 4, 5, and 6), blood samples will be collected predose (up to 1 hour prior to on-site study drugs administration). In total, 16 blood samples will be drawn as described in the Laboratory Manual in this study. Four blood samples will be drawn on Day 1 of Cycle 1 and 4 blood samples will be drawn on Day 1 of Cycle 3. An additional 8 blood samples will be collected on each Day 1 of Cycles 2, 4, 5, and 6 with 2 blood samples drawn on each day.

9.3.2. Analytical Procedures

Pharmacokinetic samples collected from both treatment arms will be assayed for abiraterone using a validated analytical method. PK samples collected from the combination arm will be assayed for apalutamide and its active metabolite JNJ-56142060 using a validated analytical method.

9.4. Biomarkers

Results from a Phase 1 study in patients with metastatic CRPC provide evidence that acquired mutation in AR (AR^{F876L}) may be associated with resistance to apalutamide treatment.[20] Multiple other biomarkers have been shown to be associated with resistance to abiraterone acetate, enzalutamide or apalutamide. Archived tumor samples (FFPE blocks or slides) and serum samples will be collected, where country regulations permit, for biomarker evaluations. Plasma samples will be collected from approximately 220 subjects during treatment (as indicated in the Time and Events Schedule) and approximately 500 subjects at the end-of-treatment; whole blood will be collected from approximately 220 subjects at the time points indicated in the Time & Events Schedule. Plasma-based circulating DNA will be used to assess the presence of the AR^{F876L} mutation and whole blood or plasma DNA to assess other markers that may be associated with resistance to AA alone and in combination with apalutamide. Serum samples will be collected to compare the effect of testosterone and steroid metabolites when subjects are treated with AAP alone and in combination with apalutamide. Archival FFPE tumor blocks or tumor slides will be collected from approximately 300 subjects in this study to investigate whether genomic classifiers can be used to identify a more homogeneous population of high-risk patients. This will potentially allow selection of the appropriate high-risk patient population for future studies of apalutamide and AA.

9.5. Patient-reported Outcomes

All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. All PRO measures will be

completed using an electronic device (ePRO). For more details refer to the ePRO user manual. Sample questionnaires for the BPI-SF, FACT-P, and EQ-5D-5L are provided in Attachment 4, Attachment 5, and Attachment 6, respectively.

For FACT-P and EQ-5D-5L, baseline questionnaires should be completed on Cycle 1 Day 1. During the Treatment Phase, the FACT-P and EQ-5D-5L are to be completed at clinic visits as outlined in the Time and Events Schedule. During the Follow-up Phase, the questionnaires will be completed remotely as outlined in the Time and Events Schedule.

A consecutive 7-day completion of the BPI-SF is required for determination of eligibility (see Section 4.1 (Inclusion Criterion #9) (see also the Time and Events Schedule). The completion of questionnaire for Day 7 must occur before or on the day of randomization. During the Treatment Phase, the questionnaire should be completed as outlined in the Time and Events Schedule. During the Follow-up Phase, the BPI-SF (7-day) will be completed remotely as outlined in the Time and Events Schedule.

9.6. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration and cause of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

9.7. Safety Evaluations

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule. Any clinically significant abnormalities persisting at the End-of-Treatment will be followed by the investigator until resolution or until a clinically stable endpoint is reached or until the end of the study.

The study will be overseen by an Independent Data Monitoring Committee (see Section 11.11). An IDMC charter will be prepared.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a family member, caregiver, surrogate, or the subject's legally acceptable representative). Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

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

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

Blood samples to assess the safety of study drug will be collected. Screening laboratory evaluations can be used for Cycle 1 Day 1 assessments if performed within 14 days of Cycle 1. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. For example, laboratory abnormalities leading to an action regarding study drug (dose change, temporary stop, delay of the start of a cycle, or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality reported as an AE, the following laboratory values should be reported in the laboratory section of the eCRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the AE, and the value supporting recovery to Grade 1 or to baseline values.

The following tests will be performed by the central laboratory as outlined in the Time & Events Schedule:

- Hematology Panel

  -hemoglobin
  -white blood cell (WBC) count
  -platelet count
  -absolute neutrophil count (ANC)

NOTE: *Any abnormal WBC evaluations will also be reported by the central laboratory.

- Serum Chemistry Panel

  -sodium
  -potassium
  -creatinine
  -fasting glucose
  -lactic acid dehydrogenase (LDH)
  -calcium
  -albumin (screening only)
  -total protein

- Liver Function tests

  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -alkaline phosphatase
  -direct and indirect (screening only if Gilbert's disease is suspected) and total bilirubin

- Fasting Lipid Panel

  - high density lipoprotein-cholesterol (HDL-C)
  - low density lipoprotein-cholesterol (LDL-C)
  - triglycerides

Testosterone will be evaluated at screening only. Thyroid stimulating hormone (TSH) and PSA will be evaluated periodically throughout the study as outlined in the Time and Events Schedule.

In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required.

Electrocardiogram (ECG)

Electrocardiograms (ECGs) (12-lead) will be recorded at screening. Abnormalities noted at screening should be included in the medical history. Computer-generated interpretations of ECGs should be reviewed for data integrity and reasonableness by the investigator. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. ECGs should not be obtained when serum potassium is <3.5 mmol/L. Hypokalemia should be corrected prior to ECG collection. Serum chemistry results must be available before an ECG can be obtained

Vital Signs

Body temperature, heart rate, respiratory rate, and blood pressure will be recorded at Screening. At all other visits, only blood pressure will be measured.

Physical Examination

The Screening physical examination will include, at a minimum, the general appearance of the subject, height and weight, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. During the Treatment Phase and at the EOT Visit, limited symptom-directed physical examination and weight assessment is required.

Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) grade

See Time and Events schedule for the timing of assessment of ECOG PS.

9.7.1. Safety Assessments

- Medical history, vital sign measurements, physical examination, body weight, and ECOG PS grade
- Concomitant therapy and procedures
- Adverse events and SAEs, including laboratory test AEs will be graded and summarized according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03
- Hematology, blood chemistry, liver function tests, fasting lipids, and TSH

An IDMC will be convened for this study and will be responsible for review of periodic evaluations of safety during the study as outlined in a separate IDMC charter.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he died before the end of the study, or has not been lost to follow up or withdrawn consent before the end of the study.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued, the subject will not be automatically withdrawn from the study.

Subjects should be encouraged to continue treatment until radiographic progression or unequivocal clinical progression. If the subject has radiographic progression without evidence of unequivocal clinical progression and alternate therapy is not initiated, treatment may continue at the discretion of the investigator. Subjects should not discontinue treatment for PSA progression in the absence of radiographic progression or unequivocal clinical progression. If a subject discontinues study treatment before evidence of radiographic progression, data on subsequent imaging assessments performed per the local standard of care will be collected if available (see Section 9.1.5). Radiographic progression is defined by PCWG2 (see Attachment 7). Bone scan worksheets may be used as source documentation for tracking progression or response (see Section 17.5).

The primary reason for discontinuation of study treatment is to be recorded in the eCRF. A study treatment discontinuation form should be emailed to the sponsor’s medical monitor prior to discontinuation in IWRS (see the SIPPM for details).

However, a subject's study treatment must be discontinued for:

- Unequivocal clinical progression defined as:
  - Deterioration in ECOG PS to grade 3 or higher
  - Need to initiate any of the following because of tumor progression (even in the absence of radiographic evidence of disease)
    - Alternative anti-cancer therapy for prostate cancer
    - The use of EBRT to relieve skeletal symptoms

  - The need for tumor-related orthopedic surgical intervention
  - Need for chronic opioid analgesics (defined as administration of additional opioid analgesics lasting for ≥3 weeks for oral, or ≥7 days for non-oral formulation). NOTE: Administration of as needed (eg, not fixed or scheduled dosage) use of opioid analgesics or extended opioid use for treatment other than the subject's prostate cancer does not require discontinuation from study treatment (eg, codeine/acetaminophen combinations, hydrocodone/acetaminophen combinations hydrocodone/ibuprofen combinations, oxycodone/acetaminophen combinations oxycodone/aspirin combinations, tramadol)

- Withdrawal of consent for continued treatment
- Subjects who have had their treatment assignment unblinded (exception IDMC recommendation to unblind the study) should discontinue treatment and enter the Follow-up Phase
- The investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment

All attempts to obtain imaging studies at the time of treatment discontinuation or End-of-Treatment Visit should be made to assess for radiographic progression.

Study data will continue to be collected after discontinuation of study treatment, unless the subject withdraws consent for further study participation.

10.3. Withdrawal from the Study

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

- Lost to follow up
- Withdrawal of consent for subsequent data collection

If a subject is lost to follow up, every reasonable effort must be made by the study-site personnel to contact the subject and to determine endpoint status and the reason for the discontinuation/withdrawal. The measures taken for follow up must be documented. The informed consent will stipulate that even if a subject decides to discontinue double-blind study drug, he will agree to be contacted periodically by the investigator to assess endpoint status. Furthermore, the subject will be asked to agree to grant permission for the investigator to consult family members or public records to determine the subject's endpoint status, in the event the subject is not reachable by conventional means (eg, office visit, telephone, e-mail, or certified mail).

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.

If a subject discontinues study treatment before the end of the Treatment Phase, End-of-Treatment and follow-up assessments should be obtained.

11. STATISTICAL METHODS

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

11.1. Analysis Populations

Intent-to-Treat Population (ITT): All eligible subjects who are randomized into the study and who will be classified according to their assigned treatment group, regardless of the actual treatment received. This population will be used for subject disposition and efficacy analyses.

Safety Population: All subjects who received at least one dose of study drug, with treatment assignments designated according to actual study treatment received. This population will be used for evaluating safety and treatment compliance.

Patient-reported Outcomes Population [PRO]: All randomized subjects who have completed at least the baseline assessment of BPI-SF, FACT-P or EQ-5D-5L questionnaires; all time-to-event analysis will be based on the ITT population.

Pharmacokinetics Populations [PK]: All randomized subjects who have at least 1 PK sample collected.

Biomarker Population: All randomized subjects who have at least 1 biomarker sample collected.

11.2. Sample Size Determination

Subjects will be randomized in a 1:1 ratio to receive apalutamide plus AAP or placebo plus AAP. The study is sized to detect the hypothesized HR for OS as well as rPFS endpoints.

This study is designed to provide sufficient power (approximately [redacted]%) to detect a HR of [redacted] in the secondary endpoint of OS based on an assumed median OS of [redacted] for the control group (AAP).[27] The assumption for OS is a HR of [redacted] which represents an improvement of [redacted] versus [redacted]) in the median time to death in the treatment group of apalutamide plus AAP compared with the control group of AAP alone. Under the assumption that the failure distribution of OS follows an exponential distribution with a constant hazard rate, approximately [redacted] death events will be required to detect the assumed HR at a maximum two-sided significance level of 0.05 (see Section 11.9 for details on significance level), with enrollment duration of approximately [redacted] (approximately 960 subjects) and an additional follow up of [redacted] to reach the total number of death events. The median time of OS in the control group of AAP alone and the enrollment projection are assumed based on the observation in the COU-AA-302 study.[27]

It is assumed that the failure distribution of the primary endpoint, rPFS follows an exponential distribution with a constant hazard rate. Based on simulations accounting for the correlation of [redacted] between rPFS and OS, it is estimated that approximately [redacted] rPFS events would be required to provide at least [redacted]% power in detecting a hazard ratio (HR) of [redacted] (median rPFS of [redacted] for the control group [AAP] versus [redacted] for the treatment group of apalutamide

plus AAP) at a 2-tailed level of significance of 0.05. The median time of rPFS in the control group of AAP and the correlation between rPFS and OS are based on the observation in the COU-AA-302 study.[27] The same enrollment assumptions as described for OS are assumed.

11.3. Efficacy Analyses

All continuous variables will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Discrete variables will be summarized with n and percent. All efficacy endpoints will be analyzed using the ITT set of population. Kaplan-Meier product limit method and Cox model will be used to estimate the distribution of the time-to-event variables and to obtain the HR along with the associated confidence intervals, respectively. Unless otherwise specified, stratified log-rank test will be used as the primary analysis method to test the treatment effect for time-to-event variables; response rate variables will be evaluated using the Chi-square statistic or the exact test if the cell counts are small. The stratification variables are presence or absence of visceral metastases, ECOG PS grade of 0 or 1, and region (EU, North America [United States/Canada], and Rest of World [ROW]).

Primary Endpoint (Analysis of the rPFS Primary Endpoint)

The progression events of the rPFS endpoint will be based on investigator radiographic assessment of progression. The final rPFS analysis will take place after approximately CCI events are observed. The timing of the first interim analysis of OS may occur at the same time as the final analysis of rPFS. Alternatively, the analyses may be performed at a different time if the number of death events needed for a valid interim analysis of OS would require a long delay in the analysis of the rPFS endpoint. The alpha-spending for the interim analysis of OS will be adjusted accordingly (see Section 11.9). A subject without an event at the time of analysis will be censored at the last known date the subject did not have a documented radiographic progression. Detailed censoring rules will be provided in the statistical analysis plan. Stratified log-rank test will be used in the analysis. Non-stratified log-rank test will also be provided as sensitivity analysis. Stratified Cox proportional-hazard model will be used to obtain the HR and its 95% CI.

Secondary Endpoints (Analysis of Secondary Endpoints)

The analyses of the secondary endpoints will be performed at the time of the first interim analysis of OS (approximately CCI events). CCI [redacted]

CCI [redacted]

[redacted] Details of the testing procedure will be provided in the statistical analysis plan.

The analyses of the secondary endpoints will be performed using stratified log-rank test. Non-stratified log-rank tests will also be provided as sensitivity analyses.

Kaplan-Meier methods will be used to estimate the medians for each treatment arm. Stratified Cox proportional-hazard models, including the same stratification factors as above, will be used to estimate the HR and its 95% confidence interval (CI). One year, 2-year, 3-year, survival rates will be estimated using the Kaplan-Meier method.

For the OS analysis, subjects without an event will be censored on the last date known to be alive. The final analysis will occur when approximately CCI events are observed.

11.4. Pharmacokinetic and Pharmacodynamic Analyses

Population PK analysis of plasma concentration-time data of apalutamide and abiraterone may be performed using nonlinear mixed-effects modeling. The population PK modeling will include all subjects with sufficient and interpretable PK assessments. The data from the population PK samples may be combined together with the data from other studies for the population PK analysis. If sufficient data are available, the relationship of exposure to apalutamide and JNJ-56142060, and abiraterone to measures of efficacy and AEs may also be analyzed. The population PK/PD analysis results will be presented in a separate report.

11.5. Biomarker Analyses

Initial biomarker analyses will be conducted on approximately 220 plasma and whole blood samples to assess the frequency of AR^{F876L} mutation and other resistance markers respectively from both treatment groups. Sample size is estimated to provide meaningful biomarker analysis based on frequency of this mutation as previously reported.[20]

Further associations may be made with clinical endpoints with:

- F876L mutation in plasma DNA collected at progression from approximately 500 subjects
- AR splice variants or other RNA anomalies in whole blood collected from approximately 220 subjects
- Testosterone and steroid metabolites in serum samples collected from approximately 220 subjects

High-risk genomic classifiers may be evaluated if it can be used to identify a more homogeneous population of high-risk patients using appropriate categorical or regression methods.

The association of the rest of the biomarkers with clinical response or time-to-event endpoints may be assessed using appropriate statistical methods, (such as analysis of variance [ANOVA], categorical or survival models), depending on the endpoints. Analyses may be performed within and between each treatment group. Other clinical covariates (such as baseline tumor characteristics and patient demographics) may also be included in the model. Correlation of baseline biomarker expression levels with clinical response or relevant time to-event endpoints may be performed to identify responsive (or resistant) subgroups. Association of biomarkers with clinical response will also be explored in the overall population to identify "high-risk" biomarker profiles that are correlated with poor outcome. Appropriate details of these exploratory analyses will be included in the statistical analysis plan. Results of these exploratory analyses will be presented in separate technical reports.

11.6. Patient-reported Outcomes

Scales from BPI-SF and FACT-P: Descriptive statistics of each scale score at baseline and follow-up assessments will be summarized by treatment groups; time to degradation in each scale will be analyzed using Kaplan-Meier method and stratified Cox proportional-hazard model. Additional analysis may be carried out, if appropriate. Analysis details will be included in the statistical analysis plan.

The EQ-5D-5L data will be summarized descriptively by treatment group and study visit. Each level of every dimension will be summarized using count and percent. EQ-5D-5L Visual Analog Scale (VAS) will be described using summary statistics (n, mean, median, etc.).

11.7. Medical Resource Utilization

Medical resource utilization will be descriptively summarized by treatment group. This report will be prepared separately and will not be a part of the clinical study report.

11.8. Safety Analyses

Subjects who receive at least 1 dose of study drug will be analyzed for safety. The safety parameters to be evaluated are the incidence, intensity, and type of AEs, vital signs measurements, and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

Adverse Events

Treatment-emergent AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA) and will be graded according to the NCI-CTCAE, Version 4.03. Treatment-emergent AEs are those events that occur or worsen on or after first dose of study drug through 30 days after the last dose of study drug and will be included in the analysis. Adverse events will be summarized by system organ class and preferred term, and will be presented overall and by treatment group. Serious adverse events and deaths will be provided in a listing. All AEs resulting in discontinuation, dose modification, dosing interruption, or treatment delay of study drug will also be listed and tabulated by preferred term.

Clinical Laboratory Tests

Clinical laboratory test results will be collected from Screening and through 30 days after last dose of study drug. Laboratory data will be summarized by type of laboratory test. Parameters with predefined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grades will be summarized. Change from baseline to the worst AE grade experienced by the subject during the study will be provided as shift tables.

Vital Signs

Descriptive statistics of blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

11.9. Interim Analyses

There will be no planned interim analysis of the primary endpoint, rPFS.

Two interim analyses and one final analysis are planned for the OS endpoint. The testing of the OS endpoint will be carried out according to the [redacted] Assuming the OS endpoint will be tested at a maximum two-sided overall alpha of 0.05, the expected total number of death events is [redacted] at final analysis. At the time of the first interim analysis, approximately [redacted]% ([redacted]) of the total death events will be observed. The second interim analysis will be performed after observing approximately [redacted]% ([redacted]) of the total death events. Assuming a maximum overall 2-tailed significance level of 0.05, the estimated cumulative alpha spend are [redacted] and [redacted] at the first and second interim analyses, respectively. The actual alpha to be spent and the exact significance level at each of the analysis will be based on the number of death events observed at the time of analysis.

11.10. Futility Analyses

A non-binding futility analysis is planned using PSA90 decline rate defined as the proportion of subjects with a decline of PSA of 90% or more from baseline. In the case that a PSA90 decline rate of 30% in the control group is observed, it is assumed that an absolute increase of [redacted]% over the control group would be clinically meaningful. This analysis will occur when approximately [redacted] subjects have been treated for at least [redacted] cycles. The purpose of this analysis is to provide an early look to ensure that sufficient antitumor activity is observed in the treatment group of apalutamide plus AAP compared with AAP. This futility analysis will not be used to substantiate an efficacy claim. Non-binding futility analyses will be implemented at the planned interim analyses for OS.

In addition, a non-binding futility analysis on rPFS will be implemented after observing approximately [redacted]% ([redacted] events) of the total number of required [redacted] events. Details for each futility analysis will be provided in the statistical analysis plan.

11.11. Independent Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to review efficacy information. The committee will

perform periodic safety review throughout the study and review the safety of the first 60 subjects randomized to the study and after treatment for at least 1 cycle. In addition, the IDMC will review the planned efficacy/futility analyses.

The IDMC responsibilities, authorities, and procedures will be documented in a separate charter.

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

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

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

- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For apalutamide the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure. For ZYTIGA® (abiraterone acetate) with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the local product information.

Adverse Event Associated With the Use of the Drug

An AE 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 AE that is not related to the use of the drug.

Doubtful

An AE 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 AE 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 AE 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 AE 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 4.03 will be used to grade the severity of AEs. Any AE not listed in the NCI-CTCAE will be graded according to the investigator's clinical judgment using the standard grades as follows:

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity.

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Grade 4 (Life-threatening): Urgent intervention indicated.

Grade 5 (Death): Death.

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

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF 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. Anticipated events will be recorded and reported as described in Attachment 8.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, 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 AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs 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). For anticipated events, if the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event the sponsor will provide a safety report in narrative format to the investigators (and the head of the institute where required). 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. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study-site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs 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/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

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

- Surgery or procedure planned before entry into the study (must be documented in the eCRF).

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

During the Follow-up Phase of the study, deaths regardless of causality will be reported in the eCRF. 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. Serious adverse events that occur after 30 days following the last drug administration thought to be related to study drug will be collected and reported via the SAE form within 24 hours of discovery or notification of the event and documented.

12.3.3. Pregnancy

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

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

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 in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality,

durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from 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 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 study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The JNJ-56021927 (apalutamide) tablet supplied for this study contains 60 mg of JNJ-56021927 (apalutamide). It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.[18]

Abiraterone acetate 250 mg tablets supplied for this study are oval, white to off-white in color. It will be manufactured and provided under the responsibility of the sponsor.

Placebo will be provided as a tablet formulation and will be matched in size, color, and shape in order to maintain the study blind.

14.2. Packaging

JNJ-56021927 (apalutamide) 60 mg tablets will be packaged in 120-count, in high-density polyethylene bottles with child-resistant closures.

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

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

The study drugs must be stored in a secure area and administered only to subjects entered into the clinical study in accordance with the conditions specified in this protocol. Additional information for AA is provided in the local product information. Subjects should be advised to keep all medications out of reach and sight of children.

Abiraterone Acetate Handling Requirements: AA is contraindicated in women who are or may potentially be pregnant. There are no human data on the use of AA in pregnancy. Maternal use of CYP17 inhibitor is expected to produce changes in hormonal levels that may affect the development of the fetus. Women who are pregnant or may be pregnant should not handle AA without protection, eg gloves.

In an oral developmental toxicity study in the rat, AA affected pregnancy.

It is not known whether abiraterone or its metabolites are present in semen. A condom is required if the subject is engaged in sexual activity with a pregnant woman. If the subject is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method. In either case, the subject should use a condom while on study drug and for 3 months following the last dose of study drug.

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

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

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

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, 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. Study drug may not be relabeled or reassigned for use by other subjects. The

investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study-sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure(s) and package insert(s) as applicable
- Pharmacy manual/SIPPM
- Laboratory Manual
- Link to NCI-CTCAE Version 4.03: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
- ePRO device and user manual
- IWRS Manual
- eDC Manual
- Imaging manual

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of combining apalutamide with AAP in subjects with chemotherapy-naïve mCRPC. All subjects will receive active treatment with AAP as standard of care. The study is blinded to adequately test the hypothesis that the addition of apalutamide will prolong rPFS in this subject population and provide additional clinical benefit and an acceptable safety profile.

Potential subjects will be fully informed of the risks and requirements of the study including the fact that limited data exists for the use of apalutamide with AAP in combination 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.

All participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the study. As rPFS is the primary endpoint, scheduled imaging is incorporated into the protocol. The timing of imaging is designed to capture progression events and allow the clinical investigator to make timely treatment decisions, yet balancing this with preventing subject overexposure to radiation. Efficacy assessments will occur as recommended by the internationally accepted RECIST 1.1 criteria and PCWG2 criteria.[16,30]

An IDMC will be established to review the safety and efficacy of the treatment combination and make recommendations as to the future conduct of the study. The sponsor will monitor blinded

data on an ongoing basis to ensure the safety of the subjects enrolled in this study. A futility analysis will provide an early look to ensure that sufficient antitumor activity is observed in the treatment group of apalutamide plus AAP compared with AAP. An ongoing Phase 1 study will also inform for the Phase 3 study.

See Section 9.1.1 for details on blood volumes. The volume of blood to be drawn is considered to be customary and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the time frame of the study, based upon the standard of the American Red Cross (2014).[1]

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the 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 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 ICF (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, unless required locally), the ICF, applicable

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- 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 study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF 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 study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

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 ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the

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

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

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

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

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

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

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his 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 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.

Exploratory 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 or local regulations. 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.

16.2.5. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (listed on the Contact Information page(s), which will be provided as a separate document). 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 study-site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel 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 subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used. The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study-site as a basis for standard medical care, must be available for the following subject identification, eligibility, and study identification; study discussion and date of signed 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. The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document). Subject- and investigator-completed scales and assessments designated by the sponsor (PROs) will be recorded directly into an electronic device and will be considered source data.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If an electronic source is utilized, references made to the CRF in the protocol include the electronic source system but information collected through electronic source may not be limited to that found in the CRF.

17.5. Case Report Form Completion

Case report forms are provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in the eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents Data must be entered into eCRFs in English. The eCRF must be completed as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

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. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 2 different ways:

- Investigator and study-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).
- Sponsor or sponsor delegate can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study-sites, review of protocol procedures with the investigator and study-site 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 database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site 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 study database they will be verified for accuracy and consistency with the data sources.

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 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/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRFs with the source documents (eg hospital/clinic/physician's office medical records); a sample may be reviewed. 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 study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study-site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded eCRF data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents 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.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/End-of-Study

17.9.1. Study Completion

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

17.9.2. End-of-Study

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

The investigator may initiate study-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 a study-site by the sponsor or investigator may include but are not limited to:

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

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study-site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-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 he has 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 JNJ-56021927 (apalutamide) 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 exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-56021927 (apalutamide), 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 study-sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Recruitment

performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of 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 primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study-site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: Summary of RECIST Criteria Version 1.1

The following information was extracted from Section 3, Section 4, and Appendix I of the New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline (version 1.1) authored by Eisenhauer et al (2009). Refer to the European Journal of Cancer article (2009;45(2):228-247) for the complete publication.[16] For modifications based on the Prostate Cancer Working Group 2 (PCWG2) criteria refer to Scher et al. J Clin Oncol (2008;26:1148-1159).[30]

3. Measurability of tumor at baseline

3.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

3.1.1 Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

The following two methods of measure are not allowed in this protocol:

- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- *Malignant lymph nodes:* To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow up, only the short axis will be measured and followed. See also 'Baseline documentation of target and non-target lesions' in section 4.2 of the RECIST guideline for information on lymph node measurement.

3.1.2 Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

3.2 Specifications by methods of measurements

3.2.1 Measurement of lesions

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

3.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up. Imaging based evaluation should always be done rather than clinical examination.

4. Tumor response evaluation

4.1 Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements.

4.2 Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al. (Reference #10 in Eisenhauer publication).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

Lymph nodes merit special mention since they are normal anatomical structures, which may be visible by imaging even if not involved by tumor. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The *short* axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm•30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II of the Eisenhauer reference). All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

4.3 Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

4.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

4.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and progressive disease, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note*: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

4.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression (see comments below) of existing non-target lesions. (*Note*: the appearance of one or more new lesions is also considered progression).

4.3.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some Phase studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy.' If 'unequivocal progression' is seen, the patient should be considered to have had overall progressive disease at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of progressive disease even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

4.4.1 Timepoint response

It is assumed that at each protocol specified timepoint, a response assessment occurs. Table 1 in this attachment provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 in this attachment is to be used.

4.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of progressive disease. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved progressive disease status, regardless of the contribution of the missing lesion.

4.4.3 Best overall response: all timepoints

The *best overall response* is determined once all the data for the patient is known.

Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best response of progressive disease. The same patient lost to follow up after the first SD assessment would be considered inevaluable.

Table 1 - Timepoint response: patients with Target (+/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

Table 2 - Timepoint response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease; NE = not evaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

Attachment 2: ECOG Performance Status

ECOG Grade Scale (with Karnofsky conversion)

0	Fully active, able to carry on all predisease 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. (Karnofsky 0)

Attachment 3: Prohibited Concomitant Medications Known to Lower the Seizure Threshold or Cause Seizures and Additional Information on CYP450 Drug Interactions

Prohibited medications known to lower the seizure threshold or cause seizures include the following:

- Aminophylline/theophylline
- Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone)
- Buproprion
- Lithium
- Meperidine and pethidine
- Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
- Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)

Additional information on CYP450 drug interactions can found on the following websites:
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Attachment 4: Sample BPI-SF

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ Time: _____

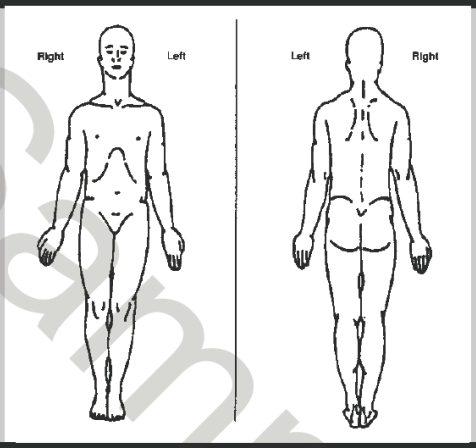
Name: _____ _____ _____

Last First MiddIle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. 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

4. Please rate your pain by circling the one nuimber 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

5. 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

6. 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

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Attachment 5: Sample FACT-P

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please cir or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Attachment 6: Sample EQ-5D-5L

Health Questionnaire

English version for the USA

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

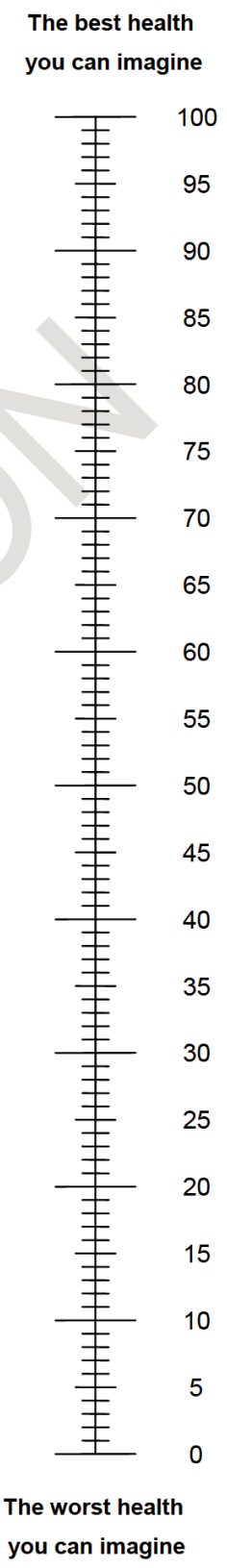
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 ❑

- 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 7: Guidance Document for PCWG2 Criteria and RECIST 1.1

Criteria of Progression for Study Eligibility by Disease Manifestation

- Target (nodal and visceral) lesions or measurable disease:
  - Use RECIST 1.1 to record soft tissue (nodal and visceral) lesions as target or non-target
- Baseline Assessment of Lymph node:
  - PCWG2: the greatest diameter of a lymph node must measure ≥2 cm by spiral CT to be considered a target lesion.
- Bone Lesions:
  - PCWG2: When the bone scan is the sole indicator of progression, PCWG2 defines progression in bone when ≥2 new lesions are seen on bone scan compared with a prior scan for study entry.
- PSA Progression :
  - PCWG2 requires a sequence of rising PSA values on at least 1 week apart and a minimum starting value of 2.0 ng/mL .

Disease Evaluation on Study

- Soft tissue lesions (nodal and non-nodal: Use RECIST 1.1 with caveats)
  - Only report changes in lymph nodes that were ≥2 cm in greatest diameter at baseline
  - Record changes in nodal and visceral soft tissue sites separately
  - Record complete elimination of disease at any site separately
  - Confirm favorable change with second scan
- Bone lesions
  - The appearance of 2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions
  - The date of progression is the date of the first scan that shows the change

ACIS study:

	Eligibility	Disease Evaluation
Bone	Inclusion criterion 6.1: radiographic progression of bone according to PCWG2.	A subject is considered to have progressed by bone scan if: a. The first bone scan with ≥2 new lesions compared with baseline is observed <12 weeks from randomization and is confirmed by a second bone scan taken ≥6 weeks later showing ≥2 additional new lesions (a total of ≥4 new lesions compared with baseline); b. The first bone scan with ≥ 2 new lesions compared with baseline is observed ≥12 weeks from randomization and the ≥2 new lesions are verified on the next bone scan ≥6 weeks later (a total of ≥ 2 new lesions compared with baseline).
Lymph Nodes	The greatest diameter of a lymph node must measure ≥2 cm by spiral CT to be considered a target lesion	Follow RECIST 1.1 Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (Section 4.3.1 of Attachment 1).
Soft tissues	Inclusion criterion 6.1: radiographic progression of soft tissues according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)	Follow RECIST 1.1
PSA	Inclusion criterion 4: Castration-resistant prostate cancer demonstrated during continuous ADT, defined as 3 rises of PSA, at least 1 week apart with the last PSA ≥2 ng/mL Inclusion criterion 6.1: Prostate cancer progression documented by PSA according to the Prostate Cancer Clinical Trials Working Group (PCWG2)	

Attachment 8: Anticipated Events

An anticipated event is an adverse event (serious or nonserious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen. For the purposes of this study, the following events will be considered anticipated events:

Disease-specific Events

Erectile dysfunction
Haematospermia
Haematuria
Incontinence
Lymphoedema
Nocturia
Painful ejaculation
Pollakiuria
PSA Increased
Urinary hesitation
Ureteral obstruction
Urethral obstruction
Urinary flow decreased
Urinary retention
Urinary tract obstruction

ADT-Related Events

Depression
Gynaecomastia
Hot flush
Libido decreased
Osteoporosis
Sexual dysfunction
Testicular atrophy

Reporting of Anticipated Events

All AEs will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1. Any anticipated event that meets serious criteria will be reported to the sponsor as described in Section 12.3.2. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) per applicable clinical trial legislation to Health Authorities and IRB/ECs (Note: Japan will not identify anticipated events for the Health Authorities). If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting.

To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/ECs. If an interim analysis of trial results leads to an unblinded, aggregate review of safety data by the study team, the sponsor may terminate the review of pre-specified anticipated events outlined above.

Safety Assessment Committee (SAC)

A Safety Assessment Committee (SAC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The SAC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The SAC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention based on a review of the aggregate data by arm.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

Attachment 9: Open-Label Extension in the Event of Subjects Being Offered Cross-over to Open-label Apalutamide in Combination With AAP After Study Unblinding

After unblinding at the final analysis, the IDMC and sponsor's decision to offer cross-over, and subsequent notification, subjects assigned to AAP alone are offered the option to receive open-label apalutamide in combination with AAP. The decision to cross-over should be made by the subject and his investigator, and should also take into consideration that there is no information about the effectiveness of adding apalutamide to AAP following treatment with AAP alone.

The Open-Label Extension Phase will begin when both the Amendment 4 is approved at the site and the sponsor has notified the site of the start of the Open-Label Extension Phase:

- Subjects who are still receiving apalutamide in combination with AAP in the double-blind phase of the study will be offered the option to continue to receive open-label apalutamide in combination with AAP until they reach a reason for discontinuation of treatment (see protocol Section 10.2) or until further notification by the sponsor on a different means for continued supply of study treatment, whichever occurs first.
- Subjects who are still receiving AAP alone in the double-blind phase of the study will be offered the option to either receive AAP alone or cross-over to receive open-label apalutamide in combination with AAP until they reach a reason for discontinuation of treatment (see protocol Section 10.2) or until further notification by the sponsor on a different means for continued supply of study treatment, whichever occurs first.

  If a subject still receiving AAP alone chooses to cross-over and start receiving open-label apalutamide in combination with AAP, the investigator will evaluate eligibility based on the criteria below.
- Subjects who have already ended treatment and are in the Follow-up Phase in the main study will be discontinued from the study and all data collection will cease.

Eligibility Criteria for Subjects who Cross-over from AAP Alone to Open-label Apalutamide in Combination With AAP after Unblinding

Subjects planned for cross-over to open-label apalutamide in combination with AAP must meet the eligibility criteria below. The laboratory evaluations listed below must be completed within 28 days before the start of receiving open-label apalutamide in combination with AAP. If a subject does not meet these criteria, he can continue on AAP alone.

1. Was still participating in the double-blind phase of the study and receiving AAP alone
2. Willing and able to provide written informed consent to receive open-label apalutamide in combination with AAP
3. ECOG PS grade of 0 or 1 or 2 (see Attachment 2)
4. Adequate organ function as defined by the following:
   a. Serum AST or serum ALT ≤2.5-times the ULN;
   b. Serum total bilirubin ≤1.5×ULN (Note: In subjects with Gilbert's syndrome, if total bilirubin is >1.5×ULN, measure direct and indirect bilirubin, and if direct bilirubin is ≤1.5×ULN, subject may be eligible)

c. Serum creatinine <2.0×ULN

d. Platelet count ≥100,000×10^9/μL independent of transfusion/growth factors within 3 months before the evaluation

e. Hemoglobin ≥9.0 g/dL (independent of transfusion/growth factors within 3 months before the evaluation)

f. Serum potassium ≥3.5 mmol/L

Study Treatment Administration

ADT administration

Refer to Section 6.1 of the protocol.

Open-label study treatment

Study treatment is administered orally on an outpatient basis and a treatment cycle is defined as 28 days (Table 8). Sufficient study drug for each treatment cycle will be distributed as specified in Table 9. Dose modifications for toxicity are provided in Section 6.3 of the protocol. Guidance for apalutamide/placebo applies to open-label apalutamide.

If a subject was on a lower dose of apalutamide or AAP in the double-blind phase of the study, he should continue on that lower dose in the Open-Label Extension Phase.

Table 8: Study Treatment Administration for the Open-Label Extension Phase

Study Treatments	Daily Dose	Schedule
apalutamide	240 mg (4×60 mg tablets)	Once daily with or without food
abiraterone acetate (AA)	1,000 mg (4×250 mg tablets)	Once daily on empty stomach. No food should be consumed for at least 2 hours before the dose of AA is taken and at least 1 hour after the dose of AA is taken. Swallow tablets whole with water.
Prednisone	10 mg (2×5 mg tablets)	5 mg twice daily (recommended to be taken with food)

If a dose of apalutamide alone, AAP alone, or both is missed, it should be omitted and will not be made up or taken with the next dose the following day. If a subject forgets to take a dose of either apalutamide or AAP, the dose should only be replaced if the subject remembers and takes the dose within a 12-hour window.

Prohibitions and Restrictions

Refer to protocol Sections 4.3, 8.1, 8.2, and 8.3.

Study Procedures for the Open-Label Extension

Subjects who meet the eligibility criteria and cross-over from AAP alone to open-label apalutamide in combination with AAP will begin open-label apalutamide and AAP treatment with Cycle 1 Day 1 of the Open-Label Extension Phase. All subjects continuing in the Open-

Label Extension Phase will follow the schedule of procedures provided in Table 9. After a subject discontinues from study treatment in the Open-Label Extension Phase, there will only be an End-of-Treatment Visit, after which no additional data are collected.

Subjects will be followed up for disease evaluation per the local practice; no efficacy data other than date and type of progression and survival (as specified in Table 9) will be collected.

Blood samples for serum chemistry and hematology will be collected as prespecified in Table 9. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during Period 1 (or until notification by the sponsor) of the Open-Label Extension Phase of the study in the AE section of the eCRF. For example, laboratory abnormalities leading to an action regarding study drug (dose change, temporary stop, delay of the start of a cycle, or permanent stop) or the start of concomitant therapy should be reported.

The following tests will be performed (by the local laboratory) as specified in Table 9:

Hematology Panel: hemoglobin, WBC count, platelet count, and ANC
Serum chemistry panel: sodium, potassium, calcium, creatinine, fasting glucose
Liver function tests: AST, ALT, alkaline phosphatase, and total bilirubin
Fasting Lipid panel: HDL-C, LDL-C, and triglycerides
TSH, with T3 and T4 to be done only if TSH is abnormal; only for subjects on apalutamide

In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required.

For Period 2, sites can follow the subjects for disease assessment and safety per the local practice. No efficacy data will be collected; no safety data other than SAEs as specified in Table 9 will be collected. However, based on local regulations, additional safety data may be collected.

Discontinuation Criteria for the Open-Label Extension

If a subject meets the discontinuation criteria as defined in Section 10.2 of the protocol, study treatment must be discontinued.

The assessments and timing are specified in the Time and Events Schedule (Table 11) and in this attachment.

Table 9: Time and Events Schedule (Open-Label Extension; Subjects Cross-over to Open-label Apalutamide in Combination With AAP After Study Unblinding)

Procedures	Comments	Open-Label Extension Phase, Period 1 (first 6 months after CCO-FA date or until notification by the sponsor)		Open-Label Extension Phase, Period 2 (after previous period until reaching criteria in Section 10.2, or notification by sponsor)
		Subjects who Cross-over to Open-label Apalutamide and AAP (ie, receiving apalutamide for first time)	Subjects Remaining on Previously Received Study Treatment	
Screening				
Informed consent	All subjects must sign the ICF for the OLE Phase	X	X	
Eligibility criteria for starting open-label apalutamide and AAP	Criteria for cross-over in Attachment 9. Lab tests for eligibility must be completed within 28 days before the start of receiving open-label apalutamide.	X		
Study Drug Dispensing				
Open-label Apalutamide+AAP (or AAP alone)		Continuous; sufficient study drug until next visit will be dispensed		Continuous; sufficient study drug until next visit will be dispensed
Study drug compliance		Bottle(s) including any unused medication will be returned at every visit in Period 1		X (via IWRS)
Visit Frequency				
Subject should visit the site	Visits with window of ± 3 days	Visits on D1 of OLE C1-5 and on D28 of C6. EOT Visit (if applicable).	Visits on D1 of OLE C1, C4, and on D28 of C6. EOT Visit (if applicable).	Per local practice
Clinical Laboratory (Local Laboratory)				No data will be collected
Hematology and blood chemistry	See Attachment 9 for required laboratory tests.	On D1 of C1-6	On D1 of C1 and C4	Per local practice
Safety				No data other than SAEs will be collected
Physical examination and vital signs		At each visit. Clinically relevant abnormalities should be reported as AEs.		Per local practice
Adverse events		Continuous during this period and until 30 days after the last dose if discontinued during this period		Per local practice
SAEs		Continuous during this period and until 30 days after the last dose if discontinued during this period		Collection of SAEs; see Section 12.3.2 of protocol
Efficacy				No data will be collected
Tumor assessments, PSA	Efficacy assessment per local practice	Date and type of PD (radiographic, clinical, or PSA progression) will be collected; no other data are collected		Per local practice
Survival		X		

AAP=abiraterone acetate plus prednisone or prednisolone; AE=adverse event; C=cycle; CCO-FA=clinical cutoff for final analysis; D=day; EOT=End-of-Treatment; ICF=informed consent form; IWRS=interactive web response system; OLE=Open-Label Extension; PD=progressive disease; PSA=prostate-specific antigen; SAE=serious adverse event.

Attachment 10: Long-Term Extension in the Event of Limited Data Collection After Study Unblinding

After unblinding at the final analysis, the IDMC and the sponsor's decision, and subsequent notification not to offer cross-over, the study will enter the Long-Term Extension Phase. The sponsor will continue to provide study drug until subjects reach a reason for discontinuation of treatment (see protocol Section 10.2) or until further notification by the sponsor on a different means for continued supply of study treatment, whichever occurs first.

The Long-Term Extension Phase will begin when both the Amendment 4 is approved at the site and the sponsor has notified the site of the start of the Long-Term Extension:

- Subjects who are still receiving AAP alone in the double-blind phase of the study will be offered the option to continue to receive AAP.
- Subjects who are still receiving apalutamide in combination with AAP in the double-blind phase of the study: depending on investigator discretion, subjects will be offered the option to either receive open-label AAP alone (ie, discontinue apalutamide) or receive open-label apalutamide in combination with AAP.
- Subjects who have already ended treatment and who are in the Follow-up Phase in the main study will be discontinued from the study and all data collection will cease.

Study Treatment Administration

ADT administration

Refer to Section 6.1 of the protocol.

Open-label study treatment

Study treatment is administered orally on an outpatient basis and a treatment cycle is defined as 28 days (Table 10). Sufficient study drug for each treatment cycle will be distributed as specified in Table 11. Dose modifications for toxicity are provided in Section 6.3 of the protocol. Guidance for apalutamide/placebo applies to open-label apalutamide.

If a subject was on a lower dose of apalutamide or AAP in the double-blind phase of the study, he should continue on that lower dose in the Open-Label Extension Phase.

Table 10: Study Treatment Administration for the Long-Term Extension Phase

Study Treatments	Daily Dose	Schedule
apalutamide	240 mg (4×60 mg tablets)	Once daily with or without food
abiraterone acetate (AA)	1,000 mg (4×250 mg tablets)	Once daily on empty stomach. No food should be consumed for at least 2 hours before the dose of AA is taken and at least 1 hour after the dose of AA is taken. Swallow tablets whole with water.
Prednisone	10 mg (2×5 mg tablets)	5 mg twice daily (recommended to be taken with food)

If a dose of apalutamide alone, AAP alone, or both is missed, it should be omitted and will not be made up or taken with the next dose the following day. If a subject forgets to take a dose of either apalutamide or AAP, the dose should only be replaced if the subject remembers and takes the dose within a 12-hour window.

Prohibitions and Restrictions

Refer to protocol Sections 4.3, 8.1, 8.2, and 8.3.

Study Procedures for the Long-Term Extension

All subjects continuing in the Long-Term Extension Phase will follow the schedule of procedures provided in Table 11.

Sites can follow the subjects for disease assessment and safety per the local practice. No efficacy data will be collected; only SAEs will be collected for safety as specified in Table 11. Based on local regulations, additional safety data may be collected.

Discontinuation Criteria for the Long-Term Extension

If a subject meets the discontinuation criteria as defined in Section 10.2 of the protocol, study treatment must be discontinued.

The assessments and timing are specified in the Time and Events Schedule (Table 11) and in this attachment.

Table 11: Time and Events Schedule (Long-Term Extension With Limited Data Collection After Study Unblinding)

Procedures	Comments	Long-Term Extension Phase (until reaching criteria in Section 10.2, or termination of the study)	
		Continuing to Receive Apalutamide +AAP	Receiving AAP only
Screening			
Informed consent	All subjects must sign the ICF for the LTE Phase	X	X
Study Drug Dispensing			
Open-label Apalutamide+AAP (or AAP alone)		Continuous; sufficient study drug until next visit will be dispensed	
Study drug compliance		X (via IWRS)	
Clinical Laboratory (Local Laboratory)			
Hematology and blood chemistry		Per local practice and local label for apalutamide and abiraterone acetate/prednisone or the USPI/ EU SmPC	
TSH	T3 and T4 only to be done if TSH is abnormal	Per local label for apalutamide or the USPI/EU SmPC	
Safety			
SAEs		Collection of SAEs; see Section 12.3.2 of protocol	

AAP=abiraterone acetate plus prednisone or prednisolone; EU=European Union; ICF=informed consent form; IWRS=interactive web response system; LTE=Long-Term Extension; SAE=serious adverse event; SmPC=Summary of Product Characteristics; TSH=thyroid-stimulating hormone; USPI=United States Package Insert.

INVESTIGATOR AGREEMENT

JNJ-56021927 (apalutamide)
Clinical Protocol 56021927PCR3001 – Amendment 4

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): Angela Lopez-Gitlitz; MD

Institution: Janssen Research & Development

Signature: PPD Date: 18 Feb 2020

(Day Month Year)

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

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Status: Approved, Date: 18 February 2020