Aragon Pharmaceuticals, Inc.*

Clinical Protocol

A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT in Subjects with Metastatic Hormone-sensitive Prostate Cancer (mHSPC)

Protocol 56021927PCR3002; Phase 3
TITAN
(Targeted Investigational Treatment Analysis of Novel Anti-androgen)

AMENDMENT 5

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.

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

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	24 June 2015
Amendment 1	8 April 2016
Amendment 2	2 February 2017
Amendment 3	22 February 2018
Amendment 4	5 September 2018
Amendment 5	16 March 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 5 (16 March 2020)

The overall reason for the amendment is to add a Long-term Extension (LTE) Phase to the study. The LTE Phase will provide apalutamide access to subjects who may continue to derive benefit from treatment (based on investigator assessment) after the Open-label Extension Phase is complete.

Applicable Section(s)	Description of Change(s)
Rationale: Information on the LTE Phase has been added to the protocol. The LTE Phase will begin on the date of cut-off for the final analysis (CCO FA) for the study or on the date of approval of this amendment (Amendment 5) at the site, whichever comes last.	
Synopsis (*Study Design*); 3.1 Overview of Study Design; 9.1.7 Long-Term Extension (new section)	A brief description of the LTE Phase was added to the main body of the protocol.
Attachment 7: Long-Term Extension Phase (new section)	A detailed description of the LTE Phase was added as an attachment. In the LTE Phase, assessments will be conducted at the discretion of the investigator. Data collection will be limited to SAEs occurring during treatment with apalutamide and up to 30 days after the last dose of apalutamide.
Rationale: Clarifications were made to Attachment 4: Anticipated Events.	
Attachment 4: Anticipated Events	Text was changed in 2 sections: Reporting of Anticipated Events and Safety Assessment Committee.
Rationale: Minor changes were incorporated.	
Throughout the protocol	Other minor grammatical, formatting, and spelling changes were made. The list of abbreviations was updated.

Amendment 4 (5 September 2018)

The overall reason for the amendment is a change to the timing of interim analyses of overall survival (OS).

Applicable Section(s)	Description of Change(s)
Rationale: Based on a current lower number of OS events, as expected, and on recent data from a Phase 3 apalutamide clinical study, the 2 interim analyses are planned for this study after observing approximately 50% and 70% of the total number of required (410) OS events.	
Synopsis (*Interim Analysis*)	The following changes are noted with strikethrough (deletion) or bold (new) text: For the ~~co~~ **dual**-primary OS endpoint, 2 interim analyses are planned for this study after observing approximately ~~60~~ **50**% (~~246~~ **205** events) and approximately ~~75~~ **70**% (~~308~~ **287** events) of the total number of required (410) events. ~~The timing of the first interim analysis of OS may occur at the same time as the primary analysis of rPFS.~~ **At the time of the first interim analysis of OS, the final analysis of the rPFS dual-primary endpoint will also be performed.** ~~However, this analysis may be performed at a different time if the number of death events needed for a valid interim analysis of OS would require an extended delay in the analysis of the rPFS endpoint.~~ No interim analysis is planned for the rPFS endpoint.
Section 11.3.2 Analysis of the Dual-Primary Endpoints	The following changes are noted with strikethrough (deletion) or bold (new) text: For the ~~co~~ **dual**-primary OS endpoint, 2 interim analyses are planned for this study after observing approximately ~~60~~ **50**% (~~246~~ **205** events) and approximately ~~75~~ **70**% (~~308~~ **287** events) of the total number of required (410) events. ~~The timing of the first interim analysis of OS may occur at the same time as the primary analysis of rPFS.~~ **At the time of the first interim analysis of OS, the final analysis of the rPFS dual-primary endpoint will also be performed.** ~~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 an extended delay in the analysis of the rPFS endpoint.~~ Recalculated the estimated cumulative alpha spend for the first and second interim analyses, which are noted with strikethrough (deletion) or bold (new) text: Assuming a significance level of 0.045, the estimated cumulative alpha spend are ~~0.013~~ **0.0091** and ~~0.025~~ **0.0224** for the first and second interim analyses, respectively.
Rationale: Highlights of drug interaction were revised based on available information on the potential for drug interactions with apalutamide.	
8.3 Restricted Concomitant Medications	Updates were made to restricted concomitant medications based on the latest available information on the potential for drug interactions with apalutamide.
Rationale: Revisions to an exclusion criterion to correct minor errors.	
4.2 Exclusion Criteria (Criterion #7)	The following changes are noted with strikethrough (deletion) or bold (new) text: 7.1. **Criterion modified per Amendment 4** **7.2.** Prior treatment with other next generation anti-androgens (eg, enzalutamide), CYP17 inhibitors (eg, abiraterone acetate), immunotherapy (eg, sipuleucel-T), radiopharmaceutical agents or other treatments for prostate cancer except those listed in Inclusion Criteria #5.1, #6.1, #10~~.1~~, and #11~~.1~~ (see also Section 8.2)

Applicable Section(s)	Description of Change(s)
Rationale: Omissions and errors were noted.	
Table 3 (Footnote c)	[c]During the Open-label Extension Phase, serum chemistry, hematology and PSA for subjects not requiring cross-over and were receiving apalutamide, **D1 of C1 then** D1 of q4 cycles; TSH, **D1 of C1, D1 of C5, then** D1 of q4 cycles, and fasting lipids **D1 of C1, D1 of C13, then** D1 of q12 cycles. Subjects crossing over from placebo to apalutamide serum chemistry, hematology and PSA; D1 of C1 to C7, then D1 of q2 cycles to C13, then D1 of q4 cycles until EOT, unless otherwise specified; TSH **D1 of C1, D1 of C5, then** D1 of q4 cycles, and fasting lipids **D1 of C1, D1 of C13, then** D1 of q12 cycles.
9.1.5 Follow-up Phase	During the Follow-up Phase, deaths regardless of causality and treatment-related SAEs will be collected and reported within 24 hours of discovery or notification of the event **on the eCRF**.
11.9 Independent Data Monitoring Committee	After the review of interim analysis data, if the **primary analysis results of rPFS and the** interim analysis results **of OS** are positive ~~and compelling~~ the IDMC may recommend unblinding to allow all subjects to receive active therapy.
Attachment 6 Crossover to Open-label Apalutamide After Study Unblinding	**Study Procedures for Subjects Previously on Placebo Who Crossover** The following changes are noted with strikethrough (deletion) or bold (new) text: Refer to the Time and Events Schedule for ~~placebo~~ subjects who crossover **from placebo** to open-label apalutamide. See Section 9 for the description of study assessments ~~in~~ **and** the Time and Events Schedule (Open-label Extension Phase). **Study Procedures for Subjects not Requiring Cross-Over and Were Receiving Apalutamide** The following changes are noted with strikethrough (deletion) or bold (new) text: Refer to the Time and Events Schedule for ~~placebo~~ subjects who were unblinded and were receiving study drug. See Section 9 for the description of study assessments ~~in~~ **and** the Time and Events Schedule (Open-label Extension Phase).
Throughout the protocol	Abbreviations were updated, and minor formatting and editorial changes were made.

Amendment 3 (22 February 2018)

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 reasons for the amendment are to provide an update on the background information given recent developments in external data relating to population and a change to the interim analysis of overall survival, and to update the visit/lab schedules during the Open-label Extension Phase of the study.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify testing procedures	
Time and Events Schedule (Open-label Extension Phase)	Added columns to the Open-label Extension Phase to outline events in the Crossover Eligibility Phase, timing of apalutamide treatment, and procedures for subjects not requiring cross-over and were receiving apalutamide and for subjects crossing over from placebo to apalutamide. Added in the notes for the Crossover Eligibility Phase, "Within 28 days before start of crossover Treatment Phase, unless otherwise specified". Added a column with information for the End-of-Treatment Visit. The End-of-Treatment Visit must occur within 30 days after the last dose of study drug. Added a column with information for the Follow-up Phase. Follow-up will continue until death, lost to follow-up, withdrawal of consent, or study termination. Added a row describing confirmation of eligibility. Added that dosing compliance and dispensing of study drug will occur during the Open-label Treatment Phase, and that only compliance will be checked at the End-of-Treatment Visit.
Time and Events Schedule (Open-label Extension Phase) footnote "a"	Added, "Eligibility verification only applies to subjects crossing over from placebo to apalutamide."
Time and Events Schedule (Open-label Extension Phase), Section 3.2 Study Design Rationale	Added a row describing testing information and timing for electronic patient-reported outcomes for the Open-label Extension Phase.
Time and Events Schedule (Open-label Extension Phase) footnote "b"	Added, "It is expected that the FACT-P and EQ-5D-5L are completed at the site for the relevant cycle visits before any other procedures. In the event that this is not possible, a + 6-day window for the completion of these PROs is acceptable."
Time and Events Schedule (Open-label Extension Phase), Section 9.4 Biomarker Evaluations	Added a row describing timing for biomarker collection in the Open-label Extension Phase. Blood samples for biomarker collection will be obtained at C1 D1 for subjects crossing over from placebo to apalutamide, and at end of treatment.
Time and Events Schedule (Open-label Extension Phase)	Added a row for Additional Endpoints to include information and timing on data collection: "Survival status, data on secondary endpoints (SREs, chronic opioid use, initiation of cytotoxic chemotherapy), first subsequent therapy for prostate cancer, and date and type of disease progression on first subsequent therapy." Added that during the Open-label Treatment Phase only SREs and chronic opioid use will be collected.

Applicable Section(s)	Description of Change(s)
Table 3	Updated table to include blood volumes for thyroid stimulating hormone levels and for total blood volume per visit collected in the Open-label Extension Phase. Added a biomarkers collection step at the Open-label Extension Phase with volumes for plasma and whole blood.
Table 3, footnote "c"	Updated serum chemistry and hematology sampling times for subjects during Open-label Extension Phase.
Section 9.1.6 Open-label Extension Phase	Added text to indicate that follow-up data collection will continue as noted in the Time and Events Schedule for the Open-Label Extension Phase.
Table 3, footnotes "e" and "f"; Section 9.4 Biomarker Evaluations; Section 11.5 Biomarker Analysis	Since the Sponsor has continued collection past 220 subjects, the number of subjects consenting to optional plasma and whole blood samples has been removed.
Rationale: Clinical Study Reports for Studies ARN-509-001 and ARN-509-003 have been completed.	
Section 1.1.2.1 Clinical Studies; References	Updated the information on Study ARN-509-001 and ARN-509-003, and added the clinical study report references to the reference list. Updated all reference fields because of these changes.
Rationale: For consistency within the apalutamide program, the Management of Drug-Related Rash table has been updated.	
Table 2	Added that for Grade 2 (or symptomatic Grade 1) rash the following changes with strikethrough (deletion) or bold (new) text: **At investigator discretion,** ~~H~~hold apalutamide/placebo for up to 28 days.
Rationale: Given recent developments in external data relating to this population, the sponsor believes that analyzing overall survival (OS) at approximately 60% of events would provide more mature data at the interim analysis of OS.	
Synopsis	The following changes are noted with strikethrough (deletion) or bold (new) text: For the co-primary OS endpoint, 2 interim analyses are planned for this study after observing approximately ~~50~~**60** % (~~206~~**246** events) and approximately 75% (~308 events) of the total number of required (410) events.
Section 11.3.2 Analysis of the Co-Primary Endpoints	The following changes are noted with strikethrough (deletion) or bold (new) text: For the co-primary OS endpoint, 2 interim analyses are planned for this study after observing approximately ~~50~~**60**% (~~206~~**246** events) and approximately 75% (~308 events) of the total number of required (410) events. Recalculated the estimated cumulative alpha for the first interim analysis and which are noted with strikethrough (deletion) or bold (new) text: Assuming a significance level of 0.045, the estimated cumulative alpha spend are ~~0.009~~**0.013** and 0.025 for the first and second interim analyses, respectively.

Applicable Section(s)	Description of Change(s)
Rationale: Updated efficacy evaluation definitions for accuracy.	
Section 9.2.1 Evaluations	Updated definition of skeletal-related event as noted in strikethrough (deletion) or bold (new) text: Skeletal-related event (SRE) is defined as the occurrence of ~~either~~ **symptomatic** pathological ~~or clinical~~ fracture, spinal cord compression, radiation to bone, or surgery to bone. Updated definition of pain progression as noted in bold (new) text: Pain progression is defined as an increase by 2 points from baseline in the BPI-SF worst pain intensity (item 3) observed at 2 consecutive evaluations ≥4 weeks apart**; with an average worst pain score of >4 in subjects who have had no decrease in opioids** or initiation of chronic opioids (see Section 10.2 for definition), whichever occurs first.
Section 9.2.3 Endpoints	Updated definition of PFS2 as noted with strikethrough (deleted) text: PFS2 is defined as the time from date of randomization to date of first occurrence of disease progression ~~(clinical or radiographic)~~ on first subsequent therapy for prostate cancer or death, whichever occurs first.
Section 10.2 Discontinuation of Study Drug	Updated definition of clinical progression as noted in bold (new) text: Radiation therapy for metastatic prostate cancer lesion(s) **(palliative radiation to lesions existing at baseline will not be considered clinical progression).**
Rationale: Provide a more efficient, but scientifically rigorous analytical method for testing primary endpoints.	
Section 11.3.2 Analysis of the Co-Primary Endpoints	Added the following text: The Fallback Method will be used to test the primary endpoints. The rPFS endpoint will be tested first. If rPFS is not statistically significant, the OS endpoint will be tested at 0.045 level of significance; if rPFS is statistically significant, the OS endpoint will be tested at 0.05 level of significance.
Rationale: Provide additional information for the crossover to open-label apalutamide after study unblinding.	
Section 4 Study Population	Added the following text: Eligibility criteria for subjects in the placebo arm who crossover to active treatment with apalutamide (in the event of a positive study result and unblinding) are described in Attachment 6.
Attachment 6 Crossover to Open-label Apalutamide After Study Unblinding	Added an attachment to outline the eligibility criteria, the study procedures, and the discontinuation criteria for the Open-label Extension Phase.
Rationale: Minor changes or corrections were incorporated	
Throughout the protocol	Other minor grammatical, formatting, and spelling changes were made.

Amendment 2 (2 February 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 reasons for the amendment are to provide guidance for the management of drug-related skin rashes and to expand the list of allowed strengths and routes of administration of leuprolide acetate for subjects participating in the pharmacokinetic (PK) sub-study for leuprolide.

Applicable Section(s)	Description of Change(s)
Rationale: The PK sub-study for leuprolide is amended to expand the list of allowed strengths and routes of administration to reflect those most frequently used in the study population	
Attachment 5 Leuprolide PK Sub-study	Leuprolide 11.25 mg, 22.5 mg, 30 mg, and 45 mg dosages are permitted and may be administered by subcutaneous or intramuscular route of administration.
Rationale: Rash is an adverse drug reaction associated with apalutamide treatment. Specific guidelines for rash management have been developed for addition to the protocol.	
Section 6.3 Toxicity and Rash Management; Section 10.2 Discontinuation of Study Drug	Revised the title of the section, added guidelines for actions to take in the event of a drug-related rash, including when to complete the skin rash eCRF, and added Table 2 with modification and treatment guidelines according to the toxicity grade of the rash. Revised the following bullet in Section 10.2 by adding a link to Tables 1 and 2: More than 2 dose level reductions for Grade 3 or higher treatment-related AEs (see Table 1 and Table 2)
Rationale: The description of the analysis of the co-primary endpoints was revised to clarify that subgroup analysis by volume of disease will be performed for both endpoints (rPFS and OS). A clarification was also included to explain that the timing for the interim analysis of OS and final analysis of rPFS may not be in alignment if the number of death events for the interim analysis of OS would require an extended delay in the analysis of the rPFS endpoint**.**	
Synopsis, Efficacy Analysis, Synopsis; Interim Analysis; Section 3.1 Overview of Study Design; Section 11.3.2 Analysis of the Co-Primary Endpoints	Synopsis sections: Appropriate modifications were made to match the updates to Section 11.3.2. Section 3.1: Removed the following sentence: The rPFS analysis will occur in conjunction with the first interim OS analysis. Section 11.3.2: The description of the subgroup analysis by volume of disease was revised. The description of the timing for the first interim analysis of OS and final analysis of rPFS was revised. It was also clarified that there will no interim analysis of rPFS.
Rationale: Language describing anticipated events in Section 12.3.1 and Attachment 4 was updated to align with recent updates to the protocol template and the anticipated events list was added to Attachment 4.	
Section 12.3.1 All Adverse Events; Attachment 4 Anticipated Events	Section 12.3.1: In paragraphs 2 and 4, added text that clarifies the handling of serious anticipated events. Attachment 4: The anticipated events list was removed from the original protocol with the previous amendment. The list was added back in with this amendment. Note that 1 additional event (urinary hesitation) was added to the list compared with the list in the original protocol. Updated language was incorporated.

Applicable Section(s)	Description of Change(s)
Rationale: Corrections to Rationales #13 and #16 in the Amendment 1 table of changes.	
Section 4.1 Inclusion Criteria; Section 4.2 Exclusion Criteria	The following corrections are noted with strikethrough (deletion) or bold (new) text: Replaced "within" or "at least" with symbols for Inclusion Criteria #5.1 **and** #6.1~~, and #10.1~~ plus Exclusion Criteria ~~4.1,~~ **#5.1**, ~~#7.1~~, #8.1, #9.1, **#10.1**, and ~~#11.1~~ **#12.1**. For Exclusion Criterion ~~#11.1~~ **#12.1**, bullet "b" (Note: in previous version of the protocol, letters were not used for bulleted lists in the eligibility criteria) describing the exclusion for uncontrolled hypertension was confusing and has resulted in many questions for other protocols, uncontrolled hypertension as an exclusion is now included in bullet "a."
Rationale: The sponsor is collecting information on all prior therapy for prostate cancer at the Screening visit.	
Time & Events Schedule (Screening, Treatment, and Follow-up Phases)	Revised as follows: Prestudy anti-cancer therapy, palliative radiation, or surgical therapy ~~for metastatic disease~~
Rationale: The Time and Events Schedules does not mention study drug dispensing at the time of study visits. This was included in the original protocol but was inappropriately removed with Amendment 1.	
Time & Events Schedules	Added study drug dispensing to the schedules.
Rationale: Minor changes or corrections were incorporated	
Section 4.1 Inclusion Criteria	Criteria 10 and 11 were new criteria at the time of Amendment 1. They were incorrectly listed in the previous amendment as if they were existing criteria that were being modified. This formatting error was corrected.
Throughout the protocol	Other minor grammatical, formatting, and spelling changes were made.

Amendment 1 (8 April 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 overall reason for the amendment is to incorporate changes to the eligibility criteria based on feedback from investigators or steering committee members. These changes are also being made to reduce screen failures and for improved clarity.
The rationale for and description of the changes are listed below, and representative revisions are sometimes provided; when revisions are provided verbatim, bold font denotes new text, and strikethrough denotes deleted text.

Applicable Section(s)	Description of Change(s)
Rationale: This study is now including subjects with low-volume and high-volume metastatic hormone-sensitive prostate cancer (mHSPC).	
Title Page; Synopsis; Throughout the protocol	The title of the protocol was modified to reflect the change in the study population. The term "low-volume" to describe the study population was removed throughout the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: With the inclusion of subjects with high-volume disease, the statistical assumptions required modification.	
Synopsis Sample Size Determination, Efficacy Analysis, Interim Analysis; Section 11.2 Sample Size Determination; Section 11.3.2 Analysis of the Co-primary Endpoints	The statistical assumptions for the overall survival analysis and timing of the analyses were modified because of the inclusion of subjects with high-volume disease.
Rationale: A secondary objective was added to evaluate the efficacy by subgroup based on subjects having high- or low-volume mHSPC at study entry.	
Synopsis Objectives and Hypothesis; Section 2.1 Objectives; Section 11.3 Efficacy Analyses; Section 11.3.2 Analysis of the Co-primary Endpoints	The following secondary objective was added: To evaluate the treatment effectiveness with the addition of apalutamide to ADT for the subpopulations of subjects with low-volume or high-volume mHSPC. A statement regarding the subgroup analysis was added to Section 11.3. Added the definition of low- and high-volume disease in Section 11.3. Added the following statement to Section 11.3.2: Additional rPFS subgroup analyses on subjects with low- or high-volume mHSPC disease will be performed as an update at the time of subsequent OS analysis without alpha spending assigned.
Rationale: The definition of low- and high-volume for this study needed to be defined for the subgroup analysis.	
Section 11.3 Efficacy Analysis	Added the definition of low- and high-volume mHSPC.
Rationale: The overall rationale for the study required modification because of the inclusion of subjects with high-volume mHSPC.	
Section 1.2 Overall Rationale for the Study; References	This section was revised to include data on subjects with high-volume mHSPC, detailed information on the low-volume subgroup was removed. Data from CHAARTED and STAMPEDE studies were updated. References were updated.
Rationale: For Inclusion Criterion #2.1, the requirement of histologic evidence of prostate adenocarcinoma from a metastatic lesion is not standard of care for this study population. This study also excludes subjects with secondary malignancies, therefore the presence of bone metastases is expected to be related to prostate cancer.	
Section 4.1 Inclusion Criteria	Removed this requirement from Inclusion Criterion #2.1.
Rationale: Based on recommendation of the Steering Committee, the study will allow subjects with a single bone lesion on bone scan to be eligible, if the lesion is confirmed to be metastatic on computed tomography (CT)/magnetic resonance imaging (MRI). Some screen failures thus far have been due to presence of <2 bone lesions on bone scan.	
Synopsis Study Population; Section 4.1 Inclusion Criteria	Modified Inclusion Criterion #3.1 to allow subjects with a single bone lesion if confirmed by CT/MRI

Applicable Section(s)	Description of Change(s)
Rationale: With the inclusion of subjects who have high-volume mHSPC, subjects who have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 2 will no longer be eligible.	
Synopsis Study Population; Section 4.1 Inclusion Criteria	Removed ECOG PS grade of 2 from Inclusion Criterion #4.1
Rationale: The criteria for prior prostate cancer therapy were modified based on Steering Committee feedback. Changes were also made to improve clarity.	
Section 4.1 Inclusion Criteria; Section 4.2 Exclusion Criteria	The wording "GnRHa", which refers to GnRH analog (agonist or antagonist) for Inclusion Criterion #5.1, was modified to "GnRH agonist" because the anti-androgen requirement only applies to subjects receiving a GnRH agonist. The following statement was confusing and the requirement was removed from Inclusion Criterion #5.1: Subjects who received prior docetaxel are not required to have at least 14 days of a first-generation anti-androgen with the GnRH agonist. Separated out the therapies described in Inclusion Criterion #6.1 as there were too many details in 1 criterion. The eligibility criteria pertaining to prior docetaxel therapy for mHSPC was separated from other prior therapies for prostate cancer. With inclusion of high-volume disease, the following requirement was deleted from Inclusion Criterion #6.1: "Must have low-volume disease on pre-docetaxel imaging (ie, not meeting exclusion criterion #4 prior to docetaxel)." Inclusion Criterion #6.1 was further modified to simplify the inclusion of subjects who received prior docetaxel therapy. There was no need to include hematologic and hepatic toxicities in this criterion as they are covered in Exclusion Criterion #6. Allowed prior therapies for mHSPC other than docetaxel are now described in Inclusion Criterion #10.1. The allowed duration of ADT was modified to ≤6 months for all eligible subjects. Added that radiation therapy for metastatic lesions must be completed prior to randomization and removed radiation as an exclusion in Exclusion Criterion #10.1. Allowed prior therapies for localized prostate cancer (previously referred to as neoadjuvant or adjuvant use) are now described in Inclusion Criterion #11.1. Also clarified that all therapies for localized prostate cancer are allowed as long as the therapies were completed ≥1 year prior to randomization. The allowed duration of ADT therapy was increased to ≤3 years total from ≤6 months. Changed wording from "GnRHa" to ADT therapy for consistency. Reference made to Inclusion Criteria #10.1 and #11.1 in Exclusion Criterion #7.1. Added a reference to Section 8.2 for Exclusion Criterion #7.1, which includes a more comprehensive list.
Rationale: Exclusion Criterion #4.1 was revised to reflect the inclusion of high-volume disease. Visceral metastases without evidence of bone metastases is exclusionary.	
Section 4.2 Exclusion Criteria	Revised Exclusion Criterion #4.1 to no longer exclude high-volume disease, but to exclude if visceral metastases are the only sites of metastases.
Rationale: Minor revision to Inclusion #3.1 for consistency with Exclusion Criterion #4.1	
Section 4.2 Exclusion Criteria	Changed metastasis to metastases as was done for Exclusion Criterion #4.1

Applicable Section(s)	Description of Change(s)
Rationale: Minor revision to wording for Inclusion Criterion #7.1	
Section 4.1 Inclusion Criteria	A minor modification was made: "Able to swallow the whole study drug tablets" to "Be able to swallow whole study drug tablets"
Rationale: Ensure consistency when describing the time interval allowed or excluded prior to randomization	
Section 4.1 Inclusion Criteria; Section 4.2 Exclusion Criteria	Replaced "within" or "at least" with symbols for Inclusion Criteria #5.1, #6.1, and #10.1 plus Exclusion Criteria #4.1, #7.1, #8.1, #9.1, and #11.1. Did not modify Exclusion Criterion #11 because it is written in this manner for other protocols.
Section 8.1 Permitted Supportive Therapies; Section 8.2 Prohibited Concomitant Therapies	Modified bullets describing timing of bisphosphonates or denosumab for consistency.
Rationale: Clarified that bisphosphonates and denosumab for the management of bone metastasis are not allowed.	
Section 4.2 Exclusion Criteria	Exclusion Criterion #8.1 was modified with the addition of "for the management of bone metastasis."
Rationale: There was no information in the eligibility criteria regarding allowed timing before randomization for the administration of blood product or growth factor support.	
Section 4.2 Exclusion Criteria	Incorporation in Exclusion #10.1 of blood product and growth factor support.
Rationale: For Exclusion Criterion #11.1, bullet "b" (Note: in previous version of the protocol, letters were not used for bulleted lists in the eligibility criteria) describing the exclusion for uncontrolled hypertension was confusing and has resulted in many questions for other protocols, uncontrolled hypertension as an exclusion is now included in bullet "a."	
Section 4.2 Exclusion Criteria	Removed this bullet (previously the second bullet): Uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic BP ≥100 mmHg). Subjects with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment. Revised the bulleted listing accordingly. Added "uncontrolled hypertension" to bullet "a."
Rationale: Clarified that arterial or venous thromboembolic events were exclusionary if they were considered "clinically significant."	
Section 4.2 Exclusion Criteria	For Exclusion Criterion #12.1, modified bullet "a" (Note: in previous version of the protocol, letters were not used for bulleted lists in the eligibility criteria) to include "clinically significant" wording.
Rationale: Clarify that exclusion is cancers other than prostate cancer.	
Section 4.2 Exclusion Criteria	Minor modification to Exclusion Criterion #5.1: **Other** prior malignancy (~~other than~~ **exceptions**: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) ≤5 years prior to randomization.
Rationale: Inclusion Criterion #1.1 was modified to take into account local differences in the legal of consent.	
Section 4.1 Inclusion Criteria	Modified Inclusion Criterion #1.1 to the following: Subject must be a man ≥18 years of age, ~~inclusive~~ **(or the legal age of consent in the jurisdiction in which the study is taking place).**

Applicable Section(s)	Description of Change(s)
Rationale: Reducing the number of required visits after Cycle 25 will reduce the burden to subjects who continue to receive benefit from treatment.	
Time and Events Schedule (Screening, Treatment and Follow-up Phases); Table 2	Modified the frequency for visits after Cycle 25 from q2 to q4 cycles.
Rationale: The frequency for completion of FACT-P and EQ-5D-5L questionnaires was not in proper alignment with clinic visits after Cycle 13.	
Time and Events Schedule	Timing of assessments for FACT-P and EQ-5D-5L was changed from Day 1 of C2 to C6 then q2 cycles to Day 1 of C2 to C7 then q2 cycles to align with clinic visits after Cycle 13.
Rationale: The Brief Fatigue Inventory (BFI), Brief Pain Index-Short Form (BPI-SF), and Analgesic Use Log are completed for 7 consecutive days at every cycle during the Treatment Phase. It was not clear in the protocol that the completion of the questionnaires and log on Day 7 would occur remotely during non-visit cycles after Cycle 13. The FACT-P and EQ-5D-5L questionnaires will also be completed remotely during non-visit cycles after Cycle 25. All questionnaires will be completely remotely during the Follow-up Phase.	
Time and Events Schedule (Screening, Treatment, and Follow-up Phases); Section 9.1.3 Treatment Phase; Section 9.2.1 Evaluations	Modified the note in the Time & Events Schedule. Removed redundant wording in Sections 9.1.3, and 9.2.1.
Rationale: Skin rashes/lesions have been reported as adverse events in previous studies with apalutamide. If photographs of the rashes/lesions are taken, these photos may be submitted to the sponsor.	
Section 9.6 Safety Evaluations	Added the following sentence under the Adverse Event subsection: If an AE of rash develops and photographs are taken, the photos may be submitted to the sponsor.
Rationale: The Time and Events Schedule did not adequately specify what scans were required.	
Time and Events Schedule (Screening, Treatment, and Follow-up Phases)	Clarified that chest, abdomen, and pelvis scans are all required.
Rationale: The Time and Events Schedule did not include a row for study drug dosing.	
Time and Events Schedule (Screening, Treatment, and Follow-up Phases); Time and Events Schedule (Open-label Extension Phase)	Added a row to describe the dosing of apalutamide/placebo during the Treatment Phase and removed the row on drug dispensing.

Applicable Section(s)	Description of Change(s)
Rationale: A series of PSA values to prove hormone sensitivity may not be available for subjects with newly diagnosed mHSPC who are eligible for this study. The United States Food and Drug Administration (FDA) requested documentation of historical PSA values so that hormone sensitivity can be assessed from available data.	
Time and Events Schedule (Screening, Treatment, and Follow-up Phases); Section 9.1.1 Overview	Added the following statement: All available PSA values that were obtained in the year prior to randomization must be recorded in the eCRF.
Rationale: Japan does not identify anticipated events for the Health Authorities. A previous Japan-specific amendment was required to include this information. With this global amendment, the restriction in Japan is noted and will obviate the need for a separate country-specific amendment for Japan.	
Attachment 4	Added the following statement: (Note: Japan will not identify anticipated events for the Health Authorities).
Rationale: The changes in Section 8.3 per country-specific amendment for the Czech Republic were incorporated into the global protocol and will obviate the need for a country-specific amendment for the Czech Republic. The rationale for this change in Section 8.3 is to provide guidance on the co-administration of apalutamide with strong CYP2C8 inhibitors (eg, gemfibrozil).	
Section 8.3 Restricted Concomitant Medications	A reference to the Investigator's Brochure was added as the source for more information on the drug interaction potential of apalutamide. The following bullet was also added: Strong CYP2C8 inhibitors (eg, gemfibrozil) should be used with caution with apalutamide.
Rationale: Clarified the restrictions of steroid use during the study, not all steroid use is restricted.	
Section 8.3 Restricted Concomitant Medications	Long-term use of **systemically administered corticosteroids** is not allowed.~~; short~~ **Short**-term use (≤4 weeks, including taper) ~~will be~~ **and locally administered steroids (eg, inhaled, topical, ophthalmic, and intra-articular) are** allowed, if clinically indicated.
Rationale: Clarification for CYP3A4 drug-drug interactions	
Section 8.3 Restricted Concomitant Medications	Revised bullet 1 as follows: Strong CYP3A4 ~~inhibitors and~~ inducers: the potential for drug-drug interactions with apalutamide has not been tested clinically. ~~JNJ-56021927 is metabolized primarily by human CYP3A4, thus co-administration with strong inhibitors or~~ **Strong** inducers of CYP3A4 **(eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, efavirenz, tipranavir, St. John's wort)** should be avoided as much as possible.
Rationale: Collection of trough pharmacokinetic samples is mandatory	
Synopsis, Population Pharmacokinetic Evaluations; Table 2; Section 9.3 Pharmacokinetic Evaluations	Remove wording "approximately 750 subjects."

Applicable Section(s)	Description of Change(s)
Rationale: Clarification that collection of the PK samples for the leuprolide study will take place in selected countries and that participation is optional.	
Synopsis Pharmacokinetic Evaluations; Time and Events Schedule (Screening, Treatment, and Follow-up Phases); Section 9.3 Pharmacokinetic Evaluations; Attachment 5	Added wording that samples are optional and from consenting subjects (in selected countries).
Rationale: Clarification that collection of biomarker samples is optional.	
Time and Events Schedule (Screening, Treatment, and Follow-up Phases); Table 2; Section 9.4 Biomarker Evaluations	Added "optional" when describing the samples being collected and "consenting" before subjects. Added "Exploratory" wording for Biomarkers in the Time and Events Schedule and clarification that sample collection is optional.
Rationale: Circulating tumor cell (CTC) collection will not be included in this protocol.	
Synopsis Biomarker Evaluations; Time and Events Schedule; Table 2; Section 9.4 Biomarker Evaluations; Section 11.5 Biomarker Analyses	Removed all reference to the collection or analysis of CTCs.
Rationale: The required total volume of blood for the leuprolide sub-study is 4 mL.	
Table 2	Corrected the total volume from 7 mL to 4 mL.
Rationale: Current protocol states that PSA results from every other cycle starting with Cycle 5 will be available to the investigators. This language was modified for clarity as PSA will be blinded only from Cycle 1 to Cycle 4.	
Section 9.6 Safety Evaluations	Revised to clarify that PSA results will be blinded from Cycle 1 to Cycle 4 and beginning at Cycle 5 the PSA results will be available to investigators.
Rationale: Central laboratories send laboratory data that are not required per protocol, but are done per standard practice in the central laboratory.	
Section 9.6 Safety Evaluations	Added the following note: Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory.

Applicable Section(s)	Description of Change(s)
Rationale: Revised to designate which version of the National Cancer Institute-Common Terminology Criteria (NCI-CTCAE) should be used for grading of adverse events	
Synopsis Overview of Study Design; Section 3.1 Overview of Study Design; Section 9.1.1 Overview; Section 9.6.1 Safety Assessments; Section 12.1.3 Severity Criteria	Version 4.03 was incorporated in appropriate sections of the protocol. Specific reference of the criteria was removed from Section 9.1.1.
Rationale: A generic name has been assigned to the compound.	
Throughout the document	The generic name for the compound was recently assigned. The name, apalutamide, will be used to refer to ARN-509 and to the development code, JNJ-56021927.
Rationale: Allow more flexibility in the duration of treatment during Long-term Follow-up	
Time and Events Schedule (Open-label Extension Phase); Synopsis Overview of Study Design; Section 3.1 Overview of Study Design; Section 9.1.6 Open-label Extension Phase	In the event of a positive study result at either of the interim analyses or at the final analysis, all subjects in the Treatment Phase will have the opportunity to enroll in an Open-label Extension Phase, which will allow subjects to receive active drug (apalutamide) for **approximately** ~~up to~~ 3 years. The wording was also modified in the Time and Events Schedule for Open-label Extension Phase.
Rationale: A link to the NCI-CTCAE Version 4.03 criteria is provided rather than a paper copy.	
Section 15 Study-Specific Materials	Added website link to the NCI-CTCAE Version 4.03 criteria.
Rationale: The sponsor continually reviews their protocol template for potential improvements. Major revisions to the protocol based on the template are noted in the following sections. Minor revisions, not noted here, have also been made throughout the document.	
Section 4.3 Prohibitions and Restrictions	Added the following: Refer to Section 8 for details regarding prohibited and restricted therapy during the study as number 1 and renumbered the other prohibitions and restrictions.
Section 9.1.1 Overview	Added the following statement to the last bullet: Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples. Updated the process for completing ePRO measures based on the recent protocol template.
Added Section 10.4 Withdrawal from the Use of Research Samples	Add new section from template.
Section 12.2 Special Reporting Situations (bullet #3)	"Inadvertent or accidental exposure" to study drug changed to "accidental or occupational exposure" to study drug.

Applicable Section(s)	Description of Change(s)
Section 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.
Section 12.3.2 Serious Adverse Events	Added the following bullet: Hospitalizations not intended to treat an acute illness of adverse event (eg, social reasons such as pending placement in long-term care facility).
Section 16.2.6 Country Selection	Clarification that drug will be launched in countries **if the need for the product exists**.
Section 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.
Section 17.5 Case Report Form Completion	Clarifications to case report form completion requirements.
Section 17.8 Monitoring	Clarification of monitoring requirements.
Section 17.9 Study Completion/End-of-Study	Title changed to indicate that the study completion is the end of study.
Rationale: The definition and use of androgen deprivation therapy (ADT) was updated to ensure consistency.	
Synopsis Dose and Administration; Section 1.1.1 Metastatic Hormone-sensitive Prostate Cancer Section 1.2; Overall Rationale for the Study; Figure 1, footnote “a”; Section 4.1 Inclusion Criteria; Section 6.2 ADT administration	In the synopsis and Section 1.1.1 clarified that ADT is defined as medical castration (ie, gonadotropin releasing hormone analog [GnRHa; agonist or antagonist]) or surgical castration (ie, bilateral orchiectomy). Also added a sentence to Section 1.1.1 describing the use of an anti-androgen to control tumor flare, which can occur during initiation of GnRH agonists. In Section 1.2 removed redundancy and ensured consistency when describing ADT. Inclusion criteria #5.1 was revised for consistency with text and with other criteria. Minor modification to the first sentence in Section 6.2.
Rationale: A clinical study report for the ARN-509-001 has been completed	
Section 1.1.2.1 Clinical Studies; Reference	Updated the information on Study ARN-509-001 and added the clinical study report reference to the reference list. Removed the Rathkopf reference. Updated all reference fields because of these changes.
Rationale: Updates to ESMO and NCCN guidelines were incorporated.	
Section 1.2 Overall Rationale for the Study; References	Incorporated updated ESMO guidelines and added the Parker et al reference from the Annals of Oncology. The text pertaining to the NCCN guidelines did not change but the reference was updated.

Applicable Section(s)	Description of Change(s)
Rationale: Incorporated the United States Preventive Services Task Force (USPSTF) recommendations on PSA screening as more frequent PSA screening in the United States was considered to account, in part, for the disparity between regions in diagnosis of mHSPC.	
Section 1.1.1 Metastatic Hormone-sensitive Prostate Cancer; References	Added a sentence with reference to the USPSTF recommendations on PSA screening. Two relevant references were added to the reference list.
Rationale: The rationales for the biomarker research and PRO evaluations were moved to the appropriate section of the protocol.	
Section 3.2 Study Design Rationale; Section 9.2.1 Evaluations; 9.4 Biomarker Evaluations	Moved the rationale wording from Sections 9.2.1 (PRO) and 9.4 (biomarkers) to Section 3.2.
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	
Section 1.1.2 Apalutamide; Section 4.2 Exclusion Criteria	Revised text accordingly.
Rationale: Provide update to clinical development program.	
Section 1.1.2.1 Clinical Studies	Updated to include Phase 3 study 56021927PCR3003.
Rationale: A list of anticipated events is provided in a separate Anticipated Events Safety Monitoring Plan (ASMP) and is not needed in the protocol.	
Attachment 4	Removed the list of anticipated events and added a sentence to refer to the ASMP for the list of anticipated events relevant to this study.
Rationale: Minor errors or inconsistencies were noted. Minor organizational changes were made.	
Throughout the protocol	Minor grammatical, formatting or spelling changes were made that are not explicitly stated below.
Title page	TITAN name and definition was added.
List of Abbreviations	Updated abbreviations list.
Time and Events Schedule (Screening, Treatment, and Follow-up Phases)	Corrected the title to include "Screening Phase."
Section 9.1.1 Overview	Reorganized this section added clarity and removed redundant information.
Section 11.5 Biomarker Analysis	For consistency, the wording "up to" 220 or 500 subjects was revised to "approximately" 220 or 500 subjects.

Applicable Section(s)	Description of Change(s)
Section 10.1 Completion; Section 17.10 On-site Audits	Removed “or she” wording, only men are enrolled in this study.

SYNOPSIS

A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT in Subjects with Metastatic Hormone-sensitive Prostate Cancer (mHSPC)

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 determine if the addition of apalutamide to androgen deprivation therapy (ADT) provides superior efficacy in improving radiographic progression-free survival (rPFS) or overall survival (OS) for subjects with mHSPC.

Secondary Objectives

- To evaluate clinically relevant improvements with addition of apalutamide to ADT including delays in pain progression and opioid use for prostate cancer, skeletal-related events (SREs), and the need for cytotoxic chemotherapy
- To characterize the safety of adding apalutamide to ADT for subjects with mHSPC
- To characterize the population pharmacokinetics (PK) and pharmacodynamics (PD) of apalutamide
- To evaluate the concentration of leuprolide and assess the PD effect of leuprolide on testosterone concentrations when used alone or in combination with apalutamide
- To evaluate the treatment effectiveness with the addition of apalutamide to ADT for the subpopulations of subjects with low-volume or high-volume mHSPC

Other Objectives

- To evaluate exploratory biomarkers predictive of response and resistance to treatment
- To evaluate patient relevant outcomes including symptoms (ie, pain, fatigue, urination) and function (ie, physical, emotional, social) and health-related quality of life
- To evaluate improvements in other clinically relevant endpoints of apalutamide plus ADT compared with ADT alone
- To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this study)

Hypothesis

Apalutamide plus ADT compared with ADT alone will improve rPFS or OS or both, and have an acceptable safety profile for subjects with mHSPC.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multinational, and multicenter Phase 3 study to determine if subjects with mHSPC will benefit from the addition of apalutamide to ADT. Enrollment of approximately 1,000 subjects is planned for this study. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be stratified by Gleason score at diagnosis (≤7 versus >7), region (North America [NA] and European Union [EU] versus Other Countries), and prior docetaxel use (yes

versus no). Subjects will then be randomly assigned in a 1:1 ratio to the apalutamide plus ADT group or matching placebo plus ADT group.

A Screening Phase of up to 28 days before randomization will establish study eligibility. Subjects will receive treatment in 28-day cycles during the Treatment Phase until disease progression or the occurrence of unacceptable treatment-related toxicity or the sponsor terminates the study. If the subject has radiographic progression without clinical progression and alternate therapy is not initiated, treatment may continue until clinical progression is observed; subjects must discontinue study drug with documented clinical progression based on protocol-specified criteria. After discontinuation of study drug, subjects will have an End-of-Treatment Visit within 30 days after the last dose of study drug. During the Follow-up Phase, data collection (every 4 months) will include survival, additional data on secondary endpoints, date and type of disease progression (radiographic, PSA, clinical or a combination) on the first subsequent therapy for prostate cancer, and subsequent therapy for prostate cancer. Data collection in follow-up will continue until the subject dies, withdraws consent, is lost to follow-up or the study is terminated by the sponsor. The Brief Pain Inventory-Short Form (BPI-SF), Brief Fatigue Inventory (BFI), and EQ-5D-5L patient-report outcome (PRO) measures will also continue in the Follow-up Phase up to 12 months after treatment discontinuation. In the event of a positive study result at either of the interim analyses or at the final analysis, all subjects in the Treatment Phase will have the opportunity to enroll in an Open-label Extension Phase, which will allow subjects to receive active drug (apalutamide) for approximately 3 years. Subjects who are receiving apalutamide in the Open-label Extension Phase may continue receiving apalutamide in the Long-Term Extension (LTE) Phase if they will continue to derive benefit from treatment (based on investigator assessment). The LTE Phase will begin on the date of the cut-off for the final analysis (CCO FA) for the study, or the date of approval of Amendment 5 at the site, whichever comes last.

Subjects will be monitored for safety starting from the signing of informed consent until 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 modifications will be made according to dose modification rules outlined in the protocol. An Independent Data Monitoring Committee (IDMC) will be commissioned for the study to provide recommendations during the planned interim efficacy analyses and regular safety reviews.

STUDY POPULATION

The study population includes subjects with a diagnosis of prostate cancer and Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 or 1. Eligible subjects should have distant metastatic disease as documented by positive bone scan (1 or more bone lesions on Technetium 99m [^{99m}Tc]). Subjects with a single bone lesion must have confirmation of the bone metastasis by computed tomography (CT) or magnetic resonance imaging (MRI). Subjects could have received up to 6 cycles of docetaxel for mHSPC with the last dose administered ≤2 months prior to randomization. All subjects could have received ≤6 months of ADT prior to randomization and could have received a maximum of 1 course of radiation or surgical intervention for mHSPC. For localized prostate cancer, subjects may have received ≤3 years total of ADT and all other forms of prior therapies including radiation therapy, prostatectomy, lymph node dissection, and systemic therapies as long as all such therapies were completed ≥1 year prior to randomization.

DOSAGE AND ADMINISTRATION

All subjects will receive ADT as standard of care (SOC) therapy. Androgen deprivation therapy is defined as medical castration (ie, gonadotropin releasing hormone GnRH analog [GnRHa; agonist or antagonist]) or surgical castration (ie, bilateral orchiectomy). The choice of GnRHa will be at the Investigator's discretion. Dosing (dose and frequency of administration) will be consistent with the prescribing information. For subjects who did not undergo surgical castration, concurrent treatment with a GnRHa should be documented in the electronic case report form (eCRF).

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

EFFICACY EVALUATIONS/ENDPOINTS

Radiographic progression-free survival (rPFS), as assessed by the investigator is defined as the time from the date of randomization to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurs first. Radiographic progression will be assessed by 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. Overall survival is defined as the time from randomization to the date of death from any cause. Survival data will be collected throughout the Treatment Phase and during the Follow-up Phase.

Efficacy Endpoints

Dual-primary: rPFS and OS

Secondary: time to pain progression, time to SREs, time to chronic opioid use, and time to initiation of cytotoxic chemotherapy,

Other: time to symptomatic local progression; time to prostate cancer –specific antigen (PSA) progression based on Prostate Cancer Working Group 2 (PCWG2) criteria; explore response markers for apalutamide, AR gene anomalies and other markers previously shown to be responsible for resistance to JNJ 56021927; time to ECOG PS deterioration; prostate cancer-specific survival; PFS2 defined as the time from the date of randomization to date of occurrence of disease progression on first subsequent therapy for prostate cancer or death, whichever occurs first; change from baseline over time in each of the subscales of Functional Assessment of Cancer Therapy-Prostate (FACT-P), EuroQol EQ-5D-5L Visual Analog Scale (VAS), BPI-SF interference subscale and BFI.

Population Pharmacokinetic Evaluations

Trough PK samples will be collected. Pre-dose blood samples for analysis of apalutamide and its active metabolite (JNJ-56142060) concentrations will be collected on Day 1 of Cycles 2, 3, 4, 5, and 6.

Leuprolide PK Sub-study

Optional PK samples will be collected from at least 60 consenting subjects (in selected countries) who received or will receive leuprolide acetate as the GnRHa at the time of randomization. Samples will be collected on Day 1 of Cycles 1, 3, 4, 5, and 6 for analysis of leuprolide and testosterone concentrations.

Biomarker Evaluations

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 apalutamide. Archival formalin-fixed paraffin embedded (FFPE) tumor blocks or tumor slides will be collected to evaluate mRNA expression of genes representing AR signaling to compare biology of high- and low-volume disease with outcome and to evaluate expression of immune markers such as OX40, GITR, and FOXP3. Other markers associated with the disease and treatment may also be evaluated based on emerging evidence from ongoing studies or published data.

Medical Resource Utilization Evaluations

Medical resource utilization data associated with medical encounters will be collected during the Treatment Phase.

Safety Evaluations

Safety evaluations include AEs, vital signs measurements (blood pressure), physical examinations, ECOG PS, and clinical laboratory tests.

STATISTICAL METHODS

Analysis Populations

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 as treated.

Sample Size Determination

An overall type I error of 5% is planned for this study. This study utilizes the dual-primary endpoints of rPFS and OS with a 0.005 level of significance allocated for the rPFS endpoint and 0.045 is allocated for OS. The study is considered a success if at least one of the dual-primary endpoints is statistically significant.

It is estimated that approximately 368 rPFS events would be required to provide at least 85% power in detecting a hazard ratio (HR) of 0.67 (median rPFS of 20 months for the control group [ADT] versus 30 months for the treatment group of apalutamide plus ADT) at a 2-tailed significance level of 0.005. The study will also provide sufficient power (approximately 80%) to detect a HR of 0.75 in the dual-primary endpoint of OS based on an assumed median OS of 44 months for the control group (ADT). Approximately 410 death events will be required to detect the assumed HR at a 2-tailed significance level of 0.045 with an enrollment duration of approximately 30 months (approximately 1,000 subjects). The total study duration will be approximately 54 months to obtain 410 deaths.

Efficacy Analysis

Kaplan-Meier product limit method and Cox proportional hazards model will be used to estimate the time-to-event variables and to obtain the HR along with the associated confidence intervals.

Interim Analysis

For the dual-primary OS endpoint, 2 interim analyses are planned for this study after observing approximately 50% (~205 events) and approximately 70% (~287 events) of the total number of required (410) events. At the time of the first interim analysis of OS, the final analysis of the rPFS dual-primary endpoint will also be performed. No interim analysis is planned for the rPFS endpoint.

Population PK and PD Analysis

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

Leuprolide PK Analysis

Descriptive statistics of leuprolide PK data will be summarized by treatment groups (with apalutamide or placebo) and dose of leuprolide acetate. Statistical analysis to compare leuprolide concentrations when administered alone or in combination with apalutamide will be performed. The percentage of subjects with testosterone levels <50 ng/dL will be summarized descriptively by treatment groups.

Biomarker Analysis

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 and the results will be reported in a separate report.

Medical Resource Utilization Analysis

The analysis of this data will be included in a separate report.

Safety Analysis

The safety parameters to be evaluated are the incidence and intensity of treatment-emergent 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.

TIME AND EVENTS SCHEDULE (SCREENING, TREATMENT, AND FOLLOW-UP PHASES)

		Screening Phase	Treatment Phase			Follow-up Phase
	Notes	28 days before randomization, unless otherwise specified	C1D1	D1 of C2 to C13, then D1 of q2 cycles to C25, then D1 of q4 cycles until EOT, unless otherwise specified	EOT Visit	q4 months
Study treatment should be initiated (C1D1) within 3 calendar days after randomization. Each treatment cycle is 28 days. During the Treatment Phase, study visits may occur within ± 2 day window (for CT/MRI and bone scans, see below). The EOT visit must occur within 30 days after the last dose of study drug. Follow-up will continue until death, lost to follow-up, withdrawal of consent, or study termination.						
Screening						
Informed consent	ICF must be signed before any study-related procedures.	X				
Inclusion/exclusion criteria		X				
Prestudy anti-cancer therapy, palliative radiation, or surgical therapy		X				
Demography/Medical history		X				
Gleason score at diagnosis		X				
Study Drug Administration						
Dosing compliance and dispense study drug	See Section 7, Treatment Compliance; Only compliance at the EOT Visit (no drug dispensing)		X	X	X	
Administer study drug JNJ-56021927 (apalutamide)/placebo	240 mg once daily on 28-day treatment cycles, see Section 6.1		<--------Continuous dosing-------->			
Safety						
Electrocardiogram, 12-lead	See Section 9.6, Electrocardiograms	X				
Physical examination	See Section 9.6, Physical Examination	X		X	X	
Vital signs	After Screening Phase, only blood pressure; see also Section 9.6, Vital Signs	X		X	X	
ECOG PS		X		X	X	

		Screening Phase	Treatment Phase			Follow-up Phase
	Notes	28 days before randomization, unless otherwise specified	C1D1	D1 of C2 to C13, then D1 of q2 cycles to C25, then D1 of q4 cycles until EOT, unless otherwise specified	EOT Visit	q4 months
Efficacy						
CT or MRI (chest, abdomen, and pelvis) ^{99m}Tc Bone Scan	Visits for ^{99m}Tc bone scans or CT/MRI may occur up to 8 days before cycles requiring images. Unscheduled assessments can occur at any time as needed if signs of disease progression are observed. See Sections 9.2.1, 9.2.2, and 9.2.3.	Within 6 weeks prior to randomization		C3, C5, then q4 cycles	Not needed if previously done ≤6 weeks	
Medical Resource Utilization	See Section 9.5		Continuous			
ePROs: For cycles with an on-site visit, complete before any tests, procedures or other consultations for that visit. For non-visit cycles and during the Follow-up Phase, the questionnaires are completed remotely.						
ePROs	The BFI and BPI-SF questionnaires and Analgesic Use Log should be completed for 7 consecutive days. Start 6 days before D1 of each cycle. See also Sections 9.1.1, 9.1.3, and 9.2.1.	Start 6 days before C1D1	X	q cycle	X	q4 months up to 12 months after treatment discontinuation
	EQ-5D-5L and FACT-P		X	D1 of C2 to C7 then q2 cycles	X	q4 months up to 12 months after treatment discontinuation
Follow-up						
Survival status, data on secondary endpoints (SREs, opioid use, initiation of cytotoxic chemotherapy), first subsequent therapy for prostate cancer, date, and type of disease progression (radiographic, PSA, clinical or combination) on first subsequent therapy (See Sections 9.1.5, 9.2.3).						X
Clinical Laboratory						
Hematology	See also Section 9.6, Clinical Laboratory Tests. All available PSA values that were obtained in the year prior to randomization must be recorded in the eCRF.	X		X	X	
Serum chemistry		X		X	X	
Liver function tests		X		X	X	
PSA		X	X	X	X	
Fasting Lipids		X		D1 of C12, C25 then q12 cycles		
TSH	If TSH is >ULN: total T3, free T4 (direct), and total T4	X		D1 of q4 cycles starting at C5	X	

		Screening Phase	Treatment Phase			Follow-up Phase
	Notes	28 days before randomization, unless otherwise specified	C1D1	D1 of C2 to C13, then D1 of q2 cycles to C25, then D1 of q4 cycles until EOT, unless otherwise specified	EOT Visit	q4 months
Ongoing Subject Review						
Concomitant Therapy	See Section 8	Continuous from signing of informed consent until 30 days after the last dose of study drug				
Adverse Events	See Section 12					
Pharmacokinetics						
Trough PK sampling for apalutamide	Obtain samples before study drug administration. See Section 9.3			D1 of C2, C3, C4, C5, and C6 only		
Leuprolide sub-study PK and PD sampling (optional for consenting subjects only)	PK and testosterone samples; see Attachment 5		X	D1 of C3, C4, C5, and C6 only		
Exploratory Biomarkers (optional for consenting subjects only)						
FFPE tumor blocks or slides	Ambient shipment of FFPE samples can occur any time after C1D1. See also Section 9.4		X			
Plasma sample collection	See Section 9.4		X	D1 of C12 only	X	
Whole blood sample collection			X	D1 of C12 only	X	

Abbreviations: BFI=Brief Fatigue Inventory; BPI-SF=Brief Pain Inventory-Short Form; C=cycle; CT=computed tomography; D=day; ECOG PS=Eastern Cooperative Oncology Group performance status; eCRF=electronic case report form; ePROs=electronic patient-reported outcomes; EOT = End-of-Treatment; FACT-P=Functional Assessment of Cancer Therapy-Prostate; FFPE=formalin-fixed paraffin-embedded; ICF=informed consent form; MRI=magnetic resonance imaging; PD=pharmacodynamic; PK=pharmacokinetics; PSA=prostate-specific antigen; q=every; SRE=skeletal-related event; ^{99m}Tc=technetium-99m; TSH=thyroid stimulating hormone; ULN=upper limit of normal

TIME AND EVENTS SCHEDULE (OPEN-LABEL EXTENSION PHASE)

		Crossover Eligibility Phase	Open-Label Treatment Phase		EOT	Follow-up Phase
	Notes		**Subjects not requiring cross-over and were receiving apalutamide**	**Subjects crossing over from placebo to apalutamide**		
		Within 28 days before start of crossover Treatment Phase, unless otherwise specified	D1 of C1 then D1 of q4 cycles	D1 of C1 to C7, then D1 of q2 cycles to C13, then D1 of q4 cycles until EOT, unless otherwise specified		
Visit window during the Open-label Extension Phase is ±1 week. The EOT Visit must occur within 30 days after the last dose of study drug. Follow-up will continue until death, lost to follow-up, withdrawal of consent, or study termination.						
Screening						
Informed consent	ICF must be signed before any study-related procedures	X				
Eligibility	Confirmation of eligibility	X[a]				
Study Drug Administration						
Dosing compliance and dispense study drug	See Section 7		X	X	X (compliance only)	
Study drug administration (JNJ-56021927/apalutamide)	240 mg once daily on 28-day treatment cycles, see Section 6.1		<--------Continuous dosing-------->			
ePROs: For cycles with an on-site visit, complete before any tests, procedures or other consultations for that visit. For non-visit cycles and during the Follow-up Phase, the questionnaires are completed remotely.						
ePROs[b]	The BFI and BPI-SF questionnaires and Analgesic Use Log should be completed for 7 consecutive days. Start 6 days before D1 of each cycle. See also Sections 9.1.1, 9.1.3 and 9.2	X	q cycle	q cycle	X	q4 mo. up to 12 mo. after treatment discontinuation
	EQ-5D-5L and FACT-P	X	D1 of C1 then D1 of q2 cycles	D1 of C1 then D1 of q2 cycles	X	q4 mo. up to 12 mo. after treatment discontinuation

		Crossover Eligibility Phase	Open-Label Treatment Phase		EOT	Follow-up Phase
	Notes		**Subjects not requiring cross-over and were receiving apalutamide**	**Subjects crossing over from placebo to apalutamide**		
		Within 28 days before start of crossover Treatment Phase, unless otherwise specified	D1 of C1 then D1 of q4 cycles	D1 of C1 to C7, then D1 of q2 cycles to C13, then D1 of q4 cycles until EOT, unless otherwise specified		
Visit window during the Open-label Extension Phase is ±1 week. The EOT Visit must occur within 30 days after the last dose of study drug. Follow-up will continue until death, lost to follow-up, withdrawal of consent, or study termination.						
Clinical Laboratory						
Hematology	See Section 9.6, Clinical Laboratory Evaluations If TSH is >ULN: total T3, free T4 (direct), and total T4		X	X	X	
Serum chemistry			X	X	X	
Liver function tests			X	X	X	
PSA			X	X	X	
Fasting Lipids			D1 of C1, D1 of C13, then D1 of q12 cycles	D1 of C1, D1 of C13, then D1 of q12 cycles	X	
TSH			D1 of C1, D1 of C5, then D1 of q4 cycles	D1 of C1, D1 of C5, then D1 of q4 cycles	X	
Ongoing Subject Review						
Concomitant Therapy	Collection of concomitant medications for AEs only, see also Section 8		X	X	X	
Adverse Events	See Sections 9.1.6 and 12		X	X	X	X
Biomarkers						
				C1 D1	X	
Additional Endpoints						
Survival status, data on secondary endpoints (SREs, chronic opioid use, initiation of cytotoxic chemotherapy), first subsequent therapy for prostate cancer, and date and type of disease progression on first subsequent therapy			X (SREs, chronic opioid use only)			X

Abbreviations: AE=adverse event; C=cycle; D=day; EOT=End-of-Treatment; ePRO=electronic patient-reported outcome; ICF=informed consent form; PSA=prostate-specific antigen; q=every; SREs=skeletal-related events; TSH=thyroid stimulating hormone; ULN=upper limit of normal

[a]Eligibility verification only applies to subjects crossing over from placebo to apalutamide.

[b]It is expected that the FACT-P and EQ-5D-5L are completed at the site for the relevant cycle visits before any other procedures. In the event that this is not possible, a + 6-day window for the completion of these PROs is acceptable.

ABBREVIATIONS

ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BFI	Brief Fatigue Inventory
BPI-SF	Brief Pain Inventory-Short Form
CCO FA	clinical cut-off for final analysis
CHAARTED	Chemo Hormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer
CI	confidence interval
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	docetaxel
EAU	European Association of Urology
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
eDC	electronic data capture
EOT	End-of-Treatment
ePRO	electronic patient-reported outcome
ESMO	European Society of Medical Oncology
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FFPE	formalin-fixed paraffin-embedded
$GABA_A$	gamma amino butyric acid chloride channel
GCP	Good Clinical Practice
GnRH	gonadotropin releasing hormone
GnRHa	gonadotropin releasing hormone analog
HDPE	high-density polyethylene
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
LTE	Long-term Extension
mCRPC	metastatic castration-resistant prostate cancer
mHSPC	metastatic hormone-sensitive prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MFS	metastasis-free survival
MRI	magnetic resonance imaging
MRU	medical resource utilization
NA	North America
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NM-CRPC	non-metastatic castration-resistant prostate cancer
OATP1B1	organic anion transporter 1B1
OS	overall survival
PCWG2	Prostate Cancer Working Group 2
PFS2	time from date of randomization to date of disease progression on first subsequent therapy for prostate cancer or death, whichever occurs first

P-gp	P-glycoprotein
PQC	product quality complaint
PRO	patient-reported outcome(s)
PSA	prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
SAC	safety assessment committee
SAE	serious adverse event
SOC	standard of care
SRE	skeletal-related event
STAMPEDE	Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy
SUSAR	suspected unexpected serious adverse reaction
SWOG	Southwest Oncology Group
^{99m}Tc	technetium 99m
TSH	thyroid stimulating hormone
UGT	uridine diphosphate glucuronosyl transferase
ULN	upper limit of normal
US	United States
USPSTF	United States Preventive Services Task Force
VAS	Visual Analog Scale
ZA	zoledronic acid

1. INTRODUCTION

JNJ-56021927 (ARN-509; apalutamide; hereafter referred to as apalutamide) is an orally available, 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 JNJ-56021927 (apalutamide), refer to the latest version of the Investigator's Brochure and Addenda for JNJ-56021927 (apalutamide).

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 common cancer in men worldwide, with an estimated incidence of 1.1 million cases and 307,000 deaths in 2012.[9] It is the most common non-cutaneous related cancer among men in Europe (EU), United States (US), and Latin America/Caribbean comprising approximately 25%, 28%, and 29% of all cancers, respectively.[9] The incidence is less common in Asian regions (WHO SEARO and WPRO) at less than 6%. In the EU and US, prostate cancer is the second leading cause of cancer-related mortality in men. Prostate cancer is the leading cause of cancer-related mortality for men in the Latin America/Caribbean region. According to GLOBOCAN 2012, prostate cancer deaths were reported in 71,779 men in the EU, 30,383 men in the US, and 51,313 men in Latin America/Caribbean.[9]

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.[31]

1.1.1. Metastatic Hormone-sensitive Prostate Cancer

Estimates from European country-specific registries indicate that approximately 15% to 30% of men diagnosed with prostate cancer had metastatic (M1) hormone-sensitive prostate cancer (mHSPC).[10,14,15,17,24,27] In the US, patients presenting with mHSPC account for approximately 4% of all prostate cancer diagnosis.[2] This disparity may result from differences in the use of PSA screening in different geographies.[30] However, the percentage of men in the US who present with mHSPC may increase because there now appears to be a decrease in PSA screening after the United States Preventive Services Task Force (USPSTF) released its recommendation against PSA screening in 2012.[6,21]

Given that prostate cancer cells depend on AR signaling for their proliferation and survival, the standard treatment for patients with mHSPC disease is androgen deprivation therapy (ADT). Androgen deprivation therapy is defined as medical castration (ie, gonadotropin releasing hormone analog [GnRHa; agonist or antagonist]) or surgical castration (ie, bilateral orchiectomy). To prevent tumor flare in subjects with overt metastases, a short period of treatment with first-generation anti-androgen may be used to reduce the flare in testosterone with

initiation of a GnRH agonist. In a report based on data from the Southwest Oncology Group (SWOG S8894), 77% of men newly diagnosed with metastatic prostate cancer lived less than 5 years and only approximately 7% of men treated with hormonal therapy were alive at or after 10 years.[33] Several prognostic factors influence survival in mHSPC. Median overall survival (OS) has been reported to range from 13 months up to 75 months depending on the presence of high-risk prognostic features such as high PSA concentration at diagnosis, high Gleason score, increased volume of metastatic disease, as well as the presence of bony symptoms.[22]

1.1.2. Apalutamide

First-generation anti-androgens such as flutamide and bicalutamide have relatively low AR binding affinity relative to dihydrotestosterone, may exhibit partial agonist activity, and may eventually lead to disease progression through putative activation of the AR. The potential for agonist activity by the first-generation 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 AR antagonists, the so-called anti-androgen withdrawal syndrome.[19] To overcome the potential deficiencies of the first-generation anti-androgens, next generation anti-androgens such as apalutamide were developed and potently inhibit AR activation, nuclear translocation, binding to co-activators, and AR-mediated gene expression.[3] Furthermore, these next generation anti-androgens do not have agonist activity. Apalutamide binds AR with 8-fold greater affinity than the first-generation agent, bicalutamide, and induces partial or complete tumor regression in preclinical (xenograph) models of both castration-sensitive and castration-resistant human prostate cancer. Additional clinical benefit beyond currently available ADT might also be achieved by the use of second-generation anti-androgens in patients with mHSPC.

1.1.2.1. Clinical Studies

Apalutamide is being evaluated in Phase 1, Phase 1/2, and Phase 3 studies in patients with non-metastatic and metastatic CRPC (NM-CRPC and mCRPC).

Study ARN-509-001:

Study ARN-509-001 is an ongoing Open-label, Phase 1/2 dose escalation and proof-of-concept study in subjects with progressive CRPC.[4] The efficacy data included anti-tumor activity, as measured by 12-week PSA percentage change response (defined as ≥50% decline from baseline), was shown in 48% of the Phase 1 subjects across all dose levels. In the Phase 2 portion of the study, the 12-week PSA percentage change response (50% decline from baseline) in the high-risk NM-CRPC cohort (Cohort 1, 51 subjects treated), the mCRPC cohort (no previous abiraterone acetate, enzalutamide or chemotherapy for mCRPC; Cohort 2, 25 subjects treated), and the post abiraterone acetate mCRPC cohort (Cohort 3, 21 subjects treated), was 89%, 88%, and 22%, respectively. As of 31 March 2017, the PSA response rate at any time during the study was 94% for subjects in Cohort 1, 92% for subjects in Cohort 2, and 28% for subjects in Cohort 3.

As of 31 March 2017, the most common drug-related treatment-emergent adverse events (TEAEs) across Cohorts 1, 2, and 3 respectively were fatigue, diarrhea, and nausea. Most

adverse events (AEs) across the cohorts were Grade 1 or 2. Grade 3 AEs in >1 subject included hypertension and hyponatremia, malignant melanoma, and fatigue in Cohort 1; anemia in Cohort 2; and back pain in Cohort 3. Grade 4 TEAEs included abdominal adhesions, duodenal ulcer, anemia, and glioblastoma multiforme in Cohort 1; dehydration, asthenia, and confusional state in Cohort 2; no Grade 4 TEAEs were reported in Cohort 3. The most common TEAE leading to discontinuation was fatigue. Serious adverse events (SAEs) were reported in 32 (33%) subjects. Hypothyroidism or increased blood thyroid stimulating hormone (TSH) was reported as an TEAE in in all 3 cohorts. Most TEAEs of rash or pruritus were Grade 1 or 2 in severity, were treated topically, and none were reported as serious. Over the Phase 2 duration of the study, the TEAE of fracture was reported in Cohorts 1 and 2, and none of the events were considered related to study drug or led to discontinuation of study drug. Falls were only reported in Cohort 1, none of the TEAEs of fall were reported as serious, and none led to discontinuation of study drug.

Currently, there are 4 ongoing, double-blind, placebo-controlled Phase 3 clinical studies: ARN-509-003, 56021927PCR3001, 56021927PCR3002, and 56021927PCR3003. Study ARN-509-003 is a double-blinded study which was unblinded as recommended by the Independent Data Monitoring Committee (IDMC) on 22 July 2017. Subjects randomized to placebo in Study ARN-509-003 have the option to switch to active treatment with apalutamide.

Study ARN-509-003:

This multicenter, randomized, double-blind, placebo-controlled Phase 3 study was designed to demonstrate superiority in the metastasis-free survival (MFS) of men with high-risk NM-CRPC treated with apalutamide versus placebo.[5] The primary data included 1,207 randomized subjects (806 subjects in the apalutamide arm and 401 subjects in the placebo arm). Treatment with apalutamide + ADT significantly decreased the risk of distant metastasis or death in subjects with NM-CPRC by 72% compared with placebo + ADT (hazard ratio [HR]=0.280; 95% confidence interval [CI]: 0.227, 0.346; p<0.0001) by blinded independent central review (US censoring rules), with a median MFS of 40.5 months for the apalutamide arm and 16.2 months for the placebo arm. The result was consistent among all MFS sensitivity analyses, noteworthy: MFS by investigator assessment (HR=0.251; 95% CI: 0.205, 0.308; p<0.0001). The MFS results favored apalutamide across all subgroups such as age, race, geographic region, number of prior lines of hormonal therapy, baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, baseline PSA value, PSA doubling time, use of bone-sparing agents, and the presence of regional nodal disease. All secondary endpoints (time to metastasis, PFS, time to symptomatic progression, OS, and time to initiation of cytotoxic chemotherapy) favored treatment with apalutamide compared to placebo.

A confirmed PSA response was observed in 90% of subjects in the apalutamide arm and 2.2% of subjects in the placebo arm. Treatment with apalutamide + ADT significantly decreased the risk of PSA progression by 94% compared with placebo + ADT (HR=0.064; 95% CI: 0.052, 0.080; p<0.0001). The median time to PSA progression was not estimable for the apalutamide arm and 3.7 months in the placebo arm. The median time from date of randomization to date of disease progression on first subsequent therapy for prostate cancer or death, whichever occurred first

(PFS2) was longer for the apalutamide arm (not estimable) compared with the placebo arm (39 months). There was a 51% reduction in the risk of disease progression during first subsequent therapy or death (PFS2) for subjects originally assigned to the apalutamide + ADT arm compared with the placebo + ADT arm (HR=0.489; 95% CI: 0.361, 0.662; p<0.0001). Patient-reported outcome results indicated that there was no detriment to overall health-related quality of life with the addition of apalutamide to ADT. Similar mean changes from baseline or median time to worsening in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) were observed in the 2 arms. For nearly all time points, no differences between apalutamide and placebo were observed in change from baseline across the EQ-5D index or visual analog scale.

The 3 most frequently reported TEAEs were fatigue, hypertension, and skin rash as a grouped term. Most events of skin rash were Grade 1 or Grade 2 and responded to administration of antihistamines and topical steroids; dose reduction and interruptions were also used to manage skin rash. Similarly, fatigue was mostly Grade 1 or Grade 2 which suggest that the fatigue associated with apalutamide treatment was not disabling or severe enough to interfere with activities of daily living. After adjusting for exposure, hypertension was similar in both arms and was not considered attributable to apalutamide. Fracture as a grouped term was the most commonly reported SAE, and considered serious because fracture in this elderly population often requires hospitalization. Ten percent of subjects in the study used bone-sparing agents such as bisphosphonates and denosumab. In addition to skin rash and fracture, AEs of special interest for apalutamide included fall, hypothyroidism (which was discovered since TSH was regularly monitored in Study ARN-509-003), and seizure. In Study ARN-509-003, 40% to 50% of the fractures reported in both arms were preceded by a fall (another AE of special interest) within 7 days; falls were not typically preceded by syncope or presyncope, but may have been associated with weight loss, weakness, or dizziness/vertigo. When adjusted for exposure, it appeared that apalutamide in combination with ADT did not have a clinically meaningful increase in the incidence of TEAEs compared with subjects who received ADT alone.

Androgen deprivation therapy has been associated with increased risk of cardiovascular events, metabolic syndrome and osteoporosis. Cardiovascular and metabolic TEAEs associated with ADT use were similar between the 2 treatment arms. Fracture as a grouped term was the most commonly reported SAE in the apalutamide arm. An increased fracture risk with apalutamide may be due to an enhanced effect on the AR with apalutamide treatment.

1.2. Overall Rationale for the Study

Recent studies including the Chemo Hormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) comparing ADT plus docetaxel versus ADT alone have provided evidence that combining a short course of docetaxel chemotherapy with ADT may provide benefit especially in patients with high-volume mHSPC.[12,16,32] Of the 790 patients with mHSPC enrolled in the CHAARTED study, 520/790 (67%) patients had high-volume disease defined as visceral metastases or at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis. After a median follow-up of 29 months there was an approximate 13.6-month improvement in median OS in the

intent-to-treat population (ITT) (median OS for ADT plus docetaxel and ADT alone was 57.6 months and 44.0 months, respectively; HR=0.61; 95% CI=0.47, 0.80; p<0.001).

In Study GETUG-AFU-15, 302/385 (78%) of the patients had low- to intermediate-risk disease and 83/385 (22%) had high-risk disease based on the Glass prognostic criteria.[11,12] The median OS from the GETUG-AFU-15 study after a median follow-up of 50 months was 58.9 months in the ADT plus docetaxel group compared with 54.2 months in the ADT group (HR=1.01; 95% CI=0.75, 1.36; p=0.955). No significant differences in median OS between the treatment groups were observed by subgroup. Pooled data for all patients by subgroup showed a longer median OS for the low-risk prognostic group (69.1 months) compared with the intermediate-risk (46.5 months) and high-risk (36.6 months) prognostic groups.

Data from the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) study also demonstrate that patients with mHSPC who are treated with the combination of ADT plus docetaxel (D) have prolonged survival compared with those treated with ADT alone.[16] Standard of care (SOC) was hormone therapy for at least 2 years. Patients were stratified and randomly assigned in a 2:1:1:1 ratio (no blinding to treatment allocation) to receive either SOC (control), SOC + D, SOC + zoledronic acid (ZA) or SOC + D + ZA. Docetaxel was administered at 75mg/m^2 for six 3-weekly cycles. A total of 2,962 patients were randomly assigned to the 4 groups. The groups were balanced with median age 65 years; 61% metastatic, 15% N+/XM0, 24% N0M0; 93% diagnosed within 6 months of randomization; median PSA was 65 ng/mL. Median follow-up was 43 months. There were 415 deaths on the control arm (84% from prostate cancer). The HRs were the following: 0.78 (95% CI 0.66, 0.93; p =0.006) for SOC+D versus SOC, 0.94 (95% CI 0.79, 1.11; p =0.450) for SOC+ZA versus SOC, and 0.82 (95% CI 0.69, 0.97; p = 0.022) for SOC+D+ZA versus SOC. Median survival was increased by 10 months from 71 months on SOC to 81 months on SOC+D. Survival data from the STAMPEDE study show a clinically and statistically significant improvement in survival among men with mHSPC from adding D, but not from adding ZA to SOC.

Androgen deprivation therapy remains an SOC therapy for patients with asymptomatic and symptomatic metastatic (M1) disease according to the European Association of Urology (EAU) guidelines.[13] The European Society of Medical Oncology (ESMO) also recommends continuous ADT as first-line treatment of metastatic hormone-naïve disease.[26] Recent updates to the National Comprehensive Cancer Network (NCCN) and the ESMO guidelines are based on the results from the CHAARTED study.[23, 26] The updated NCCN guideline divides M1 disease into 2 branches based on presence of low- or high-volume disease.[23] Androgen deprivation therapy is recommended for patients with low-volume disease. Androgen deprivation therapy combined with docetaxel (75 mg/m^2 for 6 cycles without prednisone) is recommended for patients with high-volume disease. The ESMO guideline recommends ADT plus docetaxel as first-line treatment for mHSPC in men fit enough for chemotherapy.[26]

Based on the current guidelines, ADT with or without docetaxel is considered the appropriate active control therapy for the patient population to be enrolled in this study. For this reason, prior therapy with docetaxel is allowed and is a stratification factor. There is a clear unmet medical

need for alternative treatment options in mHSPC. Treatments that can delay disease progression and associated morbidities would be of significant clinical benefit in this patient population. Study 56021927PCR3002 is designed to assess the efficacy and safety of the addition of apalutamide to ADT for subjects with mHSPC.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to determine if the addition of apalutamide to ADT provides superior efficacy in improving radiographic progression-free survival (rPFS) or OS for subjects with mHSPC.

Secondary Objectives

- To evaluate clinically relevant improvements with addition of apalutamide to ADT including delays in pain progression and opioid use for prostate cancer, skeletal-related events (SREs), and the need for cytotoxic chemotherapy
- To characterize the safety of adding apalutamide to ADT in subjects with mHSPC
- To characterize the population pharmacokinetics (PK) and pharmacodynamics (PD) of apalutamide
- To evaluate the concentration of leuprolide and assess the PD effect of leuprolide on testosterone concentrations when used alone or in combination with apalutamide
- To evaluate the treatment effectiveness with the addition of apalutamide to ADT for the subpopulations of subjects with low-volume or high-volume mHSPC

Other Objectives

- To evaluate exploratory biomarkers predictive of response and resistance to treatment
- To evaluate patient relevant outcomes including symptoms (ie, pain, fatigue, urination) and function (ie, physical, emotional, social) and health-related quality of life
- To evaluate improvements in other clinically relevant endpoints with the addition of apalutamide to ADT
- To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this study)

2.2. Hypothesis

Apalutamide plus ADT compared with ADT alone will improve rPFS or OS or both and have an acceptable safety profile in subjects with mHSPC.

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 mHSPC will benefit from the addition of apalutamide to ADT. Enrollment of approximately 1,000 subjects is planned for this study. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be stratified by Gleason score at diagnosis, prior docetaxel use, and region then randomly assigned in a 1:1 ratio to the apalutamide plus ADT or matching placebo plus ADT group (see Sections 4 and 5).

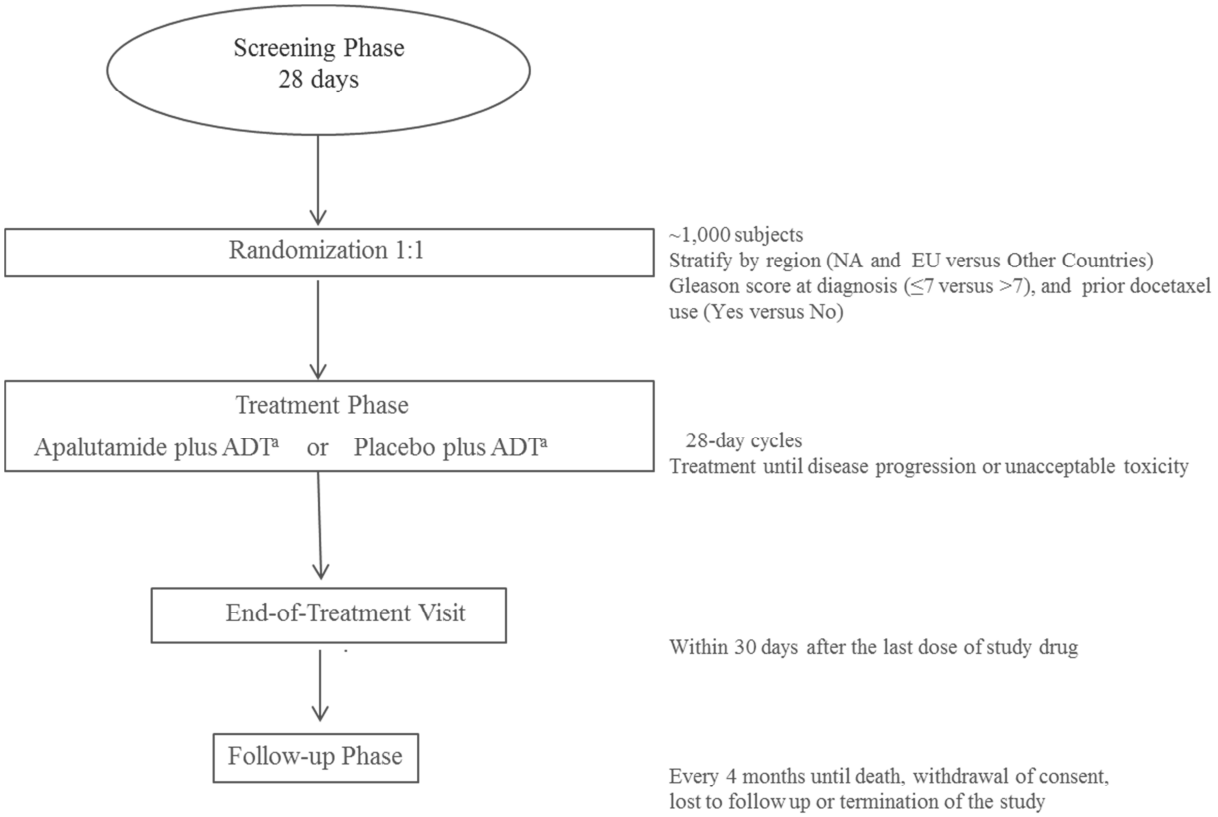
The study will include a Screening Phase of up to 28 days before randomization to establish study eligibility. Subjects will receive treatment in 28-day treatment cycles during the Treatment Phase until disease progression or the occurrence of unacceptable treatment-related toxicity. Subjects must discontinue study drug with documented clinical progression (see Section 10.2). After discontinuation of study drug, subjects will have an End-of-Treatment Visit within 30 days after the last dose of study drug. In the event of a positive study result at either of the interim analyses or at the final analysis, all subjects in the Treatment Phase will have the opportunity to enroll in an Open-label Extension Phase, which will allow subjects to receive active drug (apalutamide) for approximately 3 years (Attachment 6). Subjects who are receiving apalutamide in the Open-label Extension Phase may continue receiving apalutamide in the LTE Phase if they will continue to derive benefit from treatment (based on investigator assessment). The LTE Phase will begin on the date of the CCO FA for the study, or the date of approval of Amendment 5 at the site, whichever comes last (see Attachment 7 for details).

One analysis for rPFS is planned; 2 interim analyses and a final analysis are planned for OS. Details are provided in Section 11.3.2.

Subjects will be monitored for safety starting from the signing of informed consent until 30 days after the last dose of study drug. Adverse events including laboratory AEs will be graded and summarized using Version 4.03 of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE). Dose modifications will be made as required according to dose modification rules (see Section 6.3). An IDMC will be commissioned for the study to provide recommendation during the planned interim efficacy analyses and regular safety reviews (see Section 11.9).

A diagram of the study design is provided below in Figure 1.

Figure 1: Schematic Overview of the Study



[a]ADT=medical castration (ie, gonadotropin hormone releasing analog [GnRHa]; agonists or antagonists) or surgical castration (ie, bilateral orchiectomy); EU=European Union; NA=North America

3.2. Study Design Rationale

Study Treatment

The dose of 240-mg daily of apalutamide is the dose determined from the Study ARN-509-001 PK/PD study and is the therapeutic dose being used in Phase 3 studies (see Section 1.1.2.1).

Blinding, Control, Study Phase/Periods, Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur with active control treatment. Randomization and blinding 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 patient-reported outcome (PRO) data. Androgen deprivation therapy is currently considered SOC for this patient population according the EAU, ESMO, and NCCN guidelines (see Section 1.2).

Patient-reported Outcomes

The goal of collecting PRO data in this study is to explore patient-perceived benefits of treatment in the improvement or delay of prostate cancer symptoms (ie, pain, fatigue, urinary) and the effects on functional status. Additionally, patient reports will provide the opportunity to establish that the addition of apalutamide to ADT does not result in a worse deterioration of functional status resulting from treatment-related side effects compared with placebo plus ADT. The PROs included in this study are the Brief Pain Inventory-Short Form (BPI-SF), Brief Fatigue Inventory (BFI), FACT-P and the EQ-5D-5L. Patient-reported outcome questionnaires will be collected throughout the study (see also Section 9.1.1) as well as during the Follow-up Phase (up to 12 months after treatment discontinuation) and the Open-label Extension Phase as specified in the Time and Events schedules.

Biomarkers

The main goal of the biomarker study is to obtain additional information on resistance mechanisms. Results from a Phase 1 study in patients with mCRPC provide evidence that acquired mutation in AR (AR^{F876L}) may be associated with resistance to apalutamide treatment.[18] Recent results also suggest that expression of the androgen receptor splice variant 7 (AR-V7) in CRPC patients is associated with resistance to abiraterone acetate and enzalutamide.[1,7,20] Preclinical data show that changes in expression or development of mutations in genes including AR anomalies, AR axis genes and compensatory pathway may lead to resistance to enzalutamide or apalutamide treatment.[20] Corresponding markers representing these resistance classes can be detected in either whole blood or plasma.[25,28] Plasma-based circulating DNA will be used to assess the presence of the AR mutation and whole blood will be used to assess AR splice variants. Other markers that may be associated with resistance to apalutamide will be evaluated from whole blood or plasma.

4. STUDY 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. Waivers are not allowed. Eligibility criteria for subjects in the placebo arm who crossover to active treatment with apalutamide (in the event of a positive study result and unblinding) are described in Attachment 6.

4.1. Inclusion Criteria

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

1. Criterion modified per Amendment 1

1.1 Subject must be a man ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place)

2. Criterion modified per Amendment 1

2.1. Diagnosis of prostate adenocarcinoma as confirmed by the investigator

3. Criterion modified per Amendment 1

3.1. Metastatic disease documented by ≥1 bone lesion(s) on Technetium-99m (^{99m}Tc) bone scan. Subjects with a single bone lesion must have confirmation of bone metastasis by computed tomography (CT) or magnetic resonance imaging (MRI).

4. Criterion modified per Amendment 1

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

5. Criterion modified per Amendment 1

5.1. Androgen deprivation therapy (ie, medical or surgical castration) must have been started ≥14 days prior to randomization. Subjects who start a GnRH agonist ≤28 days prior to randomization will be required to take a first-generation anti-androgen for ≥14 days prior to randomization. The anti-androgen must be discontinued prior to randomization.

6. Criterion modified per Amendment 1

6.1. Subjects who received docetaxel treatment must meet the following criteria:

   a. Received a maximum of 6 cycles of docetaxel therapy for mHSPC
   b. Received the last dose of docetaxel ≤2 months prior to randomization
   c. Maintained a response to docetaxel of stable disease or better, by investigator assessment of imaging and PSA, prior to randomization

7. Criterion modified per Amendment 1

7.1. Be able to swallow whole study drug tablets

8. To avoid risk of drug exposure through the ejaculate (even men with vasectomies), subjects must use a condom during sexual activity while on study drug and for 3 months following the last dose of study drug. Donation of sperm is not allowed while on study drug and for 3 months following the last dose of study drug.

9. Each subject must sign an informed consent form (ICF) indicating that he understands the purpose of and procedures, required for the study, and is willing to participate in the study. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol (see Section 4.3).

10. Other allowed prior treatment for mHSPC:

   a. Maximum of 1 course of radiation or surgical intervention; radiation therapy for metastatic lesions must be completed prior to randomization

b. ≤6 months of ADT prior to randomization

11. Allowed prior treatments for localized prostate cancer (all treatments must have been completed ≥1 year prior to randomization)

a. ≤3 years total of ADT

b. All other forms of prior therapies including radiation therapy, prostatectomy, lymph node dissection, and systemic therapies

4.2. Exclusion Criteria

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

1. Pathological finding consistent with small cell, ductal or neuroendocrine carcinoma of the prostate

2. Known brain metastases

3. Criterion modified per Amendment 1

3.1. Lymph nodes as only sites of metastases

4. Criterion modified per Amendment 1

4.1. Visceral (ie, liver or lung) metastases as only sites of metastases

5. Criterion modified per Amendment 1

5.1. Other prior malignancy (exceptions: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) ≤5 years prior to randomization

6. Clinical laboratory values during the Screening Phase:

a) hemoglobin <9.0 g/dL

b) neutrophils <1.5 x 10^9/L

c) platelets <100 x 10^9/L

d) total bilirubin >1.5 x upper limit of normal (ULN) [NOTE: in subjects with Gilbert's syndrome, if total bilirubin is >1.5 x ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 x ULN, subject may be eligible]

e) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 x ULN

f) serum creatinine >2.0×ULN

g) serum albumin <3.0 g/dL

7. Criterion modified per Amendment 1

7.1. Criterion modified per Amendment 4

7.2. Prior treatment with other next generation anti-androgens (eg, enzalutamide), CYP17 inhibitors (eg, abiraterone acetate), immunotherapy (eg, sipuleucel-T), radiopharmaceutical agents or other treatments for prostate cancer except those listed in Inclusion Criteria #5.1, #6.1, #10, and #11 (see also Section 8.2)

8. Criterion modified per Amendment 1

8.1. Initiation of treatment with a bisphosphonate or denosumab for the management of bone metastasis ≤28 days prior to randomization

9. Criterion modified per Amendment 1

9.1. Medications known to lower the seizure threshold must be discontinued or substituted ≥28 days prior to randomization (see Section 8.2)

10. Criterion modified per Amendment 1

10.1. Administration of other investigational therapeutic agents, blood product support, growth factor support or invasive surgical procedure (not including surgical castration) ≤28 days prior to randomization or currently enrolled in an investigational study

11. Current or prior treatment with anti-epileptic medications for the treatment of seizures. History of seizure or condition that may predispose to seizure (including, but not limited to prior cerebrovascular accident, transient ischemic attack, or loss of consciousness within 1 year prior to randomization; brain arteriovenous malformation; or intracranial masses such as a schwannoma or meningioma that is causing edema or mass effect).

12. Criterion modified per Amendment 1

12.1. Current evidence of any of the following:

a) Severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, uncontrolled hypertension, clinically significant arterial or venous thromboembolic events (eg, pulmonary embolism), or clinically significant ventricular arrhythmias ≤6 months prior to randomization

b) Gastrointestinal disorder affecting absorption

c) Active infection requiring systemic therapy such as human immunodeficiency virus (HIV)

d) Active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction

13. Subject has known allergies, hypersensitivity, or intolerance to apalutamide or its excipients (refer to Investigator's Brochure)

14. Any condition or situation that in the opinion of the investigator, would preclude participation in this study

4.3. Prohibitions and Restrictions

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

1. Refer to Section 8 for details regarding prohibited and restricted therapy during the study

2. If the subject is engaged in sexual activity with a partner, a condom is required.

   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 (IUS) system;
   - 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 Treatment Phase and for 3 months after the last dose of study drug.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Stratification and Randomization

Subjects will be stratified by Gleason score at diagnosis (≤7 versus >7), region (North America [NA] and European Union [EU] versus Other Countries), and prior docetaxel use (Yes versus No). Subjects will be randomly assigned to the active or control group in a 1:1 ratio. The randomization will be balanced by using randomly permuted blocks. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

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 in the event of an emergency for an individual subject.

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. Otherwise, the blind should be broken only if the specific course of action for a safety issue 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 by the IWRS, in the appropriate section of the electronic case report form (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.

Unblinding may also be performed after the subject discontinues from the Treatment Phase of study because of radiographic progression and the investigator feels this information is essential to determine the next course of therapy. Unblinding a subject for this situation may only take place after discussion with the sponsor’s medical officer. 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

6.1. Study Drug Administration

Study drug will be administered on a continual basis, but for the purpose of scheduling the study assessments and treatment compliance, a treatment cycle is defined as 28 days. Subjects will be randomly assigned in a 1:1 ratio to receive either apalutamide or matching placebo

- JNJ-56021927 (apalutamide) 240-mg (4 x 60-mg tablets); taken orally once daily with or without food or
- Placebo (4 tablets); taken orally once daily with or without food

If a dose of apalutamide (or placebo) is missed it should be omitted and will not be made up or taken with the next dose the following day. Please refer to the pharmacy manual/study-site investigational product manual for further details. Study drug administration must be captured in the source documents and the eCRF.

See the Time and Events Schedule for details on timing of drug administration during PK collection.

6.2. ADT Administration

All subjects who did not undergo surgical castration, will receive and remain on a stable regimen of ADT. The choice of the GnRHa (agonist or antagonist) will be at discretion of the Investigator. Dosing (dose and frequency of administration) will be consistent with the prescribing information. For subjects who did not undergo surgical castration, concurrent treatment with a GnRHa must be documented in the eCRF.

6.3. Toxicity and Rash Management

Table 1 summarizes apalutamide/placebo dose modifications for drug-related toxicities. Dose modifications for drug-related rashes are summarized in Table 2. Once the dose is reduced for drug-related toxicities, a re-escalation of the dose should be discussed with the sponsor.

Table 1: Dose Modifications of Apalutamide/Placebo (except for rash, if rash occurs, see Table 2)

Severity	**Number of apalutamide/placebo tablets**
Grade 1 or 2	No change or hold until return to baseline
≥Grade 3	Hold until Grade 1 or baseline, resume at full dose
Recurrence ≥Grade 3	Hold until Grade 1 or baseline; 2 dose reductions are allowed for recurrent treatment-related toxicity (180 mg [3 tablets]) and 120 mg [2 tablets]). Discontinue if toxicity persists after 2 dose reductions.
First occurrence of seizure of any grade or Grade 4 neurotoxicity	Discontinue
Note: Adverse events are graded according to NCI-CTCAE Version 4.03	

If the skin rash has any component of desquamation, mucosal involvement, or pustules, stop dosing with apalutamide/placebo, refer to dermatology for evaluation, and a skin biopsy is recommended (in addition to the interventions listed in Table 2) (and complete the skin rash eCRF). If the skin rash is Grade 3 or higher, asking the subject to consent to documentation by a photograph and further evaluation by dermatology should also be considered (and complete the skin rash eCRF). Also complete the skin rash eCRF if the skin rash leads to permanent discontinuation of study drug.

Table 2 Management of Drug-Related Rash

Severity	Intervention

Grade 1	• Continue apalutamide/placebo at current dose
	• Initiate dermatological treatment[a]
	  ○ Topical steroid cream AND
	  ○ Oral antihistamines
	• Monitor for change in severity[a]

Grade 2 (or symptomatic Grade 1)[b]	• At investigator discretion, hold apalutamide/placebo for up to 28 days
	• Initiate dermatological treatment[a]
	  ○ Topical steroid cream AND
	  ○ Oral antihistamines
	• Monitor for change in severity[a]
	  ○ If rash or related symptoms improve, reinitiate apalutamide/placebo when rash is Grade ≤1. Consider dose reduction at 1 dose level reduction.

Grade ≥3[d]	• Hold apalutamide/placebo for up to 28 days
	• Initiate dermatological treatment[a]
	  ○ Topical steroid cream AND
	  ○ Oral antihistamines AND
	  ○ Consider short course of oral steroids
	• Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the subject to a dermatologist
	  ○ Reinitiate apalutamide/placebo at 1 dose level reduction[c] when rash is Grade ≤1.
	  ○ If the dose reduction will lead to a dose less than 120 mg, the study drug must be stopped (discontinued)
	• If after 28 days, rash has not resolved to Grade ≤1, contact the sponsor to discuss further management and possible discontinuation of study drug

Note: Rash may be graded differently according to the type of rash and associated symptoms. For example, maculopapular rash is graded by body surface area covered and not severity of the rash. Please consult NCI-CTCAE Version 4.03 for specific grading criteria for other types of rash.

a. Obtain bacterial/viral cultures if infection is suspected
b. Subject presents with other rash-related symptoms such as pruritus, stinging, or burning
c. If a subject previously started oral corticosteroids continue for at least 1 week after resumption of reduced dose of apalutamide/placebo. If the proposed total oral steroid use will exceed 28 days, contact the sponsor.
d. If there is blistering or mucosal involvement, stop apalutamide/placebo dosing immediately and contact the sponsor

7. TREATMENT COMPLIANCE

Accurate records of all drug shipments as well as tablets dispensed and returned will be maintained. This inventory must be available for inspection by designated sponsor or regulatory authority representatives at any time. Drug supplies are to be used only in accordance with this protocol and under the supervision of the investigator. Study drug administration and dosing compliance will be assessed at each study visit, starting with Cycle 2. A count of all study drug provided by the sponsor will be conducted during the Treatment Phase and Open-label Extension Phase of this study.

The investigator or designated study-site personnel will be responsible for providing additional instruction to any subject who is not compliant with taking the study drug. 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 (see also Section 14.5).

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy and concomitant therapies must be recorded on the subject's eCRF throughout the study beginning with the signing of the ICF until 30 days after the last dose of study drug. Medications (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 Therapies

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

- Intermittent short course of opioid analgesics is allowed for pain control (see also Section 10.2 regarding the use of chronic opioid analgesics for pain)
- Surgical interventions and procedures such as transurethral resection of the prostate (TURP) and placement of ureteral stents for the management of complications due to local progression
- Bisphosphonates and denosumab for management of bone-related metastasis should be used according to their market authorized approved label. Subjects should be either on a stable dose of such agents for ≥28 days prior to randomization, or agree not to initiate such therapy until radiographic progression is documented. Bisphosphonates and denosumab at doses for prevention of osteoporosis are allowed
- Conventional multivitamins, selenium and soy supplements
- Transfusions and hematopoietic growth factors per institutional practice guidelines (Note that blood product support and growth factor support are not allowed in the period of ≤28 days prior to randomization)
- Immunoglobulin therapy for non-cancer-related treatment per institutional practice guidelines

8.2. Prohibited Concomitant Therapies

As a class effect, AR antagonists have been associated with seizures due to an off-target mechanism of action (gamma amino butyric acid chloride channel [$GABA_A$] inhibition). Drugs known to lower the seizure threshold or cause seizures are prohibited and a representative list is included below:

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

Other prohibited therapies include the following:

- Investigational agents
- Abiraterone acetate or other CYP17 inhibitor
- Other hormonal agents for the treatment of prostate cancer
- Other antineoplastic agents
- Radiation therapy for new painful metastatic prostate cancer lesions that were not present on baseline imaging
- 5-α-reductase inhibitors
- Chemotherapy
- Immunotherapy or vaccine therapy for cancer treatment
- Other anti-androgens (eg, bicalutamide, nilutamide, flutamide, cyproterone acetate, enzalutamide)
- Bisphosphonates or denosumab for management of bone metastasis unless such therapy was started >28 days prior to randomization and subjects have been on a stable dose. Bisphosphonate or denosumab at doses for osteoporosis prophylaxis is allowed
- 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, which are thought to have endocrine effects on prostate cancer
- Radiopharmaceuticals such as strontium (^{89}Sr) or samarium (^{153}Sm) or similar analogs such as radium-223 (^{223}Ra)
- Spironolactone

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

8.3. Restricted Concomitant Medications

Investigators should 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. Highlights of drug interaction are summarized below. Additional information is provided in Attachment 3.

- Medications that inhibit CYP2C8 or CYP3A4: Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl apalutamide). No initial dose adjustment is necessary; however, consider reducing the apalutamide dose based on individual tolerability (see Section 6.3). Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.
- Effect of apalutamide on drug metabolizing enzymes: Apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of apalutamide with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 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.
- Long-term use of systemically administered corticosteroids during the study is not allowed. Short-term use (≤4 weeks, including taper) and locally administered steroids (eg, inhaled, topical, ophthalmic, and intra-articular) are allowed, if clinically indicated.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

- The Time and Events Schedule summarizes the frequency and timing of efficacy, biomarkers, PROs, MRU, PK, and safety measurements applicable to this study
- Refer to Section 9.2 for additional details on the efficacy evaluations
- PK trough samples will be collected (see also Section 9.3)
- Refer to Section 9.4 for details on biomarker evaluations
- Medical resource utilization data will be collected (see also Section 9.5)

- Refer to Section 9.6 for additional details on the safety evaluations
- The total blood volume per subject is dependent on number of cycles of treatment. A summary per visit is provided in Table 3. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
- All available PSA values that were obtained in the year prior to randomization must be recorded in the eCRF

All PRO measures will be completed by the subject using a handheld electronic patient-reported outcome (ePRO) device. During screening, study-site personnel will train the subjects on how to use the ePRO device, including instructions to capture the data according to the study design and not to wait until the study-site visit to record information. Subjects will be provided with written instructions on how to get 24-hour technical support, if needed, for operation of the ePRO device.

During clinic visits, all PRO measures should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions. For cycles without a scheduled clinic visit and where a PRO measure is required, the questionnaires will be completed remotely. During the Follow-up Phase all PRO questionnaires will completed remotely (see also the Time and Events Schedule, Sections 9.1.3, and 9.2.1 for more details on the PRO measures).

Table 3: Summary of Blood Volumes (mL) Per Visit

	SCR	C1D1	C3D1	C5D1	C12D1	D1 of Cycles 2, 3, 4, 5, and 6	D1 of C2 to C13, then D1 of q2 cycles to C25, then D1 of q4 cycles until EOT, unless otherwise specified	EOT	Open-label Extension Phase[c]
Safety/Efficacy									
Serum Chemistry (including LFTs, lipids)[a]	2.5						2.5[a]	2.5	2.5
Hematology	2.0						2.0	2.0	2.0
TSH (T3, T4, & free T4[b])	3.5			3.5[b]			3.5[b]	3.5	3.5
PSA[c]	2.5	2.5					2.5	2.5	2.5
Total blood volume per visit	**10.5**	**2.5**					**7.0 or 10.5**	**10.5**	**10.5**
Trough PK sampling						**2.0**			
Leuprolide Sub-study[d]		**4.0**				**4.0**			
Biomarkers (BM)									
Plasma		10.0			10.0			10.0	10
Whole blood		2.5			2.5			2.5	2.5
Total blood volume for BM per visit		**12.5**			**12.5**			**12.5**	

BM=biomarkers; C=cycle; D=day; EOT=End-of-Treatment; LFT=liver function tests; PK=pharmacokinetics; PSA=prostate-specific antigen; q2 cycles=every 2 cycles; q4 cycles=every 4 cycles; q12 cycles = every 12 cycles; SCR=screening; TSH=thyroid stimulating hormone

[a]Fasting lipids at SCR and D1 of C12, C25 then q12 cycles

[b]TSH at SCR, D1 of q4 cycles starting at Cycle 5, and EOT

[c]During the Open-label Extension Phase, serum chemistry, hematology and PSA for subjects not requiring cross-over and were receiving apalutamide, D1 of C1 then D1 of q4 cycles; TSH, D1 of C1, D1 of C5, then D1 of q4 cycles, and fasting lipids D1 of C1, D1 of C13, then D1 of q12 cycles. Subjects crossing over from placebo to apalutamide serum chemistry, hematology and PSA; D1 of C1 to C7, then D1 of q2 cycles to C13, then D1 of q4 cycles until EOT, unless otherwise specified; TSH D1 of C1, D1 of C5, then D1 of q4 cycles, and fasting lipids D1 of C1, D1 of C13, then D1 of q12 cycles.

[d]For at least 60 consenting subjects participating in the optional leuprolide sub-study an additional 4 mL of blood will be drawn on D1 of C1, C3, C4, C5, and C6 (see Attachment 5).

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 Events Schedule. Screening procedures will be performed up to 28 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 after receiving approval from the sponsor. 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. Re-screening 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 ICF before re-screening. Subjects rescreened within 28 days of planned randomization may use the initial screening laboratory results, CT/MRI and bone scans to determine eligibility. Re-screening and subsequent randomization activities 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 drug is discontinued. Subjects should start study drug within 3 calendar days after randomization. Visits for each cycle will have a ±2-day window except for CT/MRI and bone scans (imaging visits may occur up to 8 days before cycles). Study visits will be calculated from the Cycle 1 Day 1 date. 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 drug or at screening (whichever value was last) will be defined as the baseline values.

After the PRO questionnaires have been administered, a symptom-directed physical exam and laboratory testing scheduled for the same visit will be conducted. Adverse events and changes to concomitant medications will be recorded. Subjects will be evaluated throughout this phase for possible toxicities. Dose modifications for toxicity will be made as according to criteria described in Section 6.3.

During the Treatment Phase, investigators will review all clinical, laboratory and imaging data, and will use this information to make decisions about dose modification and study medication discontinuation. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. The subject should refrain from taking study drugs on the morning of study visits designated for trough PK sampling until seen at the site. Treatment will continue until disease progression or the occurrence of unacceptable treatment-related toxicity. 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 clinical progression is documented (see Section 10.2). Once the subject discontinues study drug, the subject will complete the End-of-Treatment (EOT) Visit.

9.1.4. End-of-Treatment Visit

An EOT Visit will 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 the subject withdrew consent to study participation. Subjects who discontinued from treatment due to progression, AE, or other reasons should have the EOT Visit completed before starting any subsequent therapy 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.

9.1.5. Follow-up Phase

The Follow-up Phase should begin once a subject discontinues study drug for any reason. During the Follow-up Phase information will be collected every 4 months until death, withdrawal of consent, lost to follow-up or termination of the study. The information collected during follow-up will include the following: survival, data on secondary endpoints (see Section 9.2.3), first subsequent therapy for prostate cancer, date and type of disease progression (radiographic, PSA, clinical or a combination) on the first subsequent systemic therapy for prostate cancer, and PROs (see Time and Events Schedule). Some follow-up information may be performed by telephone interview or chart review or other convenient methods, and will be reported on the eCRF.

During the Follow-up Phase, deaths regardless of causality and treatment-related SAEs will be collected and reported within 24 hours of discovery or notification of the event on the eCRF.

9.1.6. Open-label Extension Phase

In the event of a positive study result (for rPFS or OS) at any of the planned analyses and notification of unblinding, all subjects in the Treatment Phase will have the opportunity to enroll in the Open-label Extension Phase of this protocol (Attachment 6). The Open-label Extension Phase will allow subjects to receive active drug (apalutamide plus ADT) for approximately 3 years. Subjects who were previously receiving placebo in the Treatment Phase will be allowed to receive apalutamide. All subjects must sign the ICF for the Open-label Extension Phase. Laboratory evaluations and follow-up data collection will continue as noted in the Time and Events Schedule for the Open-label Extension Phase. Adverse events and concomitant medications for AEs will be collected from the signing of the ICF for the Open-label Extension Phase until 30 days after the last dose of study drug.

9.1.7. Long-Term Extension Phase

Subjects who are receiving apalutamide in the Open-label Extension Phase may continue receiving apalutamide in the LTE Phase if they will continue to derive benefit from treatment (based on investigator assessment). The LTE Phase will begin on the date of the CCO FA for the study, or the date of approval of Amendment 5 at the site, whichever comes last (see Attachment 7 for details).

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 [abdomen, chest, and pelvis], ^{99m}Tc bone scans). The same imaging modality 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 attributed to another cause, worsening ECOG PS status grade, or physical examination findings consistent with disease progression, are recorded.

- Serum PSA evaluations (performed at a central laboratory); see also Section 9.6
- Skeletal-related event (SRE) is defined as the occurrence of symptomatic pathological fracture, spinal cord compression, radiation to bone, or surgery to bone.
- Pain progression is defined as an increase by 2 points from baseline in the BPI-SF worst pain intensity (item 3) observed at 2 consecutive evaluations ≥4 weeks apart; with an average worst pain score of >4 in subjects who have had no decrease in opioids or initiation of chronic opioids (see Section 10.2 for definition), whichever occurs first.

Patient-reported Outcomes

See the Time and Events Schedule for the timing of all questionnaires.

The BPI-SF includes a front and back body diagram for the subject to identify the location of his pain, 4 pain severity items (worse, least, average and now) and 7 pain interference items all rated on 0 to 10 scales. Item level analysis is used for the 4 pain severity items. The interference items measure how much pain has interfered with 7 daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. BPI pain interference is scored as the mean of the 7 interference items.[36]

In the Analgesic Use Log, subjects will be asked if they have taken any treatments or medications for their pain other than study drug. If they answer "yes" they will be taken to a list of pain medications to select the medications they have taken. If the medication they have taken is not on the list they can select "other".

The BFI was developed to assess the severity and impact of cancer-related fatigue. This instrument includes a total of 9 items, 3 severity items (now, average and worse) and 6 fatigue interference items all rated on 0 to 10 scales. Item level analysis is used for the fatigue severity items. A global fatigue score will be obtained by averaging all the interference items on the BFI.

The FACT-P will provide an assessment of the subject's self-reported functional status, well-being, and prostate cancer-related symptoms. The FACT-P questionnaire includes a general functional status scale (consisting of 4 subscales: physical well-being, social and family well-being, emotional well-being, and functional well-being) and a prostate-cancer-specific subscale with items including urination, bowel movement, erectile function. Total score is calculated with general function and prostate-cancer-specific scores, and ranges from 0 to 156 (higher scores indicate better functional status).

The EQ-5D-5L is a standardized measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL Group, 1990). The EQ-5D-5L is applicable to a wide range of health conditions and treatments. EQ-5D-5L essentially consists of 2 elements: The EQ-5D-5L descriptive system and the EQ Visual Analog Scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following

5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and unable to/extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state which can be converted into a single summary index (EQ-5D-5L index) by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The EQ VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. The EQ VAS can be used as a quantitative measure of health outcome as judged by the individual respondents. The EQ-5D-5L assessment will provide estimates of utility to include in future cost-effectiveness models.

9.2.2. Tumor Response Criteria

Tumor response will be assessed utilizing imaging measurements, as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1, Attachment 1).[8] In this study, RECIST has been modified based on Prostate Cancer Working Group 2 (PCWG2) criteria, which are specific for this patient population. Prostate-specific antigen measurements will be evaluated according to PCWG2 criteria.[29]

Evaluation of rPFS will be assessed by the investigator as detailed in the Imaging Manual. (see also Section 9.2.3 for definitions). All subject scans (CT/MRI and ^{99m}Tc 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 or Investigator Site File.

9.2.3. Endpoints

The primary and secondary endpoints described below will be used to demonstrate clinical benefit.

Dual-Primary Endpoints

The dual-primary endpoints are rPFS and OS.

rPFS

Radiographic progression-free survival, as assessed by the investigator is defined as the duration from the date of randomization to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurs first.

Radiographic progressive disease in this protocol is defined as one of the following:

- Progression of soft tissue lesions measured by CT or MRI as defined by modified RECIST 1.1 (Attachment 1)
- A subject is considered to have radiographic progression by bone scan if:
  - 1. Subjects who are observed to have ≥2 new bone lesions on the Cycle 3 bone scan compared with the baseline bone scan will need to have a confirmatory bone scan performed at ≥6 weeks later and their scans will be subjected to the 2+2 rule as follows:
    - Subjects with a confirmatory scan that shows ≥2 new bone lesions compared with the Cycle 3 bone scan (ie, at least 4 new lesions compared with the baseline bone scan) will be considered to have radiographic progression by bone scan. The date of progression will be the date of the Cycle 3 bone scan.
    - Subjects who have a confirmatory scan that does not show ≥2 new bone lesions compared with the Cycle 3 bone scan will not be considered to have radiographic progression by bone scan. In order to be considered to have radiographic progression by bone scan, these subjects will need to have a subsequent bone scan with observation of ≥2 new bone lesions compared with the Cycle 3 bone scan. The date of progression would be the date of the FIRST subsequent bone scan with ≥2 new bone lesions compared with the Cycle 3 bone scan.
  - 2. Subjects whose Cycle 3 bone scan does not show ≥2 new bone lesions compared with baseline bone scan will not need to have a confirmatory bone scan performed and will not be considered to have radiographic progression by bone scan at that time. In order to be considered to have radiographic progression by bone scan, these subjects will need to have a subsequent bone scan with ≥2 new bone lesions compared with the baseline bone scan. The date of radiographic progression by bone scan will be the date of the FIRST subsequent bone scan with ≥2 new bone lesions compared with the baseline bone scan.

OS

Overall survival is defined as the time from date of randomization to date of death from any cause.

Secondary Endpoints

- Time to pain progression is defined as the time from the date of randomization to the date of the first observation of pain progression (see also Section 9.2.1)
- Time to SRE is defined as the time from the date of randomization to the date of the first observation of an SRE as defined in Section 9.2.1
- Time to chronic opioid use is defined as the time from date of randomization to the first date of confirmed chronic opioid use (see also Section 10.2)
- Time to initiation of cytotoxic chemotherapy is defined as the time from date of randomization to the date of initiation of cytotoxic chemotherapy

Other Endpoints

- Time to symptomatic local progression such as urethral obstruction or bladder outlet obstruction, is defined as the time from date of randomization to date of symptomatic local progression, whichever occurs first

- Time to PSA progression is defined as the time from the date of randomization to the date of PSA progression based on PCWG2 criteria[29]
- Explore response markers for apalutamide, AR gene anomalies and other markers previously shown to be responsible for resistance to apalutamide
- Prostate cancer-specific survival is defined as the time from randomization to the date of death if attributed to prostate cancer
- PFS2 is defined as the time from date of randomization to date of first occurrence of disease progression on first subsequent therapy for prostate cancer or death, whichever occurs first
- Time to ECOG PS grade deterioration is defined as the time from date of randomization to the first date of deterioration in ECOG PS grade (defined as the worsening of ECOG PS grade by at least 1 point)
- Change from baseline over time in each of the subscales of FACT-P, EQ-5D-5L VAS, BPI-SF interference subscale and BFI

9.3. Pharmacokinetic Evaluations

Trough pharmacokinetic samples for analysis of apalutamide and its active metabolite (JNJ-56142060) will be collected as described in the Laboratory Manual. See the Time and Events Schedule for the timing of sample collections.

Pharmacokinetic samples for analysis of leuprolide will also be collected from at least 60 consenting subjects (in selected countries) who received or will receive leuprolide acetate as the GnRHa. See Attachment 5 for details on this sub-study.

9.3.1. Analytical Procedures

Pharmacokinetic samples collected from both treatment groups will be assayed for apalutamide and JNJ-56142060 using a validated analytical method. Pharmacokinetic samples collected from the leuprolide PK sub-study will be assayed for leuprolide using a validated analytical method.

9.4. Biomarker Evaluations

Optional Plasma samples will be collected from consenting subjects on Day 1 of Cycles 1 and 12, and from consenting subjects in the Open-label Extension Phase and the EOT Visit. Whole blood will also be collected from consenting subjects at the same time points as the plasma samples. The timing of sample collection at Cycle 12 is intended to evaluate early emergence of acquired resistance such as AR mutation.[18]

Optional Archival formalin-fixed paraffin-embedded (FFPE) tumor blocks or tumor slides will be collected from consenting subjects in this study to evaluate mRNA expression of genes representing high-risk disease, AR signaling strength, and other important subtypes of prostate cancer. The information obtained could allow a comparison of the biology of high- and low-volume disease with outcome and guide therapies in these settings. Tissue slides will also be evaluated by immunohistochemistry for immune markers such as OX40, GITR, and FOXP3. This will allow selection of high-risk patients with increased tumor immune infiltrates.

Other markers associated with the disease and treatment may also be evaluated based on emerging evidence from ongoing studies or published data. Planned biomarker analyses will be deferred if emerging study data show no likelihood of providing useful scientific information.

9.5. Medical Resource Utilization

Medical resource usage data associated with medical encounters will be collected in the eCRF by the investigator and staff for all subjects during the Treatment Phase. For each reported AE, MRU information associated with that AE should also be recorded when possible. 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 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)

9.6. 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.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative). Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF. If an AE of rash develops and photographs are taken, the photos may be submitted to the sponsor.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. Required laboratory tests must be performed within 2 days of the scheduled visit. 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 (see also Time & Events Schedule):

- Hematology Panel*

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

*A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory.

- Serum Chemistry Panel

  -sodium
  -potassium
  -creatinine
  -total protein
  -lactic acid dehydrogenase (LDH)
  -calcium
  -albumin (at Screening only)

- Liver Function tests

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

- Fasting Lipid Panel

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

- Other Laboratory Tests

  -Testosterone*
  -TSH (see Time and Events Schedule for more details)
  -PSA**

*Testosterone concentrations will only be determined for those subjects participating in the leuprolide acetate sub-study (see Attachment 5).
**The PSA results for Cycles 1 to 4 will be blinded to the investigator. Beginning with Cycle 5 and for all subsequent cycles, the PSA results will be available to the investigator.

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.

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, 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 are required.

Eastern Cooperative Oncology Group (ECOG) PS

When scheduled, ECOG PS assessments as with PRO questionnaires should be obtained prior to any other study procedures planned for the same day.

9.6.1. Safety Assessments

- Medical history, vital signs (blood pressure), ECG (screening only), ECOG PS, and limited symptom-directed physical examination and body weight
- Concomitant therapy and procedures
- Adverse events and SAEs, including laboratory test AEs will be graded and summarized according to NCI-CTCAE; Version 4.03)
- Blood chemistry, hematology, fasting lipids, TSH (see Time and Events Schedule for more details on TSH)

An IDMC will be commissioned for this study and will be responsible for review of periodic evaluations of safety and efficacy during the study as outlined in a separate IDMC charter (see also Section 11.9).

9.7. 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 has 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 Drug

If a subject's study drug must be discontinued before disease progression this will not result in automatic withdrawal of the subject from the study. If the subject has radiographic progression

without clinical progression and alternate therapy is not initiated, treatment may continue until clinical progression is observed. All attempts should be made to capture radiographic progression even in subjects who have evidence of clinical progression.

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

- Clinical progression defined as:
  - Deterioration in ECOG PS grade to grade 3 or higher (related to prostate cancer progression)
  - Need to initiate any of the following because of tumor progression (even in the absence of radiographic evidence of disease)
    - Subsequent anti-cancer therapy for metastatic prostate cancer
    - Radiation therapy for metastatic prostate cancer lesion(s) (palliative radiation to lesions existing at baseline will not be considered clinical progression)
    - Surgical interventions for complications due to metastatic prostate cancer progression. (Note: Surgical interventions for complications of local-regional progression are not considered clinical progression)
    - Need for chronic opioid analgesics: For subjects entering the study without receiving opioids, chronic opioid use is defined as administration of opioid analgesics lasting for ≥3 weeks for oral or ≥7 days for non-oral formulations. For subjects entering the study already receiving opioids, chronic opioid use is defined as a ≥30% increase in total daily dose of the opioid analgesics lasting for ≥3 weeks for oral or ≥7 days for non-oral formulations. 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)
- More than 2 dose level reductions for Grade 3 or higher treatment-related AEs (see Table 1 and Table 2)
- Seizure of any grade or Grade 4 neurotoxicity
- Subjects who have had their treatment assignment unblinded for any reason except for IDMC recommendation to unblind the study
- 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 EOT Visit should be made to assess for radiographic progression. Study drug will be continued for subjects who have increasing PSA values in the absence of radiographic or clinical progression. Although serial PSA measurements will be performed in this study, progression or change in PSA values should not be used as the lone indicator for disease progression or treatment discontinuation. If a

subject discontinues study drug, but does not withdraw consent for follow-up, scheduled assessments should continue according to the Follow-up Phase in the Time and Events Schedule.

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
- Study is terminated by the sponsor

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 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).

If a subject discontinues study treatment before documented disease progression or occurrence of unacceptable toxicity, end-of-treatment and follow-up assessments should be obtained.

If a subject withdraws consent for study participation 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.

10.4. Withdrawal From the Use of Research Samples

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

- The collected samples will be retained and used in accordance with the subject's original separate informed consent for optional research samples.
- The subject may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study-site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study-site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of 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. Subject Information

ITT Population: The ITT population includes all randomized subjects classified according to their assigned treatment group, regardless of the actual treatment received. Subject disposition and efficacy analyses will be performed on data from the ITT population.

Safety Population: The safety population includes all subjects who received at least 1 dose of study drug as treated.

Patient-reported Outcomes Population [PRO]: The PRO population includes randomized subjects who have completed at least the baseline assessment of BPI-SF, BFI, FACT-P or EQ-5D-5L questionnaires.

Biomarker Population: The biomarker population includes 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 ADT or placebo and ADT. An overall type I error of 5% is planned for this study. This study utilizes the dual-primary endpoints of rPFS and OS with a 0.005 level of significance allocated for the rPFS endpoint and 0.045 is allocated for OS. The study is considered a success if at least one of the dual-primary endpoints is statistically significant. The study is sized to detect the hypothesized HR for the rPFS and OS endpoints.

It is assumed that the failure distribution of the dual-primary endpoint, rPFS follows an exponential distribution with a constant hazard rate. It is estimated that approximately 368 rPFS events would be required to provide at least 85% power in detecting a HR of 0.67 (median rPFS of 20 months for the control group [ADT] versus 30 months for the treatment group of apalutamide plus ADT) at a 2-tailed significance level of 0.005. The assumption of 20 months for the control group is an estimate based on published data.[12,16,32] The study will also provide sufficient power (approximately 80%) to detect a HR of 0.75 in the dual-primary endpoint of OS with an assumed median OS of 44 months (based on published data in a similar patient population) for the control group (ADT).[12,32] Approximately 410 death events will be required to detect the assumed HR at a 2-tailed significance level of 0.045 with enrollment duration of

approximately 30 months (approximately 1,000 subjects). The total study duration will be approximately 54 months to obtain 410 deaths.

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 analysis set. Kaplan-Meier product limit method and Cox proportional hazards model will be used to estimate the time-to-event variables and to obtain the HR along with the associated confidence intervals. Unless otherwise specified, stratified log-rank test will be used to test the treatment effect for time-to-event variables. 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. Subgroup analysis will be performed based on data from subjects with low-volume and those with high-volume mHSPC. High-volume mHSPC is based on an adaptation of the CHAARTED study and is defined as 1) visceral metastases and at least 1 bone lesion or 2) at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis (see also Section 1.2).[32] Low-volume mHSPC is defined as the presence of bone lesion(s) not meeting the definition of high-volume mHSPC.

11.3.1. Analysis of the PRO Data

Descriptive statistics of each PRO scale score from the FACT-P, BPI-SF, and BFI 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. The EQ-5D-5L VAS will be described using summary statistics (n, mean, median, etc.).

11.3.2. Analysis of the Dual-Primary Endpoints

[redacted]

The progression events of the rPFS endpoint will be based on the investigator radiographic assessment of progression. No interim analysis is planned for the rPFS endpoint.

For the dual-primary OS endpoint, 2 interim analyses are planned for this study after observing approximately 50% (~205 events) and approximately 70% (~287 events) of the total number of required (410) events. At the time of the first interim analysis of OS, the final analysis of the rPFS dual-primary endpoint will also be performed. [redacted]. The exact significance levels

will be determined according to the observed number of events at the time of analysis. At the time of the first interim analysis of OS, it is anticipated that all 1,000 subjects will have been enrolled into the study.

In addition, 2-year and 3-year survival rates will be estimated using the Kaplan-Meier method. Additional subgroup analyses for rPFS and OS on subjects with low- or high-volume mHSPC disease will be performed at the time of subsequent OS analysis without alpha spending assigned.

11.3.3. Analysis of the Secondary Endpoints

The analysis of the secondary endpoints will be performed at the time of the first interim analysis in a similar manner as for the dual-primary endpoints.

11.4. Pharmacokinetic Analyses

Population PK analysis of plasma concentration-time data of apalutamide will 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 to measures of efficacy and AEs may also be analyzed. The population PK/PD analysis results will be presented in a separate report. For details on the analysis of the samples from the leuprolide sub-study, see Attachment 5.

11.5. Biomarker Analyses

Initial biomarker analyses will be conducted on 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 based on previously reported data and is sufficient to estimate the frequency of AR mutation and AR-V7 splice variants (95% CI) and to provide 80% power to detect associations with treatment response at a significance level of 0.05.[1,18]

Further associations may be made with clinical endpoints with:

- F876L mutation in plasma DNA collected at EOT
- AR splice variants or other RNA anomalies in whole blood
- Other DNA anomalies in plasma samples
- AR signaling strength in archival tumor samples and blood samples collected at baseline

Immunohistochemistry on FFPE samples may be performed to identify patients with high, medium and low expression of immune markers and their association with treatment response using appropriate categorical or regression methods.

The association of the rest of the biomarkers with clinical response or relevant survival endpoints may be assessed using appropriate statistical methods (eg, 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 or relevant time-to-event endpoints will also be explored in the overall population. 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. Medical Resource Utilization

The analysis will be prepared separately and will not be a part of the clinical study report.

11.7. Safety Analyses

The safety parameters to be evaluated are the incidence, intensity, and type of AEs, vital signs (blood pressure), ECG, and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA) and will be graded according to NCI-CTCAE (Version 4.03). Treatment-emergent AEs are AEs 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 NCI-CTCAE (Version 4.03) 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.

Electrocardiogram (ECG)

Electrocardiogram data obtained at screening will be summarized by ECG parameter.

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.

11.8. Interim Analyses

There will be no planned interim analysis of the dual-primary endpoint, rPFS. For a description of the OS interim analyses see Section 11.3.2.

11.9. Independent Data Monitoring Committee

An IDMC will be commissioned 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 IDMC will perform periodic safety reviews throughout the study as outlined in the IDMC charter. The committee will also meet to review interim data (see Section 11.3.2). After the review of interim analysis data, if the primary analysis results of rPFS and the interim analysis results of OS are positive the IDMC may recommend unblinding to allow all subjects to receive active therapy.

The IDMC will consist of at least one medical oncologist or urologist or both and at least one statistician. 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 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 ADT (GnRHa choice based on investigator's decision for subjects who did not have surgical castration; see Section 6.2), the expectedness of an AE will be determined by whether or not it is listed in the specific GnRHa product information sheet (eg, package insert/summary of product characteristics).

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/patient 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.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 4. Some countries will not identify anticipated events for the Health Authorities.

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 reported as individual SAEs, 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 investigational 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:

- Hospitalizations not intended to treat an acute illness of AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the 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 SAE definition (refer to Section 12.1.1).

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 SAE, the study-site personnel must report the PQC to the sponsor according to the SAE 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.

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 packaged in 120-count, 160 cc high-density polyethylene (HDPE) bottles with child-resistant closures.

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.

Refer to the pharmacy manual/study-site investigational product and procedures 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:

- Protocol
- Investigator Brochure and addenda
- Pharmacy manual/study-site investigational product and procedures manual
- Analgesic Use Log
- Laboratory manual
- Link to NCI-CTCAE http://evs.nci.nih.gov/ftp1/CTCAE/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 ADT in subjects with mHSPC. All subjects will receive active treatment with ADT as SOC. 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. 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 AEs 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 one of the dual-primary endpoints, 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 patient overexposure to radiation. Efficacy assessments will occur as recommended by the internationally accepted RECIST 1.1 criteria and PCWG2 criteria.[8,29]

An IDMC will be commissioned 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.

The blood collection includes laboratory assessments associated with screening and treatment including PK and biomarker samples. The volume of blood to be drawn is considered to be normal and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the time frame of the study.

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 AEs 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. Long-term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. The research may begin at any time during the study or the post-study storage period.

16.2.6. 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 exists, 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 AEs and follow-up of AEs; 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 a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following 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 investigator or 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 data base. 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 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 after 410 deaths have occurred at approximately 54 months after the first subject is randomized 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 sub-study 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.[8]

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 eCRF. 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: ie, 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: ie, 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 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 PS Grade Scale

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: Additional Information on CYP450 Drug Interactions

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

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

Attachment 4: Anticipated Events

An anticipated event is an adverse event (serious or non-serious) 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

cauda equina syndrome

erectile dysfunction

haematospermia

haematuria

incontinence

lymphoedema

nocturia

painful ejaculation

pathological fracture

pollakiuria

prostate-specific antigen increased

spinal cord compression

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 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) as 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 (ASMP).

Attachment 5: Leuprolide PK Sub-study

- To participate in this optional PK sub-study, subjects must consent to the PK sub-study indicating their willingness to participate.
- Optional PK samples will be collected from at least 60 consenting subjects (in selected countries) who received or will receive leuprolide acetate as the GnRH analog at the time of randomization. The subjects participating in this sub-study do not need to be the same subjects who provide trough PK samples for apalutamide (see Section 9.3).
- Samples will be collected on Day 1 of Cycles 1, 3, 4, 5, and 6 for analysis of leuprolide acetate concentrations and testosterone (see Laboratory Manual for details on sample collection).
- Samples should be collected prior to on-site study drug (ie, apalutamide) administration.
- Samples must be collected prior to leuprolide acetate administration if the injection is scheduled to be given on the same day.
- Testosterone samples to be collected from this sub-study will be analyzed using an ultrasensitive assay (see Laboratory Manual for details).
- Eligibility criteria for inclusion in this sub-study include the following:
  - Subjects must receive intramuscular or subcutaneous leuprolide acetate and must have received the first dose at least 21 days prior to randomization. The 11.25 mg, 22.5 mg, 30 mg, and 45 mg dosages are permitted.
  - Subjects must have no planned adjustment in the dose or frequency of leuprolide acetate administration during Cycles 1 to 6.
- For the analysis of leuprolide concentrations, to ensure that the PK samples are reflective of leuprolide concentrations at steady-state, blood samples collected within 21 days after the leuprolide injection may be excluded from the PK analysis.
- Descriptive statistics of leuprolide PK data will be summarized by treatment group and dose of leuprolide acetate. Statistical analysis comparing leuprolide concentrations when administered alone versus in combination with apalutamide will be performed. The percentage of subjects with testosterone concentrations <50 ng/dL) will also be summarized descriptively by treatment group. The results of these analyses will be provided in a separate report.

Attachment 6: Crossover to Open-label Apalutamide After Study Unblinding

At the time the decision is made to unblind the study, investigators will be notified by the sponsor. Subjects randomized to placebo who are currently on study treatment will be offered treatment with open-label apalutamide at 240 mg/ day.

Subjects previously randomized to apalutamide will continue on protocol and follow the current schedule of activities as indicated in the Time and Events Schedule (Open-label Extension Phase) and will be given open-label apalutamide. Subjects will be followed for progression per Investigator decision. Any procedures for assessing progression can be scheduled per standard of care at the discretion of the Investigator.

Eligibility Criteria for Placebo Subjects to Crossover to Open-label Apalutamide

Subjects randomized to placebo must meet the criteria below to be eligible to crossover to open-label apalutamide:

1a. Subject is willing and able to provide written informed consent to crossover to open-label apalutamide

2a. Subjects who had study treatment withheld for ≥28 consecutive days at the time of unblinding will need approval from the medical monitor to be eligible for crossover.

Study Procedures for Subjects Previously on Placebo Who Crossover

Subjects will start open-label apalutamide with Cycle 1 and will be evaluated every 28 days from Cycles 1-7, then every 2 cycles to C13, then every 4 cycles until End-of-Treatment, unless otherwise specified. The Open-label Extension Phase will allow subjects to receive active drug (apalutamide plus ADT) for approximately 3 years. Refer to the Time and Events Schedule for subjects who crossover from placebo to open-label apalutamide. See Section 9 for the description of study assessments and the Time and Events Schedule (Open-label Extension Phase).

Study Procedures for Subjects not Requiring Cross-Over and Were Receiving Apalutamide

Subjects will start open-label apalutamide with Cycle 1 and will be evaluated every 4 cycles for approximately 3 years unless otherwise specified. Refer to the Time and Events Schedule for subjects who were unblinded and were receiving study drug. See Section 9 for the description of study assessments and the Time and Events Schedule (Open-label Extension Phase).

Discontinuation Criteria for Open-label Extension Phase

Subjects who discontinue open-label apalutamide will continue in the Follow-up Phase per Section 9.1.5.

- If a subject meets the criteria as defined in Section 10 of the protocol, apalutamide must be discontinued.

Attachment 7: Long-Term Extension Phase (After Open-label Extension Phase)

The Long-term Extension (LTE) Phase will provide apalutamide access to subjects who may continue to derive benefit from treatment (based on investigator assessment) after the Open-label Extension Phase is complete.

The LTE Phase will begin on the date of clinical cut-off for the final analysis (CCO FA) or on the date of approval of Amendment 5 at the site, whichever comes last. The sponsor will send notification when CCO FA has been reached. At the initiation of the LTE Phase, subjects in the Open-Label Extension Phase who may continue to derive benefit from apalutamide (based on investigator assessment) will have the option to enter the LTE Phase. In the LTE Phase:

- Subjects must sign an updated informed consent prior to entry.
- Subjects will remain on the same once daily dose of apalutamide as they were receiving in the Open-label Extension Phase.
- Dispensing of apalutamide will occur every 1 to 6 months in accordance with local practice. Subjects will be supplied with 1 to 6 months of apalutamide at each visit.
- Subjects can be withdrawn if an alternative access to apalutamide (eg, patient-assistance program, dedicated long-term extension/access study or commercial source) is available and feasible, in accordance with local regulations.

At the initiation of the LTE Phase, subjects in the Follow-up Phase (who are not receiving treatment with apalutamide) will be withdrawn from the study with no further follow-up, unless they have an unresolved SAE, see Section 12.3. Subjects in the Open-label Extension Phase who elect not to participate in LTE Phase will have an End-of-Treatment Contact as described below prior to being withdrawn from the study.

Study Evaluations in the LTE Phase

Investigators should monitor and assess the subjects for response, safety and disease progression according to routine practice and local label requirements. Timing of assessments is at the discretion of the investigator. Data collection will be limited to SAEs, which will be reported up to 30 days after the last dose of study drug as specified in Section 12.3. No safety or efficacy analyses are planned for the LTE Phase.

Prohibitions and Restrictions in the LTE Phase

Refer to Section 4.3 for information on prohibitions and restrictions that subjects must follow in the LTE Phase.

Toxicity and Rash Management in the LTE Phase

Refer to Section 6.3 for information on dose modifications for drug-related toxicities that occur during the LTE Phase.

Concomitant Therapy in the LTE Phase

Refer to Section 8.1 for information on permitted supportive care therapies, Section 8.2 for prohibited concomitant therapies, and Section 8.3 for restricted concomitant therapies during the LTE Phase.

Withdrawal from the LTE Phase

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

- Lost to follow-up
- Patient decision
- The investigator believes that it is the best interest of the subject to discontinue treatment (eg, for safety or tolerability reasons or if the subject is no longer receiving benefit), or alternative access to apalutamide is available and feasible.
- Study is terminated by the sponsor

Subjects who are withdrawn from the LTE Phase should have an End-of Treatment Contact as described below.

End-of Treatment Contact:

An end-of-treatment (EOT) contact will occur 30-37 days after the last dose of apalutamide. Investigators should report SAEs occurring within 30 days after the last dose of apalutamide as specified in Section 12.3. Any unused study medication should be returned to the site on (or before) the EOT contact. At the discretion of the investigator, the EOT contact can take place as a scheduled visit or phone call.

INVESTIGATOR AGREEMENT

JNJ-56021927 (apalutamide)
Clinical Protocol 56021927PCR3002 Amendment 5

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: 16 MARCH 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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Approved, Date: 16 March 2020