Clinical Trial Protocol

# 1. Title

Title

A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Subjects with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

Protocol Number

JNJ-56021927PCR3002 Amendment 5

Protocol Date

16 March 2020

Sponsor

Janssen Research & Development, LLC

Study Phase

Phase 3

Indication

Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

Study Title

A Multinational, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy and Safety of Apalutamide in Combination with Androgen Deprivation Therapy (ADT) Compared to ADT Alone in Subjects with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

# 2. Background

BACKGROUND

Disease Overview

Prostate cancer is a common malignancy affecting men, particularly in the aging population. It is characterized by the growth of cancer cells in the prostate gland, which is responsible for producing seminal fluid. When prostate cancer is detected at an early, localized stage, the prognosis is generally favorable with various treatment options available. However, in the metastatic hormone-sensitive prostate cancer (mHSPC) stage, the cancer has spread beyond the prostate gland to other parts of the body and continues to rely on androgens for growth.

Androgen deprivation therapy (ADT) is the cornerstone of treatment for mHSPC. ADT reduces androgen levels or blocks their effect on prostate cancer cells, slowing disease progression. Despite initial responsiveness, most patients eventually progress to a more aggressive form of the disease known as metastatic castration-resistant prostate cancer (mCRPC), which is associated with a poor prognosis.

Current Treatment Landscape

The current standard of care for patients with mHSPC involves ADT alone or in combination with other systemic therapies. The addition of docetaxel to ADT has shown improved survival in some patients with mHSPC. However, there is a need for new treatment options that can further improve outcomes, delay progression, and maintain quality of life.

Rationale for the Study

Apalutamide (JNJ-56021927) is an orally available, non-steroidal androgen receptor (AR) antagonist that has shown potential in the treatment of prostate cancer by inhibiting the action of androgens on prostate cancer cells. The development of apalutamide for mHSPC is based on its ability to potently block AR signaling, which is a critical driver of prostate cancer growth and progression.

Preclinical studies and early clinical trials have suggested that apalutamide has an acceptable safety profile and may provide clinical benefit in prostate cancer. This has led to the hypothesis that the addition of apalutamide to ADT could improve outcomes for patients with mHSPC compared to ADT alone.

Study Justification

The Phase 3 study protocol JNJ-56021927PCR3002 Amendment 5 aims to evaluate the efficacy and safety of apalutamide in combination with ADT versus ADT alone in subjects with mHSPC. The study is designed to address the unmet medical need for therapies that can extend survival and delay disease progression while maintaining quality of life in this patient population.

Given the mechanism of action of apalutamide and the preliminary data supporting its use, this study seeks to provide robust evidence on whether apalutamide can offer a significant clinical advantage over the current standard of care in mHSPC. The results of this study could potentially lead to a new therapeutic option for patients with mHSPC, contributing to improved patient outcomes and a broader range of treatment strategies.

# 3. Objectives

1. Objectives

1.1 Primary Objective

The primary objective of this Phase 3 study is to evaluate the efficacy of apalutamide in combination with androgen deprivation therapy (ADT) compared to ADT alone in improving radiographic progression-free survival (rPFS) and overall survival (OS) in subjects with metastatic hormone-sensitive prostate cancer (mHSPC).

1.2 Secondary Objectives  
• To assess the impact of apalutamide plus ADT on delaying pain progression and opioid use for prostate cancer-related pain management.  
• To evaluate the effect of the combination therapy on the incidence of skeletal-related events (SREs) and the need for cytotoxic chemotherapy.  
• To characterize the safety profile of apalutamide when added to ADT in the study population.  
• To investigate the population pharmacokinetics (PK) and pharmacodynamics (PD) of apalutamide.  
• To assess the PD effect of leuprolide on testosterone concentrations when used alone or in combination with apalutamide.  
• To determine the effectiveness of apalutamide plus ADT in subpopulations of subjects with low-volume or high-volume mHSPC.

1.3 Other Objectives  
• To explore biomarkers that may predict response to treatment and potential resistance mechanisms.  
• To evaluate patient-relevant outcomes, including symptom management (e.g., pain, fatigue, urination) and functional aspects (e.g., physical, emotional, social), as well as health-related quality of life.  
• To compare other clinically relevant endpoints between the apalutamide plus ADT and ADT alone treatment arms.  
• To collect medical resource utilization data for future economic modeling.

1.4 Hypothesis

The hypothesis of this study is that apalutamide in combination with ADT will demonstrate improved rPFS and OS compared to ADT alone and will have an acceptable safety profile in subjects with mHSPC.

# 4. Study Design

6. Study Design

6.1 Overview of Study Design

This Phase 3 study is a randomized, double-blind, placebo-controlled, multinational, and multicenter trial designed to assess the efficacy and safety of apalutamide in combination with androgen deprivation therapy (ADT) compared to ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). The trial aims to enroll approximately 1,000 subjects who meet the inclusion criteria and none of the exclusion criteria. These subjects will be stratified based on 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). Following stratification, subjects will be randomly assigned in a 1:1 ratio to either the apalutamide plus ADT group or the matching placebo plus ADT group.

6.2 Study Phases

6.2.1 Screening Phase

The Screening Phase will last up to 28 days before randomization to establish study eligibility.

6.2.2 Treatment Phase

During the Treatment Phase, subjects will receive treatment in 28-day cycles until disease progression, unacceptable treatment-related toxicity occurs, or the study is terminated by the sponsor. Treatment may continue past radiographic progression if there is no clinical progression and no alternate therapy is initiated. Upon documented clinical progression based on protocol-specified criteria, subjects must discontinue the study drug.

6.2.3 End-of-Treatment Visit

An End-of-Treatment Visit will occur within 30 days after the last dose of study drug.

6.2.4 Follow-up Phase

The Follow-up Phase will involve data collection every 4 months, including survival status, secondary endpoint data, and information on subsequent therapies for prostate cancer. Data collection will continue until the subject's death, withdrawal of consent, loss to follow-up, or study termination by the sponsor. Patient-reported outcome measures will be collected up to 12 months after treatment discontinuation.

6.2.5 Open-label Extension Phase

If the study results are positive, subjects in the Treatment Phase will have the opportunity to enroll in an Open-label Extension Phase to receive active drug (apalutamide) for approximately 3 years.

6.2.6 Long-Term Extension (LTE) Phase

Subjects benefiting from apalutamide in the Open-label Extension Phase may continue treatment in the LTE Phase, which will begin on the date of the final analysis cut-off or the date of approval of Amendment 5 at the site, whichever is later.

6.3 Study Population

Eligible subjects include those with a diagnosis of prostate cancer, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 or 1, and documented distant metastatic disease. Subjects may have received limited prior treatments for mHSPC and localized prostate cancer.

6.4 Dosage and Administration

All subjects will receive standard of care ADT, with the choice of gonadotropin-releasing hormone (GnRH) analog at the Investigator's discretion. Apalutamide or matching placebo will be administered orally at a dose of 240 mg (4 x 60-mg tablets) once daily, with or without food.

6.5 Efficacy Evaluations/Endpoints

The primary efficacy endpoints are radiographic progression-free survival (rPFS) and overall survival (OS). Secondary and other endpoints include time to pain progression, skeletal-related events (SREs), opioid use, cytotoxic chemotherapy initiation, symptomatic local progression, and prostate cancer-specific antigen (PSA) progression, among others.

6.6 Safety Evaluations

Safety will be monitored from the signing of informed consent until 30 days after the last dose of study drug. Adverse events (AEs), vital signs, physical examinations, ECOG PS, and clinical laboratory tests will be evaluated and graded using NCI-CTCAE (Version 4.03).

6.7 Statistical Methods

6.7.1 Analysis Populations

The intent-to-treat (ITT) population will be used for the primary analysis of efficacy, while the safety population will include all subjects who received at least one dose of the study drug.

6.7.2 Sample Size Determination

The study is powered to detect a hazard ratio (HR) of 0.67 for rPFS and 0.75 for OS with a total of approximately 368 rPFS events and 410 death events required for the respective endpoints.

6.7.3 Efficacy Analysis

Time-to-event variables will be estimated using the Kaplan-Meier method and Cox proportional hazards model.

6.7.4 Interim Analysis

Two interim analyses for OS are planned after approximately 50% and 70% of the required events have been observed.

6.7.5 Population PK and PD Analysis

Population pharmacokinetic analysis will be performed using nonlinear mixed-effects modeling, and relationships between apalutamide exposure and efficacy or AEs may be analyzed.

6.7.6 Biomarker Analysis

Associations between biomarkers and clinical response or time-to-event endpoints will be assessed using appropriate statistical methods.

6.8 Monitoring and Oversight

An Independent Data Monitoring Committee (IDMC) will provide recommendations during the planned interim efficacy analyses and regular safety reviews.

# 5. Population

6.3 Study Population

6.3.1 Inclusion Criteria

1. Subjects must have a histologically or cytologically confirmed diagnosis of prostate cancer.  
2. Subjects are required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at the Screening Phase.  
3. Subjects must have evidence of distant metastatic disease, documented by a positive bone scan with one or more bone lesions on Technetium 99m (99mTc). If only a single bone lesion is present, it must be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI).  
4. Subjects may have received up to six cycles of docetaxel for mHSPC, with the last dose administered no more than 2 months prior to randomization.  
5. Subjects may have received androgen deprivation therapy (ADT) for no longer than six months prior to randomization.  
6. Subjects may have undergone a maximum of one course of radiation or surgical intervention for mHSPC.  
7. For localized prostate cancer, subjects may have received up to three years total of ADT, and all other forms of prior therapies including radiation therapy, prostatectomy, lymph node dissection, and systemic therapies, provided these therapies were completed at least one year prior to randomization.

6.3.2 Exclusion Criteria

1. Subjects with severe concurrent disease, infection, or comorbidity that, in the judgment of the investigator, would make the subject inappropriate for enrollment.  
2. Subjects with known brain metastases or leptomeningeal disease.  
3. Subjects who have received more than six cycles of docetaxel for mHSPC.  
4. Subjects who have received any other systemic treatment for mHSPC within one year prior to randomization, except for up to six months of ADT.  
5. Subjects who have undergone major surgery or radiation therapy within four weeks prior to randomization.  
6. Subjects with a history of another malignancy within the past five years, except for adequately treated basal cell or squamous cell skin cancer or any in situ cancer.  
7. Subjects with a known hypersensitivity to any component of the study drugs or their analogs.  
8. Subjects who have participated in a study of an investigational agent or used an investigational device within 4 weeks of the first dose of treatment.

6.3.3 Stratification Factors

Subjects will be stratified based on the following factors prior to randomization:

1. Gleason score at diagnosis (≤7 versus >7).  
2. Geographic region (North America [NA] and European Union [EU] versus Other Countries).  
3. Prior docetaxel use (yes versus no).

6.3.4 Randomization

Eligible subjects will be randomly assigned in a 1:1 ratio to either the apalutamide plus ADT group or the matching placebo plus ADT group. Randomization will be conducted using a computer-generated randomization schedule.

6.3.5 Study Enrollment

Approximately 1,000 subjects are planned to be enrolled in the study to ensure adequate power for the efficacy analyses. Enrollment will be competitive across participating sites and will continue until the target number of subjects is reached.

# 6. Procedures

7. Procedures

7.1 Treatment Administration

7.1.1 Apalutamide Administration  
Subjects will be administered apalutamide at a dose of 240 mg, consisting of four 60-mg tablets, taken orally once daily. The medication can be ingested with or without food.

7.1.2 Placebo Administration  
Subjects in the control arm will receive a matching placebo consisting of four tablets, taken orally once daily, with or without food.

7.1.3 Androgen Deprivation Therapy (ADT)  
All subjects will receive ADT as part of standard of care. ADT will be administered as medical castration using a gonadotropin-releasing hormone (GnRH) analog or as surgical castration via bilateral orchiectomy. The specific GnRH analog and dosing schedule will be determined by the Investigator and will be consistent with the product's prescribing information.

7.2 Efficacy Assessments

7.2.1 Radiographic Progression-Free Survival (rPFS)  
rPFS will be assessed by the investigator and is defined as the time from randomization to the first documentation of radiographic progressive disease or death from any cause, whichever occurs first. Radiographic progression will be evaluated by CT/MRI for soft tissue lesions per modified RECIST 1.1 criteria and by bone scan for bone lesions.

7.2.2 Overall Survival (OS)  
OS is defined as the time from randomization to the date of death from any cause. Survival status will be collected during both the Treatment and Follow-up Phases.

7.3 Secondary and Other Efficacy Endpoints  
Secondary endpoints include time to pain progression, time to skeletal-related events (SREs), time to chronic opioid use, and time to initiation of cytotoxic chemotherapy. Other efficacy endpoints include time to symptomatic local progression, time to prostate cancer-specific antigen (PSA) progression, and patient-reported outcomes such as changes in pain, fatigue, and quality of life.

7.4 Pharmacokinetic (PK) and Pharmacodynamic (PD) Evaluations

7.4.1 Apalutamide PK  
Trough PK samples will be collected on Day 1 of Cycles 2 through 6 for analysis of apalutamide and its active metabolite concentrations.

7.4.2 Leuprolide PK Sub-study  
In selected countries, optional PK samples will be collected from consenting subjects receiving leuprolide acetate for analysis of leuprolide and testosterone concentrations.

7.5 Biomarker Evaluations  
Biomarker evaluations will be conducted using plasma-based circulating DNA and archival tumor tissue to assess AR gene anomalies and other potential resistance markers.

7.6 Medical Resource Utilization (MRU) Evaluations  
MRU data will be collected during the Treatment Phase to inform future economic modeling.

7.7 Safety Evaluations  
Safety will be assessed through the monitoring of adverse events (AEs), vital signs, physical examinations, ECOG performance status, and clinical laboratory tests. AEs will be graded using NCI-CTCAE Version 4.03.

7.8 Dose Modifications  
Dose modifications for apalutamide will be made according to the dose modification rules outlined in the protocol.

7.9 Data Collection and Monitoring  
Data collection will include survival, secondary endpoint data, and information on subsequent therapies for prostate cancer. An Independent Data Monitoring Committee (IDMC) will provide oversight and recommendations during interim efficacy analyses and regular safety reviews.

7.10 Study Discontinuation Criteria  
Subjects must discontinue the study drug upon documented clinical progression based on protocol-specified criteria or the occurrence of unacceptable treatment-related toxicity.

7.11 End-of-Treatment and Follow-up Visits  
An End-of-Treatment Visit will occur within 30 days after the last dose of study drug. During the Follow-up Phase, subjects will be monitored every 4 months for survival and secondary endpoint data collection.

7.12 Open-label and Long-Term Extension Phases  
Eligible subjects may participate in an Open-label Extension Phase to receive apalutamide for approximately 3 years. Subjects benefiting from treatment may continue in the Long-Term Extension Phase based on investigator assessment.

# 7. Statistical Analysis

6.7 Statistical Methods

6.7.1 Analysis Populations

Intent-to-Treat Population  
The intent-to-treat (ITT) population will include all randomized subjects and will be used for the primary analysis of subject disposition and efficacy.

Safety Population  
The safety population will comprise all subjects who received at least one dose of the study drug.

6.7.2 Sample Size Determination

The study will maintain an overall type I error rate of 5%, with a significance level of 0.005 allocated for the rPFS endpoint and 0.045 for OS. The study will be considered successful if at least one of the dual-primary endpoints shows statistical significance.

To detect a hazard ratio (HR) of 0.67 for rPFS with 85% power at a two-sided significance level of 0.005, approximately 368 rPFS events are required. For OS, to detect a HR of 0.75 with approximately 80% power at a two-sided significance level of 0.045, about 410 death events are needed. The study aims to enroll approximately 1,000 subjects over 30 months, with a total study duration of approximately 54 months to observe the required number of events.

6.7.3 Efficacy Analysis

Time-to-event variables such as rPFS and OS will be estimated using the Kaplan-Meier product limit method. The Cox proportional hazards model will be used to obtain hazard ratios along with 95% confidence intervals.

6.7.4 Interim Analysis

Two interim analyses for OS are planned after approximately 50% (205 events) and 70% (287 events) of the required 410 events are observed. Concurrently, the final analysis for the rPFS endpoint will be conducted during the first interim OS analysis.

6.7.5 Population PK and PD Analysis

Population pharmacokinetic analysis will be performed using nonlinear mixed-effects modeling. The relationship between apalutamide exposure and efficacy or adverse events may be analyzed if sufficient data are available.

6.7.6 Leuprolide PK Analysis

Descriptive statistics will summarize leuprolide PK data, and comparisons will be made between leuprolide concentrations when administered alone or in combination with apalutamide. The proportion of subjects with testosterone levels below 50 ng/dL will be descriptively summarized by treatment groups.

6.7.7 Biomarker Analysis

Associations between biomarkers and clinical response or time-to-event endpoints will be assessed using appropriate statistical methods such as ANOVA, categorical, or survival models. A detailed Statistical Analysis Plan will be prepared for these exploratory analyses.

6.7.8 Medical Resource Utilization Analysis

Medical resource utilization data will be analyzed and included in a separate report.

6.7.9 Safety Analysis

Safety evaluations will include the incidence and severity of treatment-emergent adverse events, changes in physical examination findings, vital signs, and clinical laboratory results. Adverse events will be graded according to the NCI-CTCAE Version 4.03. Exposure to the study drug and reasons for discontinuation of study treatment will be tabulated and analyzed.

# 8. Safety

6. Safety Evaluations

6.6.1 Adverse Events Monitoring  
Safety will be monitored 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 the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE; Version 4.03). All AEs will be recorded with their onset date, severity, relationship to the study drug, action taken, and outcome.

6.6.2 Vital Signs, Physical Examinations, and ECOG Performance Status  
Vital signs measurements (blood pressure, heart rate, temperature, and respiratory rate), physical examinations, and Eastern Cooperative Oncology Group (ECOG) performance status will be evaluated at baseline and periodically throughout the study.

6.6.3 Clinical Laboratory Tests  
Clinical laboratory tests including hematology, blood chemistry, and urinalysis will be conducted at baseline and at specified intervals during the study to monitor for potential treatment-related toxicities.

6.6.4 Dose Modifications and Discontinuation  
Dose modifications for apalutamide will be made according to the dose modification rules outlined in the protocol. Subjects may have their dose reduced, interrupted, or discontinued based on the severity and type of AE experienced.

6.6.5 Independent Data Monitoring Committee (IDMC)  
An Independent Data Monitoring Committee (IDMC) will be commissioned to provide recommendations during the planned interim efficacy analyses and regular safety reviews. The IDMC will monitor safety data and may recommend modifications to the study or early termination if safety concerns arise.

6.6.6 Reporting of Serious Adverse Events and Unanticipated Problems  
Serious adverse events (SAEs) and unanticipated problems posing risks to subjects or others will be reported to the regulatory authorities, ethics committees, and the sponsor in accordance with regulatory requirements and the study protocol.

6.6.7 Safety Analysis  
The safety analysis will include a tabulation of AEs and SAEs, laboratory abnormalities, and other safety parameters. The incidence and severity of treatment-emergent AEs will be summarized by treatment group. Exposure to study drug and reasons for discontinuation of study treatment due to AEs will also be reported.

6.6.8 Post-Study Drug Monitoring  
After discontinuation of the study drug, subjects will be monitored for any ongoing or emerging AEs during the End-of-Treatment Visit and the 30-day post-treatment safety follow-up period.

6.7 Safety Endpoints  
The primary safety endpoints will include the incidence, severity, and causality of AEs and SAEs. Secondary safety endpoints will include changes in laboratory values, vital signs, and ECOG performance status.

6.8 Statistical Methods for Safety Analysis  
Descriptive statistics will be used to summarize safety data. The number and percentage of subjects experiencing AEs and SAEs will be tabulated by system organ class and preferred term. Time to onset and duration of AEs, as well as the proportion of subjects with AEs leading to dose modification or discontinuation, will be summarized. Comparisons between treatment groups will be made using appropriate statistical tests.