# Background

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## Disease Background Metastatic hormone-sensitive prostate cancer (mHSPC) is a stage of prostate cancer where the tumor cells have spread beyond the prostate gland and remain sensitive to hormone therapy, which typically reduces androgen levels to inhibit cancer growth. Despite initial responsiveness to androgen deprivation therapy (ADT), most patients with mHSPC eventually progress to a state resistant to hormone therapy, leading to significant morbidity and mortality. It is estimated that prostate cancer is one of the most commonly diagnosed cancers in men, contributing substantially to cancer-related deaths worldwide.

## Current Treatment Landscape The standard of care for patients with mHSPC typically involves ADT, which can be achieved via surgical castration or medical castration using gonadotropin-releasing hormone (GnRH) analogs, either agonists or antagonists. While ADT is initially effective in controlling disease progression, its impact diminishes over time as resistance develops. There is increasing interest in combining ADT with other therapeutic agents to improve long-term outcomes such as radiographic progression-free survival (rPFS) and overall survival (OS).

## Product Background Apalutamide (JNJ-56021927, ARN-509) is an orally administered, small-molecule non-steroidal antagonist of the androgen receptor. It functions as a potent and selective anti-androgen, blocking the action of androgens that drive prostate cancer cell growth. Apalutamide is being developed as an adjunct to standard ADT for the treatment of prostate cancer, aiming to enhance therapeutic efficacy and delay disease progression while maintaining an acceptable safety profile.

## Study Rationale The hypothesis underpinning this study is that the addition of apalutamide to ADT could offer superior efficacy compared to ADT alone, as measured by improvements in rPFS and OS in patients with mHSPC. By enhancing the blockade of androgen receptor signaling, apalutamide in combination with standard ADT may delay disease progression and improve survival outcomes. The current study seeks to rigorously evaluate these potential benefits and provide a comprehensive understanding of the safety and pharmacokinetics of apalutamide administration in this patient population. The results are anticipated to inform clinical practice and potentially establish a new standard of care for individuals with mHSPC.

# Objectives

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## Primary Objective(s) 1. 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 metastatic hormone-sensitive prostate cancer (mHSPC).

## Primary Endpoint(s) 1. Radiographic progression-free survival (rPFS), measured as the time from randomization to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurs first. 2. Overall survival (OS), defined as the time from randomization to the date of death from any cause.

## Secondary Objectives 1. To evaluate clinically relevant improvements with the addition of apalutamide to ADT, including delays in pain progression and opioid use, skeletal-related events (SREs), and the need for cytotoxic chemotherapy. 2. To characterize the safety profile of adding apalutamide to ADT for subjects with mHSPC. 3. To characterize the population pharmacokinetics (PK) and pharmacodynamics (PD) of apalutamide. 4. To evaluate the concentration of leuprolide and assess its PD effect on testosterone concentrations when used alone or in combination with apalutamide. 5. To evaluate treatment effectiveness with the addition of apalutamide to ADT in subpopulations of subjects with low-volume or high-volume mHSPC.

## Secondary Endpoint(s) 1. Time to pain progression, time to initiation of chronic opioid use, and time to the first occurrence of a skeletal-related event (SRE), measured from the date of randomization. 2. Incidence, severity, and nature of adverse events associated with treatment. 3. Pharmacokinetic parameters of apalutamide and its active metabolite, JNJ-56142060, determined through plasma concentration-time data. 4. Concentration of leuprolide and percentage of subjects achieving testosterone levels <50 ng/dL, determined through plasma analyses.

## Other Objectives 1. To evaluate exploratory biomarkers predictive of response and resistance to treatment. 2. To evaluate patient-relevant outcomes, including symptoms (pain, fatigue, urination), function (physical, emotional, social), and health-related quality of life. 3. To evaluate improvements in other clinically relevant endpoints of apalutamide plus ADT compared with ADT alone. 4. To collect medical resource utilization (MRU) data for potential future economic modeling.

# Study Design

# Study Design

## Overall Design This study is a Phase 3, randomized, double-blind, placebo-controlled, multinational, and multicenter trial designed 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). Approximately 1,000 subjects will be randomized in a 1:1 ratio to receive either apalutamide plus ADT or matching placebo plus ADT.

## Study Schema Participants will undergo a Screening Phase of up to 28 days to assess eligibility based on inclusion and exclusion criteria. Eligible participants will be stratified by Gleason score at diagnosis (≤7 versus >7), region (North America/European Union versus Other Countries), and prior docetaxel use (yes versus no). Randomization will follow stratification.

### Study Phases: 1. \*\*Screening Phase:\*\* Up to 28 days before randomization. 2. \*\*Treatment Phase:\*\* 28-day treatment cycles until disease progression, unacceptable toxicity, or sponsor decision. Option to continue apalutamide upon radiographic progression without clinical progression. 3. \*\*Follow-up Phase:\*\* Regular data collection every 4 months post-discontinuation until death, withdrawal, loss to follow-up, or study termination. 4. \*\*Open-label Extension Phase:\*\* Available contingent on positive interim/final results. 5. \*\*Long-Term Extension Phase:\*\* Continued apalutamide treatment based on benefit assessment.

## Study Duration The anticipated overall duration of the study is approximately 54 months. Enrollment is projected to occur over 30 months, with an expected follow-up period to accommodate the collection of primary endpoints and observe 410 death events necessary for overall survival analysis.

## Treatment Groups - \*\*Apalutamide + ADT Group:\*\* Apalutamide 240 mg (4 x 60 mg tablets) orally once daily in combination with ADT. - \*\*Placebo + ADT Group:\*\* Matching placebo tablets orally once daily in combination with ADT. Androgen deprivation therapy (ADT) involves either medical castration via a gonadotropin-releasing hormone (GnRH) analog or surgical castration, chosen at the investigator's discretion.

## Study Procedures - \*\*Randomization:\*\* Stratified by Gleason score, region, and prior docetaxel use. - \*\*Treatment Administration:\*\* In 28-day cycles. - \*\*Safety Monitoring:\*\* From consent signing to 30 days post last dose. Includes AE monitoring, vital signs, physical examinations, and laboratory assessments. - \*\*Efficacy Assessments:\*\* rPFS and OS via radiographic evaluations using CT/MRI per RECIST 1.1 and bone scans. - \*\*Pharmacokinetics/Pharmacodynamics (PK/PD):\*\* Blood samples for both apalutamide and its metabolite will be collected on Day 1 of Cycles 2-6. - \*\*Biomarker Analysis:\*\* Includes circulating DNA and archival tumor samples. - \*\*Patient-Reported Outcomes (PROs):\*\* Tools such as BPI-SF, BFI, and EQ-5D-5L will be used before treatment, during each cycle, and in follow-up.

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| **## Schedule of Assessments** |
| Assessment |
| Eligibility & Stratification |
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Subjects will have their safety monitored and assessments conducted as per the protocol schedule to ensure clinical oversight and that adverse events are captured accurately during and after treatment administration. This rigorous design seeks to ascertain the potential benefits and safety profile of apalutamide in combination with ADT for patients with mHSPC.

# Population

# Study Population

## Overview of Study Population The study population will include male subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). Participants must demonstrate an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, indicating full activity or slight restriction in physically strenuous activity. Subjects should also exhibit evidence of distant metastatic disease, as confirmed by specific diagnostic imaging.

## Inclusion Criteria 1. \*\*Diagnosis\*\*: Subjects must have a confirmed diagnosis of prostate cancer. 2. \*\*Performance Status\*\*: ECOG performance status grade 0 (fully active) or 1 (restricted in physically strenuous activity but ambulatory). 3. \*\*Metastatic Disease\*\*: Presence of distant metastatic disease as documented by a positive bone scan showing one or more bone lesions. Subjects with a single bone lesion must have further confirmation via computed tomography (CT) or magnetic resonance imaging (MRI). 4. \*\*Docetaxel Therapy\*\*: Subjects may have received up to six cycles of docetaxel for mHSPC, with the last dose administered within two months prior to randomization. 5. \*\*Androgen Deprivation Therapy\*\*: Subjects may have received up to six months of androgen deprivation therapy (ADT) prior to randomization. 6. \*\*Prior Localized Treatment\*\*: For localized prostate cancer, subjects may have undergone androgen deprivation therapy for a total of up to three years and may have received prior treatments such as radiation therapy, prostatectomy, lymph node dissection, and systemic therapies, provided these were completed at least one year before randomization. 7. \*\*Radiation or Surgery for mHSPC\*\*: A maximum of one course of radiation or surgical intervention for mHSPC is allowed.

## Exclusion Criteria 1. \*\*Prior Systemic Therapy\*\*: Subjects who have received systemic therapy for prostate cancer that was not completed at least one year prior to randomization, apart from specific exceptions outlined in the inclusion criteria. 2. \*\*Other Malignancies\*\*: Diagnosis of any malignancy considered active within the past two years except for adequately treated basal cell or squamous cell skin cancer, or superficial bladder cancer. 3. \*\*Significant Cardiac History\*\*: Subjects with a history of significant cardiovascular disease, such as severe arrhythmias, angina, congestive heart failure, or myocardial infarction within six months prior to randomization. 4. \*\*Uncontrolled Comorbid Conditions\*\*: Presence of uncontrolled intercurrent illness that could jeopardize the safety of the participant or the study compliance.

## Withdrawal Criteria Subjects will be withdrawn from the study if they: 1. Withdraw consent or request discontinuation. 2. Develop significant protocol deviations or compliance concerns. 3. Experience unacceptable treatment-related toxicity. 4. Demonstrate disease progression in a manner that necessitates discontinuation as per the protocol-defined criteria.

## Replacement Policy Subjects who are withdrawn prior to randomization will be replaced to ensure the study's enrollment targets are met. Subjects who discontinue post-randomization will not be replaced to maintain the integrity of the randomization and data analysis.