# Background

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# # Disease Background

Metastatic hormone-sensitive prostate cancer (mHSPC) is a stage of prostate cancer where the disease has spread beyond the prostate gland but still responds to treatments that lower testosterone levels. Prostate cancer remains one of the most commonly diagnosed cancers in men globally, and its progression to metastatic disease significantly affects patient survival and quality of life. Patients with mHSPC often face a poor prognosis, with the potential for rapid disease progression and increased mortality. Despite the availability of several therapies, managing mHSPC remains a substantial clinical challenge, highlighting the need for novel therapeutic strategies to improve outcomes.

# # Current Treatment Landscape

The standard of care for mHSPC involves androgen deprivation therapy (ADT), which lowers androgen levels or blocks androgen receptor activity to control tumor growth. ADT can be achieved through surgical castration or more commonly through medical castration using gonadotropin-releasing hormone (GnRH) analogs. While initial responses to ADT can be effective, resistance to therapy often develops, and patients typically progress to castration-resistant prostate cancer (CRPC). Recent advances have included the addition of agents like docetaxel and novel androgen receptor (AR) signaling inhibitors to ADT regimens. However, the optimal combination of treatments and understanding which patients might benefit most from additional therapies remain areas of active investigation.

# # Product Background

Apalutamide (JNJ-56021927), an orally administered non-steroidal anti-androgen, acts as a potent antagonist of the androgen receptor. It selectively binds to the AR, inhibiting its interaction with DNA, and thereby halting the proliferation of prostate cancer cells. Apalutamide has been shown to delay disease progression and improve survival outcomes in patients with non-metastatic CRPC and is actively being tested for its efficacy in other stages of prostate cancer, including mHSPC. Its favorable pharmacokinetic and safety profiles make it an attractive candidate for combination with ADT to potentially amplify therapeutic benefits for patients with mHSPC.

# # Study Rationale

The hypothesis underpinning this study is that the addition of apalutamide to ADT may provide superior efficacy in improving radiographic progression-free survival (rPFS) and overall survival (OS) for subjects with mHSPC compared with ADT alone. Previous studies suggest that apalutamide’s mechanism of action can enhance the effects of traditional ADT by extensively inhibiting androgen receptor signaling pathways. This Phase 3 study aims to rigorously test this combination therapy's benefits and safety to establish a potential new standard for treating mHSPC. The study will also explore secondary measures such as delays in pain progression and reduce skeletal-related events, with the intent to improve not just survival, but also the quality of life for patients navigating this challenging stage of prostate cancer.

# Objectives

# Objectives

# # Primary Objective

1. 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 Endpoints

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

# # Secondary Objectives

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

# # # Secondary Endpoints

1. 1. Time to pain progression.
2. 2. Time to chronic opioid use.
3. 3. Time to occurrence of skeletal-related events (SREs).
4. 4. Time to initiation of cytotoxic chemotherapy.
5. 5. Incidence and severity of adverse events (AEs).
6. 6. Plasma pharmacokinetic profile of apalutamide and its active metabolite JNJ-56142060.
7. 7. Testosterone concentration levels and leuprolide concentrations in subjects.

# # Other Objectives

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

# # # Other Endpoints

1. 1. Biomarkers indicative of treatment response or resistance.
2. 2. Change from baseline in each of the subscales of the Functional Assessment of Cancer Therapy-Prostate (FACT-P), EuroQol EQ-5D-5L Visual Analog Scale (VAS), Brief Pain Inventory - Short Form (BPI-SF) interference subscale, and Brief Fatigue Inventory (BFI).
3. 3. Time to symptomatic local progression.
4. 4. Time to prostate cancer-specific antigen (PSA) progression based on Prostate Cancer Working Group 2 (PCWG2) criteria.
5. 5. Time to Eastern Cooperative Oncology Group (ECOG) performance status deterioration.
6. 6. Prostate cancer-specific survival.
7. 7. Time to disease progression on first subsequent therapy (PFS2).
8. 8. Data on medical resource utilization (collected during the Treatment Phase).

# Study Design

# Study Design

# # Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multinational, multicenter study designed to evaluate the efficacy and safety of apalutamide plus androgen deprivation therapy (ADT) versus placebo plus ADT in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). Approximately 1,000 subjects will be enrolled and stratified by Gleason score at diagnosis (≤7 versus >7), geographic region (North America/European Union versus Other Countries), and prior docetaxel use (yes versus no). Subjects will then be randomized in a 1:1 ratio to receive either apalutamide plus ADT or a matching placebo plus ADT.

# # Study Schema

1. 1. Screening Phase: Up to 28 days before randomization to determine eligibility.
2. 2. Treatment Phase: Subjects receive study treatment in 28-day cycles until disease progression, unacceptable toxicity, or termination of the study by the sponsor.
3. 3. Follow-up Phase: Data collection on survival and secondary endpoints every 4 months until death, withdrawal of consent, loss to follow-up, or study termination.
4. 4. Open-label Extension Phase: Subjects may enroll to receive apalutamide if the study results are positive, for approximately 3 years.
5. 5. Long-Term Extension Phase: Starts at the cut-off date for final analysis or last amendment approval date, allowing subjects who benefit to continue apalutamide treatment.

# # Study Duration

The study has an estimated total duration of approximately 54 months, comprising up to 28 days for screening, approximately 30 months for enrollment, and continuation through treatment and follow-up for about 54 months total to collect required event data.

# # Treatment Groups

1. 1. Experimental Group: Apalutamide 240 mg (4 x 60 mg tablets) orally once daily plus ADT.
2. 2. Control Group: Matching placebo (4 tablets) orally once daily plus ADT.
3. ADT can be administered as medical castration using a GnRH analog at the Investigator's discretion or through surgical castration. GnRH analog administration will be documented in the electronic case report form if not surgically castrated.

# # Study Procedures

* Screening Procedures: Include verification of eligibility criteria, documentation of prostate cancer diagnosis, performance status assessment, and relevant imaging and laboratory tests.
* Treatment Administration: Apalutamide/placebo and ADT will be administered as per protocol-defined dosing schedules.
* Safety Monitoring: Involves regular assessment of adverse events, laboratory evaluations, vital signs, and ECOG performance status.
* Efficacy Evaluations: rPFS and OS data collected through radiographic assessments per modified RECIST 1.1 criteria and overall survival review.
* Patient-Reported Outcomes: Patient quality of life assessed using BPI-SF, BFI, and EQ-5D-5L up to 12 months post-treatment discontinuation.
* Pharmacokinetic and Pharmacodynamic Evaluations: Include trough levels for apalutamide and its metabolites, optional leuprolide PK sub-study for designated consenting subjects.
* Biomarker Analysis: Plasma-based DNA and tumor markers assessed for predictive value of response or resistance.
* Interim and Final Analyses: Include planned interim analyses for the OS endpoint after approximately 50% and 70% of events have occurred and final efficacy analyses.

# # Schedule of Assessments

| Assessment | Screening | Cycles 1-6 | Every 4 Cycles Thereafter | End of Treatment | Follow-up Phase (Every 4 months) |  
|------------|-----------|------------|--------------------------|------------------|----------------------------------|  
| Informed Consent | X | - | - | - | - |  
| Eligibility Verification | X | - | - | - | - |  
| Randomization | X | - | - | - | - |  
| Study Drug Administration | - | X | X | Until progression | - |  
| Radiographic Evaluation | X | On Study | Every 4 Cycles | - | X |  
| Adverse Event Monitoring | - | X | X | X | - |  
| Vital Signs and ECOG PS | X | Every Cycle | Every 4 Cycles | X | - |  
| Laboratory Tests | X | Every Cycle | Every 4 Cycles | X | - |  
| PROs: BPI-SF, BFI, EQ-5D-5L | X | Cycle 1 Day 1, every 4 Cycles | Every 4 Cycles | X | Up to 12 months post-treatment |  
| Pharmacokinetic Sampling | - | Day 1 of Cycles 2, 3, 4, 5, 6 | - | - | - |  
| End-of-Treatment Visit | - | - | - | X | - |  
| Survival, Secondary Endpoints Data Collection | - | - | - | - | X |

This study design and procedure framework ensures rigorous evaluation of apalutamide's efficacy and safety for mHSPC, closely monitoring both therapeutic benefits and potential adverse effects.

# Population

# Study Population

# # Overview of Study Population The study population for this clinical trial consists of male subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). Eligible participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of grade 0 or 1, indicating full activity or restricted activity but ambulatory and capable of light work, respectively. The study focuses on patients with confirmed metastatic disease as evidenced by at least one bone lesion visible on a Technetium 99m (99mTc) bone scan. In cases of a solitary bone lesion, confirmation via computed tomography (CT) or magnetic resonance imaging (MRI) is mandatory.

# # Inclusion Criteria To be eligible for study participation, subjects must meet all the following criteria:

1. 1. Aged 18 years or older, with histologically or cytologically confirmed prostate adenocarcinoma.
2. 2. Presentation of metastatic disease confirmed by positive bone scan with a minimum of one bone lesion. Single bone metastasis requires further confirmation by CT or MRI.
3. 3. ECOG performance status of 0 or 1.
4. 4. Subjects may have received up to six cycles of docetaxel for mHSPC, with the final dose being administered within two months prior to randomization.
5. 5. Hormone-sensitive status indicated by responsiveness to androgen deprivation therapy (ADT).
6. 6. Written informed consent provided by the subject, demonstrating understanding of the study and willingness to comply with protocol requirements.

# # Exclusion Criteria Subjects will be excluded from the study if they meet any of the following conditions:

1. 1. Prior treatment with any other investigational agents or anti-androgens including apalutamide.
2. 2. Radiation therapy or surgical intervention for mHSPC within less than one year before randomization, or more than one course except localized prostate treatment.
3. 3. Hypersensitivity to any components of apalutamide or similar compounds.
4. 4. Contraindications to undergo imaging required for tumor assessment.
5. 5. Significant concurrent medical condition or laboratory finding that, in the Investigator’s opinion, makes the subject unsuitable for study participation.
6. 6. Current or past history of central nervous system metastases.

# # Withdrawal Criteria Subjects may be withdrawn from the study for the following reasons:

1. 1. Subject’s decision to withdraw consent at any time.
2. 2. Investigator’s determination that continuing in the study is not in the subject's best interest or due to adverse events compromising subject safety.
3. 3. Subject’s non-compliance with study procedures or protocol.
4. 4. Requirement for treatment outside the study protocol that may affect the study outcomes.

# # Replacement Policy Subjects who are withdrawn from or drop out of the study prior to receiving any dose of the study drug will be replaced to maintain the intended study power and sample size. Subjects who discontinue after initial dosing will not be automatically replaced unless it occurs within four weeks of randomization and is necessary to maintain statistical power or sample size adequacy according to the study's statistical plan.