# Background

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## Disease Background

Prostate cancer is one of the most common cancers among men, characterized by the growth of cancerous cells in the prostate gland. Metastatic hormone-sensitive prostate cancer (mHSPC) is a state wherein the disease has spread beyond the prostate and remains responsive to hormonal therapy. Despite advances in treatment, mHSPC continues to pose significant challenges due to its progression, ultimately leading to castration-resistant prostate cancer (CRPC) if not adequately managed.

## Current Treatment Landscape

The conventional treatment for metastatic hormone-sensitive prostate cancer typically involves androgen deprivation therapy (ADT), either through surgical castration or medical castration using gonadotropin-releasing hormone analogs (GnRHa). While ADT is initially effective in reducing testosterone levels and controlling tumor progression, most patients inevitably develop resistance over time. The advent of newer hormonal agents has provided additional therapeutic options; however, optimal treatment strategies and combinations continue to be evaluated for improved outcomes.

## Product Background

JNJ-56021927, known as apalutamide, is an orally available, non-steroidal, potent, and selective antagonist of the androgen receptor (AR). It acts by inhibiting the AR signaling pathway, which plays a critical role in the growth and survival of prostate cancer cells. Apalutamide has demonstrated efficacy in preclinical and clinical settings for the treatment of prostate cancer, and it is being investigated for its potential benefits in combination with ADT in patients with mHSPC.

## Study Rationale

The rationale for this study arises from the need to enhance treatment options for patients with mHSPC by combining apalutamide with standard ADT. The primary objective is to assess whether the addition of apalutamide to ADT improves radiographic progression-free survival (rPFS) or overall survival (OS) compared to ADT alone. Secondary outcomes will explore additional clinical benefits, such as the delay in pain progression, use of opioids, skeletal-related events (SREs), and initiation of cytotoxic chemotherapy. The study also aims to characterize the safety profile and pharmacokinetics/pharmacodynamics of apalutamide, thereby providing comprehensive data to support its potential role in the treatment paradigm of mHSPC.

# Objectives

# Objectives

## 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) in subjects with metastatic hormone-sensitive prostate cancer (mHSPC).

## Primary Endpoint(s) 1. Radiographic progression-free survival (rPFS) as defined by the time from randomization to first documentation of radiographic disease progression or death from any cause. 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 for prostate cancer, 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 the pharmacodynamic effect of leuprolide on testosterone concentrations when used alone or in combination with apalutamide. 5. To evaluate the treatment effectiveness with the addition of apalutamide to ADT in the subpopulations of subjects with low-volume or high-volume mHSPC.

## Secondary Endpoint(s) 1. Time to pain progression. 2. Time to the initiation of chronic opioid use. 3. Time to skeletal-related events (SREs). 4. Time to initiation of cytotoxic chemotherapy. 5. Safety assessments including incidence and severity of adverse events (AEs), vital sign measurements, and laboratory results.

## 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) and 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 future economic modeling, noting that the construction and reporting of the economic model will be conducted separately from this study.

Each of these objectives is tied closely to specific endpoints to allow for clear, measurable outcomes that align with the study's hypotheses and overall goals.

# Study Design

# Study Design

## Overall Design

This study is a randomized, double-blind, placebo-controlled, multinational, and multicenter Phase 3 clinical trial. It aims to assess the efficacy and safety of adding apalutamide to androgen deprivation therapy (ADT) compared to ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). Approximately 1,000 subjects will be enrolled, adhering to strict inclusion and exclusion criteria. Key stratification factors for randomization will include Gleason score at diagnosis, geographic region, and prior docetaxel use. Participants will be randomly assigned 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 to evaluate eligibility based on set inclusion and exclusion criteria.
2. 2. Treatment Phase: Subjects receive treatment in 28-day cycles. Treatment continues until disease progression, unacceptable toxicity, or study termination by the sponsor.
3. 3. End-of-Treatment Visit: Conducted within 30 days of the last dose of the study drug.
4. 4. Follow-up Phase: Includes data collection every 4 months for survival, secondary endpoints, and subsequent therapies.
5. 5. Open-label Extension Phase: Initiated upon positive study results, allowing active treatment with apalutamide.
6. 6. Long-Term Extension Phase: Applicable for subjects continuing to derive benefit from the study drug.

## Study Duration

The study is anticipated to last approximately 54 months. This includes an enrollment period of 30 months, followed by continued observation to reach the required number of events for primary endpoint analysis.

## Treatment Groups

1. 1. Group 1: Apalutamide (240 mg) plus ADT.
2. 2. Group 2: Placebo plus ADT.
3. ADT is administered as standard of care, through medical castration with GnRH analogs or surgical castration, with the choice of GnRHa at the investigator's discretion.

## Study Procedures

1. 1. Baseline Assessments: Comprehensive initial evaluations including physical examination, ECOG performance status, laboratory tests, and imaging studies.
2. 2. Treatment Administration: Daily oral administration of apalutamide or placebo, alongside continuous ADT.
3. 3. Ongoing Assessments: Regular health evaluations throughout treatment cycles, monitoring for efficacy and safety through physical examinations, laboratory tests, and imaging studies.
4. 4. Safety Monitoring: Continuous adverse event reporting, with evaluations using NCI-CTCAE criteria and dose modifications as required.
5. 5. Specific Subsets and Exploratory Analyses:
6. - Pharmacokinetic sampling for both apalutamide and leuprolide.
7. - Biopsy and blood tests for biomarker evaluation.
8. - Health-related quality of life assessments via specific PRO measures.

## Schedule of Assessments

| Assessment/Visit | Screening Phase | Every Cycle (28 days) | End-of-Treatment | Follow-up (Every 4 Months) |  
|-------------------------|-----------------|-----------------------|-------------------|----------------------------|  
| Informed Consent | X | | | |  
| Eligibility Review | X | | | |  
| Randomization | | X | | |  
| Physical Examination | X | X | X | |  
| Laboratory Tests | X | X | X | |  
| Imaging Studies | X | X (As Specified) | | X |  
| Adverse Event Monitoring| | Continuous | X | X |  
| PRO Measures | | X | X | X (up to 12 months) |  
| Pharmacokinetic Sampling| | X (Selected Cycles) | | |  
| Biomarker Collection | X | | | |

This structure ensures consistent and thorough data collection across all phases of the study, optimizing the reliability and validity of study outcomes.

# Population

# Study Population

## Overview of Study Population

The study population will consist of male subjects with a confirmed diagnosis of metastatic hormone-sensitive prostate cancer (mHSPC). All subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of grade 0 or 1. Eligible participants must have evidence of distant metastatic disease, confirmed through imaging studies. Prior to randomization, specific treatment parameters and timelines pertinent to the mHSPC intervention will be assessed.

## Inclusion Criteria

1. 1. Male subjects aged 18 years or older with a diagnosis of prostate cancer.
2. 2. ECOG performance status of 0 or 1.
3. 3. Evidence of metastatic disease as confirmed by a positive bone scan (one or more bone lesions on Technetium 99m [99mTc]) with a requirement for CT or MRI confirmation if there is a single bone lesion.
4. 4. Up to 6 cycles of prior docetaxel therapy for mHSPC are allowed, with the last dose administered no more than 2 months before randomization.
5. 5. Prior treatment can include up to 6 months of androgen deprivation therapy (ADT) for mHSPC before randomization.
6. 6. Subjects may have received a maximum of one course of radiation or surgical intervention for mHSPC.
7. 7. For previous localized prostate cancer, a maximum of 3 years of total ADT and other therapies (radiation therapy, prostatectomy, lymph node dissection, systemic therapies) is permissible, provided such treatments were completed at least one year before randomization.

## Exclusion Criteria

1. 1. Previously received more than 6 cycles of docetaxel for mHSPC.
2. 2. Currently has clinically significant comorbid conditions that could interfere with the study assessments or the safety of the subject including uncontrolled infection or significant cardiovascular disease.
3. 3. Previous treatment with apalutamide or other androgen receptor inhibitors.
4. 4. History of another malignancy within 3 years prior to randomization, except adequately treated basal cell or squamous cell skin cancer or in-situ cancers.
5. 5. Participation in another clinical study with an investigational agent or intervention within 30 days prior to randomization.
6. 6. Any condition that, in the opinion of the investigator, would interfere with the study endpoints or patient's safety.
7. ## Withdrawal Criteria
8. 1. Development of unacceptable toxicity related to the study drug that cannot be managed with dose adjustments.
9. 2. Subject withdrawal of consent.
10. 3. Investigator decision that continuation in the study is not in the best interest of the subject.
11. 4. Sponsor decision to terminate the study.

## Replacement Policy

Subjects who withdraw from the study during the Screening Phase will be replaced to meet the enrollment target. However, subjects who discontinue after randomization will not be replaced. The study will aim to achieve a robust sample size to ensure the statistical power and validity of the efficacy and safety analyses remain unaffected by attritional losses.

# Procedures

## Study Procedures

## Study Procedures Overview This section outlines the procedures to be conducted throughout the study, including screening, treatment, and follow-up phases, to ensure protocol adherence and gather necessary data.

## Screening/Baseline Procedures 1. Informed Consent - Timing: Must be obtained prior to conducting any study-specific procedures. - Specific Requirements: Educate participants on study objectives, procedures, risks, and benefits. - Responsible Personnel: Study Coordinator or Investigator.

1. 2. Demographics and Medical History
2. - Timing: At screening visit.
3. - Specific Requirements: Collect demographic data and comprehensive medical history.
4. - Responsible Personnel: Clinical Research Associate (CRA) or Study Nurse.
5. 3. Physical Examination
6. - Timing: At screening and baseline visits.
7. - Specific Requirements: Complete physical examination as per standard medical practice.
8. - Responsible Personnel: Physician or Qualified Healthcare Professional.
9. 4. Vital Signs
10. - Timing: At screening and baseline visits.
11. - Specific Requirements: Includes blood pressure, heart rate, respiratory rate, and temperature.
12. - Responsible Personnel: Study Nurse or CRA.
13. 5. ECOG Performance Status
14. - Timing: At screening visit.
15. - Specific Requirements: Assess ECOG performance status to determine eligibility.
16. - Responsible Personnel: Investigator or Study Nurse.
17. 6. Laboratory Assessments
18. - Timing: At screening and prior to randomization.
19. - Specific Requirements: Blood samples for hematology, clinical chemistry, and PSA levels.
20. - Responsible Personnel: Laboratory Technician.
21. 7. Disease Assessment Imaging
22. - Timing: At baseline.
23. - Specific Requirements: Bone scan and CT/MRI for disease confirmation.
24. - Responsible Personnel: Radiologist.
25. 8. ECG
26. - Timing: At screening visit.
27. - Specific Requirements: Standard 12-lead ECG.
28. - Responsible Personnel: Technician or Qualified Healthcare Professional.
29. 9. Inclusion/Exclusion Criteria Review
30. - Timing: Prior to randomization.
31. - Specific Requirements: Confirm eligibility based on protocol-specified criteria.
32. - Responsible Personnel: Investigator.

## Treatment Phase Procedures 1. Drug Administration - Timing: Daily dosing. - Specific Requirements: Apalutamide or placebo with or without food as per randomization. - Responsible Personnel: Subject and Investigator oversight.

1. 2. Safety Monitoring
2. - Timing: At each study visit.
3. - Specific Requirements: Monitor for adverse events and intolerances.
4. - Responsible Personnel: Study Nurse or Investigator.
5. 3. Efficacy Assessments
6. - Timing: As per schedule.
7. - Specific Requirements: Radiographic assessment for progression, PSA measurement.
8. - Responsible Personnel: Investigator or CRA.
9. 4. Laboratory Tests
10. - Timing: At every treatment cycle.
11. - Specific Requirements: Blood samples for routine lab tests, PK sampling.
12. - Responsible Personnel: Laboratory Technician.
13. 5. Quality of Life Assessments
14. - Timing: Regular intervals during treatment.
15. - Specific Requirements: Administration of BPI-SF, BFI, and EQ-5D-5L questionnaires.
16. - Responsible Personnel: CRA or Study Nurse.
17. 6. Adverse Event Monitoring
18. - Timing: Continuous throughout the study.
19. - Specific Requirements: Document and assess all adverse events.
20. - Responsible Personnel: Investigator.
21. 7. Concomitant Medication Review
22. - Timing: At each visit.
23. - Specific Requirements: Document all concurrent medications.
24. - Responsible Personnel: Study Nurse.

## Follow-up Procedures 1. Safety Follow-up - Timing: 30 days post-treatment end. - Specific Requirements: Conduct safety evaluations, adverse event follow-up. - Responsible Personnel: Investigator or CRA.

1. 2. Disease Assessment
2. - Timing: Every 4 months during follow-up.
3. - Specific Requirements: Document progression and subsequent therapies.
4. - Responsible Personnel: Investigator.
5. 3. Survival Status
6. - Timing: Every 4 months during follow-up phase.
7. - Specific Requirements: Record survival and cause of death if applicable.
8. - Responsible Personnel: CRA.
9. 4. Subsequent Therapy Documentation
10. - Timing: At follow-up visits.
11. - Specific Requirements: Detail any subsequent cancer therapies.
12. - Responsible Personnel: Investigator or CRA.

## Safety Assessments - Conduct thorough physical examinations and vital signs at specified intervals. - Monitor laboratory tests for clinically significant changes. - Continual adverse event monitoring and ECG assessments as needed.

## Efficacy Assessments - Perform radiographic assessments using RECIST criteria. - Track PSA levels and assess clinical progression. - Pain assessments and quality of life measures via questionnaires.

## Laboratory Assessments - Include comprehensive hematology, clinical chemistry, and specialized PK samples. - Process samples for PSA and testosterone.

## Other Assessments - Implement patient-reported outcomes and resource utilization tracking. - Collect biomarker samples for exploratory analysis.

# Statistical

# Statistical Analysis

## Statistical Hypotheses The primary hypotheses of the study are: 1. The addition of apalutamide to androgen deprivation therapy (ADT) results in a statistically significant improvement in radiographic progression-free survival (rPFS) compared to ADT alone. 2. The addition of apalutamide to ADT results in a statistically significant improvement in overall survival (OS) compared to ADT alone.

## Sample Size Determination An overall type I error rate of 5% will be controlled across the dual-primary endpoints using a split alpha level: 0.005 for rPFS and 0.045 for OS. It is estimated that 368 events of rPFS are needed to achieve at least 85% power to detect a hazard ratio (HR) of 0.67 at a two-tailed significance level of 0.005. For OS, approximately 410 deaths will ensure 80% power to detect a HR of 0.75, assuming a median OS of 44 months for the control group. Approximately 1,000 subjects will be enrolled with a study duration of 54 months.

## Analysis Populations - Intent-to-Treat (ITT) Population: Includes all randomized subjects. Used for all efficacy analyses. - Safety Population: Includes all randomized subjects who received at least one dose of study medication. Analyses of safety outcomes will use this population.

## Statistical Methods Time-to-event data for rPFS and OS will be analyzed using the Kaplan-Meier method to estimate medians and will employ the Cox proportional hazards model to estimate hazard ratios with corresponding 95% confidence intervals. Secondary and exploratory endpoints such as time to pain progression, time to skeletal-related events (SREs), and time to initiation of cytotoxic chemotherapy will be similarly analyzed. For continuous exploratory endpoints and changes in quality of life measures, analysis of covariance (ANCOVA) will be employed, while categorical endpoints will use logistic regression as appropriate.

## Interim Analyses Two interim analyses for overall survival are planned at approximately 50% (205 events) and 70% (287 events) of expected OS events. A Lan-DeMets alpha spending function will guide early stopping for efficacy. No interim analysis is planned for rPFS.

## Missing Data Handling Missing data will be addressed using multiple imputation techniques assuming data is missing at random. Sensitivity analyses will assess the robustness of inferences to the missing data assumptions.

## Multiplicity Adjustments A hierarchical testing procedure will be adopted due to the dual-primary endpoints. The overall type I error rate will be controlled using a two-part approach where rPFS (alpha = 0.005) and OS (alpha = 0.045) results will be independently assessed. Adjustments for multiple comparisons among secondary endpoints will be performed using the Hochberg procedure or similar methodology, ensuring control of the family-wise error rate.

This statistical analysis plan ensures the rigorous assessment of the effects of apalutamide in combination with ADT, with appropriate consideration for multiplicity and assumptions concerning missing data.

# Safety

# Safety

## Safety Parameters The safety parameters in this study include the incidence and intensity of treatment-emergent adverse events (AEs), clinically significant changes in physical examination findings, vital signs, and clinical laboratory results. These safety parameters help assess the overall safety profile of apalutamide when added to ADT in subjects with mHSPC.

## Adverse Event Definitions Adverse events will be defined and graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. AEs will be categorized based on their severity as follows: - Grade 1: Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. - Grade 4: Life-threatening consequences; urgent intervention indicated. - Grade 5: Death related to AE.

## Adverse Event Reporting AEs will be documented from the time of informed consent until 30 days after the last dose of the study drug. All serious adverse events (SAEs) must be reported to the sponsor within 24 hours of the investigator becoming aware. Non-serious AEs should be documented in the subject's case records and reported as per the periodic safety reporting schedule.

## Safety Monitoring Safety monitoring will be continuous throughout the study. It includes regular assessment of AEs, vital signs, clinical laboratory tests, and physical examinations. Dose modifications or discontinuations due to safety concerns will follow the protocol-specified rules.

## Risk Management Potential risks associated with apalutamide include common anti-androgen related AEs such as fatigue, hypertension, and skin rash. Risk management strategies include regular monitoring, dose adjustment protocols, and predefined discontinuation criteria for specific safety concerns. Informed consent will ensure subjects are aware of these risks before participation.

## Data Monitoring Committee An Independent Data Monitoring Committee (IDMC) will be responsible for overseeing the safety of subjects and the integrity of the data throughout the study. The IDMC will review interim data and provide recommendations on whether to continue, modify, or stop the study based on safety and efficacy data.

## Stopping Rules Stopping rules include criteria for the discontinuation of the study drug in individual subjects due to unacceptable toxicity and criteria for early study termination based on interim safety and efficacy results. The IDMC will conduct planned interim efficacy analyses and regular safety reviews to determine if the study should continue as planned or if amendments are required for safety reasons. Interim analyses of overall survival are planned after approximately 50% and 70% of expected death events.

By following these procedures, the study aims to ensure the safety and well-being of all participants while collecting crucial data on the safety profile of apalutamide in combination with ADT.