Clinical Trial Protocol

# 1.1 Table of Contents

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# 1.2 Background

Background

Disease Background  
Prostate cancer is one of the most common malignancies affecting men worldwide. Metastatic hormone-sensitive prostate cancer (mHSPC) is a stage of the disease where cancer has spread beyond the prostate gland and remains sensitive to treatments that lower testosterone levels. Despite the initial response to androgen deprivation therapy (ADT), most patients eventually progress to castration-resistant prostate cancer, which is associated with poorer outcomes and limited treatment options. The need for more effective therapeutic strategies in the management of mHSPC remains critical to improve survival and quality of life in this patient population.

Current Treatment Landscape  
The cornerstone of treatment for mHSPC is androgen deprivation therapy (ADT), achieved either through surgical castration or medical castration using gonadotropin-releasing hormone (GnRH) analogs. While ADT is initially effective in controlling the disease by reducing testosterone levels, disease progression is inevitable. Recent advances have integrated systemic therapies such as docetaxel and novel hormonal agents, including abiraterone acetate and enzalutamide, into the treatment regimen at earlier stages, demonstrating improved survival outcomes. Despite these advancements, there is still a significant unmet need for therapies that can delay progression and improve long-term outcomes for patients with mHSPC.

Product Background  
Apalutamide (JNJ-56021927) is a next-generation, non-steroidal anti-androgen that acts by selectively binding to the androgen receptor, inhibiting its activity. This mechanism effectively prevents the androgen receptor from translocating to the nucleus and activating target genes that contribute to cancer cell proliferation and survival. Apalutamide has been developed in the context of addressing the limitations of current treatments, particularly in prolonging progression-free survival in patients with prostate cancer. Its efficacy and safety profile have been previously demonstrated in clinical settings, leading to interest in its potential benefits when combined with ADT in the mHSPC population.

Study Rationale  
This Phase 3 study is designed to evaluate whether the addition of apalutamide to standard ADT provides superior clinical benefits compared to ADT alone in subjects with mHSPC. The rationale for this study stems from the hypothesis that combining apalutamide with ADT can synergistically enhance therapeutic outcomes by more effectively inhibiting androgen receptor signaling, thereby delaying disease progression and potentially improving overall survival. Furthermore, the study aims to explore secondary and exploratory outcomes, including pain progression, opioid use, skeletal-related events, and quality of life measures, to comprehensively assess the potential advantages of adding apalutamide to the treatment regimen. The study is also positioned to provide insights into the safety and population pharmacokinetics of apalutamide in this patient cohort, with a focus on identifying biomarkers associated with response and resistance to therapy.

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

Primary Endpoint(s)  
1. Radiographic progression-free survival (rPFS) as assessed by the investigator.  
2. Overall survival (OS) from randomization to 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 initiation of cytotoxic chemotherapy.  
2. To characterize the safety 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 PD 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 for the subpopulations of subjects with low-volume or high-volume mHSPC.

Secondary Endpoint(s)  
1. Time to pain progression.  
2. Time to skeletal-related events (SREs).  
3. Time to chronic opioid use.  
4. Time to initiation of cytotoxic chemotherapy.  
5. Incidence and severity of adverse events (AEs).  
6. Evaluation of apalutamide and its metabolite concentrations over time.  
7. Description of testosterone concentrations in subjects treated with leuprolide alone or in combination with apalutamide.  
8. Subgroup analyses for low-volume and high-volume mHSPC.

Other Objectives  
1. To evaluate exploratory biomarkers predictive of response and resistance to treatment.  
2. To evaluate patient-relevant outcomes, including symptoms (e.g., pain, fatigue, urination) and function (e.g., 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 that may be used in future economic modeling.

Other Endpoint(s)  
1. Biomarker response and resistance assessments.  
2. Change from baseline in patient-reported outcomes (PROs) using instruments like BPI-SF, BFI, and EQ-5D-5L.  
3. Health-related quality of life measures compared between treatment arms.  
4. Documentation of medical encounters and resource utilization during treatment.

# 13.1 Study Design

Study Design

Overall Design  
This is a Phase 3, randomized, double-blind, placebo-controlled, multinational, and multicenter clinical study 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). The study aims to determine whether the addition of apalutamide to ADT can improve radiographic progression-free survival (rPFS) and overall survival (OS). Eligible subjects will be randomized in a 1:1 ratio to receive either apalutamide plus ADT or matching placebo plus ADT, with the randomization stratified by Gleason score at diagnosis, geographic region, and prior docetaxel use.

Study Schema  
The study consists of the following phases:

1. • Screening Phase\*\*: Up to 28 days before randomization to establish study eligibility.
2. • Treatment Phase\*\*: Subjects will receive treatment in 28-day cycles until disease progression, unacceptable toxicity, or study termination.
3. • Follow-up Phase\*\*: Data collection, every 4 months, will include survival and secondary endpoints until death, withdrawal, lost to follow-up, or study termination.
4. • Open-label Extension Phase\*\*: Initiated upon positive interim or final analysis results; subjects can receive active drug (apalutamide) for approximately 3 years.
5. • Long-Term Extension Phase\*\*: For subjects benefiting from apalutamide, extends treatment post-final analysis cut-off or site approval of Amendment 5.

Study Duration  
The study is expected to enroll subjects over 30 months, with an estimated total study duration of 54 months to achieve the required number of death events for the overall survival endpoint. The total planned enrollment is approximately 1,000 subjects.

Treatment Groups

|  |  |  |
| --- | --- | --- |
| Group | Intervention | Description |
| ------------------ | -------------------------- | ------------------------------------------------------------------ |
| Group 1 | Apalutamide + ADT | Subjects receive 240 mg (4 x 60 mg tablets) of apalutamide daily along with ADT |
| Group 2 | Placebo + ADT | Subjects receive matching placebo tablets along with ADT |

In both groups, ADT may be administered as medical or surgical castration, with medical castration using a GnRH analog selected at the investigator's discretion. The dosing for GnRHa will follow standard prescribing information, and concurrent GnRHa therapy must be documented for subjects without surgical castration.

Study Schema

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graph TD  
 A[Screening] --> B[Randomization]  
 B --> C[Treatment Group 1]  
 C --> F[Follow-up]  
 B --> D[Treatment Group 2]  
 D --> F[Follow-up]  
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# 19.1 Population

Study Population

Overview of Study Population  
The study includes subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC), characterized by the presence of distant metastatic disease confirmed by bone scan, computed tomography (CT), or magnetic resonance imaging (MRI). Eligible subjects will have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, indicating they are fully active or restricted in physically strenuous activity but ambulatory.

Inclusion Criteria  
1. Male subjects aged 18 years or older.  
2. Diagnosis of prostate cancer with documentation of metastatic disease via:  
 - Positive bone scan with at least one bone lesion.  
 - For subjects with a single bone lesion, confirmation by CT or MRI is required.  
3. ECOG performance status of 0 or 1.  
4. Prior receipt of up to 6 cycles of docetaxel for mHSPC, with the last dose administered no more than 2 months before randomization.  
5. Maximum of 6 months of androgen deprivation therapy (ADT) prior to randomization.  
6. Maximum of one course of radiation or surgical intervention for mHSPC.  
7. For localized prostate cancer, prior treatments including radiation therapy, prostatectomy, lymph node dissection, and systemic therapies were completed at least 1 year before randomization.  
8. Ability to swallow oral medication.  
   
## Exclusion Criteria  
1. Prior treatment with second-generation anti-androgens or inhibitors, such as apalutamide, abiraterone acetate, or enzalutamide.  
2. Known history of severe hypersensitivity reaction to study drugs or their excipients.  
3. Significant concurrent medical condition that could interfere with study participation or interpretation of results.  
4. Active or symptomatic viral hepatitis or chronic liver disease.  
5. Use of herbal products known to affect the PSA velocity within 4 weeks prior to randomization.  
6. Existing conditions that the investigator deems would affect patient compliance or completion of the study.

Withdrawal Criteria  
1. Subject voluntarily withdraws consent for the study.  
2. Investigator determines that continued participation would not be in the best interest of the subject.  
3. Persistent significant study protocol non-compliance.

Replacement Policy  
Subjects who withdraw or are withdrawn from the study will not be replaced. The original sample size was calculated to account for potential early terminations to ensure sufficient power to detect a difference in primary endpoints.

# 24.1 Procedures

Study Procedures

Study Procedures Overview  
This section outlines the specific procedures conducted throughout the study, detailing the activities during each phase: screening, treatment, and follow-up. Procedures are structured to ensure comprehensive and consistent data collection across all sites.

Screening/Baseline Procedures  
Prior to enrollment, the following assessments will be completed within a 28-day period to determine participant eligibility:

1. • Informed Consent\*\*: Ensure participants understand the study's purpose, procedures, potential risks, and benefits. Responsible personnel: Principal Investigator or delegated study team member.
2. • Demographics and Medical History Collection\*\*: Document participant demographic data and comprehensive medical history. Responsible personnel: Study Coordinator.
3. • Physical Examination\*\*: Conduct a thorough physical examination to assess general health status. Responsible personnel: Qualified Medical Practitioner.
4. • Vital Signs Measurement\*\*: Record blood pressure, heart rate, temperature, and respiratory rate. Responsible personnel: Nurse or study nurse.
5. • Laboratory Assessments\*\*:
6. • Hematology and clinical chemistry panels.
7. • PSA levels and testosterone concentration.
8. • Responsible personnel: Lab Technician or qualified personnel.
9. • Disease Assessment\*\*: Radiographic imaging (CT/MRI and bone scan) to confirm metastatic hormone-sensitive prostate cancer (mHSPC). Responsible personnel: Radiologist.
10. • Inclusion/Exclusion Criteria Review\*\*: Evaluate participants against the study's criteria to confirm eligibility. Responsible personnel: Principal Investigator.

Treatment Phase Procedures  
Participants who meet eligibility criteria will be randomized into either the apalutamide plus ADT or placebo plus ADT group. Treatment will be administered in 28-day cycles.

1. • Drug Administration\*\*:
2. • Administer 240-mg apalutamide or matching placebo daily.
3. • Maintain consistent use of ADT (either medical or surgical) per SOC.
4. • Responsible personnel: Pharmacist or study nurse.
5. • Safety Monitoring\*\*:
6. • Regular monitoring for adverse events and dose adjustments as necessary.
7. • Responsible personnel: Study Physician.
8. • Efficacy Assessments\*\*:
9. • Conduct radiographic assessments per modified RECIST 1.1 guidelines.
10. • Evaluate progression-free survival and overall survival.
11. • Responsible personnel: Oncologist or designated radiologist.
12. • Laboratory Tests\*\*:
13. • Monthly hematology and clinical chemistry panels.
14. • Regular monitoring of testosterone levels.
15. • Responsible personnel: Lab Technician.
16. • Quality of Life Assessments\*\*:
17. • Administer questionnaires such as BPI-SF, BFI, and EQ-5D-5L.
18. • Responsible personnel: Study Coordinator.
19. • Adverse Event Monitoring\*\*:
20. • Continuously assess for and record any treatment-emergent adverse events (AEs).
21. • Responsible personnel: Study Physician or nurse.
22. • Concomitant Medication Review\*\*:
23. • Document all medications administered concurrently.
24. • Responsible personnel: Study Coordinator.

Follow-up Procedures  
Upon discontinuation of study treatment, subjects will enter a follow-up phase.

1. • Safety Follow-Up\*\*: Conduct safety assessments 30 days post-treatment. Responsible personnel: Study Physician.
2. • Disease Assessment\*\*:
3. • Document disease progression, radiographic and clinical.
4. • Responsible personnel: Oncologist.
5. • Survival Status\*\*: Update survival status every 4 months. Responsible personnel: Study Coordinator.
6. • Subsequent Therapy Documentation\*\*: Record any additional therapies received for prostate cancer. Responsible personnel: Study Coordinator.

Safety Assessments  
- Routine physical examinations and vital sign checks.  
- Laboratory tests including hematology and chemistry panels.  
- Continuous adverse event monitoring and reporting.  
- ECG monitoring as clinically indicated.

Efficacy Assessments  
- Radiographic and clinical assessments to measure rPFS and OS.  
- Patient-reported outcomes using validated scales.  
- Quality of life measures throughout the study.

Laboratory Assessments  
- Regular analysis of hematology and clinical chemistry.  
- Biomarker sampling to investigate treatment resistance or response.  
- Conduct PK/PD assessments where indicated, with special long-term storage instructions for bio-samples.

Other Assessments  
- \*\*Pharmacokinetic Evaluations\*\*: Collection of trough PK samples on specified days.  
- \*\*Biomarker Analysis\*\*: Evaluation of circulating DNA and AR gene anomalies.  
- \*\*Medical Resource Utilization\*\*: Collect and document data for future economic analyses. Responsible personnel: Health Economist.

Each procedure must be conducted with attention to patient comfort, adherence to protocol guidelines, and specific ethical considerations. All data should be accurately recorded in the electronic case report form (eCRF).

# 33.1 Statistical

Statistical Analysis

Statistical Hypotheses  
The primary hypothesis of this study is that the combination of apalutamide with androgen deprivation therapy (ADT) will statistically significantly improve radiographic progression-free survival (rPFS) or overall survival (OS), or both, compared to ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). The null hypothesis states that there is no difference in rPFS or OS between the two treatment groups. Each primary endpoint will be tested within a pre-specified significance level with the use of appropriate methods to adjust for multiplicity.

Sample Size Determination  
The study is designed to control the overall type I error rate at 5% with a 2-tailed significance level. For the two primary endpoints, a significance level of 0.005 is allocated for rPFS and 0.045 for OS. The study requires approximately 368 rPFS events to provide at least 85% power to detect a hazard ratio (HR) of 0.67 and 410 OS events to ensure 80% power to detect a HR of 0.75, assuming median OS of 44 months in the control arm. Enrollment will be approximately 1,000 subjects over 30 months with a total study duration of 54 months to observe the required number of events.

Analysis Populations  
The Intent-to-Treat (ITT) population, consisting of all randomized subjects, will be used for efficacy analysis. Safety analysis will be conducted on the Safety Population, which includes all subjects who receive at least one dose of the study drug. The ITT population will also be employed for the primary analysis of subject disposition and for other efficacy endpoints.

Statistical Methods  
Time-to-event data such as rPFS and OS will be analyzed using the Kaplan-Meier method to estimate survival functions. The Cox proportional hazards model will be employed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to compare the treatment groups. Secondary endpoints such as time to pain progression, skeletal-related events (SREs), opioid use, and initiation of cytotoxic chemotherapy will also be analyzed using similar methods.

Interim Analyses  
Two interim analyses for OS will be conducted at approximately 50% (205 events) and 70% (287 events) of the 410 required OS events. An O'Brien-Fleming alpha spending function will guide interim statistical analysis for OS, ensuring control for type I error. The final analysis of the rPFS will be conducted at the first interim analysis of OS when the required events for rPFS have been observed. No interim analysis is planned solely for the rPFS endpoint.

Missing Data Handling  
Missing data for key endpoints such as rPFS and OS will be managed using a censoring strategy where subjects without observed events by the cutoff time will be censored at the last known follow-up date. Sensitivity analyses using multiple imputation for missing data will also be considered to validate the robustness of the primary findings.

Multiplicity Adjustments  
A closed testing procedure will be utilized to control the overall type I error rate due to multiple endpoints. The study will employ branching logic where primary endpoints are hierarchically tested for significance, meaning that if rPFS is significant and OS subsequently demonstrates significance, both endpoints can be declared positive. Adjustments will be made according to pre-specified allocation of alpha levels.

# 41.1 Safety

Safety

Safety Parameters  
Safety evaluations in this study will focus on the incidence and intensity of treatment-emergent adverse events (AEs), clinically significant changes in physical examinations, vital signs, and clinical laboratory results. Specific parameters include hematology and clinical chemistry panels, ECOG performance status changes, and any required dose modifications based on adverse findings.

Adverse Event Definitions  
Adverse Events are defined following the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. AEs will be categorized based on severity, with grades ranging from mild (Grade 1) to severe (Grade 4), and any instances leading to death will be designated as Grade 5. Attention will be given to any serious adverse events (SAEs), which include those resulting in death, life-threatening situations, hospitalization, incapacitation, congenital anomaly, or significant medical intervention.

Adverse Event Reporting  
All AEs will be recorded from the time of informed consent signing until 30 days post the final dose of study medication. Investigators are required to report SAEs within 24 hours of awareness. AEs will be assessed for causality related to the study drug, and any associated dose modification will be documented according to protocol-specific guidelines.

Safety Monitoring  
Safety monitoring consists of routine evaluations including physical examinations, vital sign checks, laboratory tests, and performance status assessments throughout the Screening, Treatment, and Follow-up Phases. Any significant abnormalities identified during these evaluations will trigger further investigation and appropriate medical management as required.

Risk Management  
Risk management strategies involve prompt identification and mitigation of potential risks associated with the study drug. This includes the application of predefined dose modification rules in response to AEs and close monitoring of potential drug interactions. Continuous education for trial staff and subjects on possible side effects and their management is also emphasized.

Data Monitoring Committee  
An independent Data Monitoring Committee (IDMC) has been established to provide oversight on safety data and interim efficacy analysis. The IDMC will conduct regular safety reviews and make recommendations concerning trial continuance, modifications, or early termination based on risk-benefit assessments.

Stopping Rules  
The trial may be halted following IDMC recommendations if a predefined threshold of adverse events is exceeded, jeopardizing subject safety, or if it becomes ethically unguided to continue due to overwhelming efficacy or futility. Emergency unblinding procedures are in place for situations requiring urgent safety interventions.

Safety oversight in this study is designed to ensure not only the ethical conduct of the trial but also the safety and well-being of all participants throughout its duration.