Clinical Trial Protocol

# Background

Background

Disease Background  
Metastatic hormone-sensitive prostate cancer (mHSPC) is a form of prostate cancer where the disease has spread beyond the prostate gland but remains responsive to therapies that suppress androgen activity. Prostate cancer itself is one of the most commonly diagnosed cancers in men, and its progression to the metastatic stage significantly impacts survival rates and quality of life. The disease burden is substantial, given its prevalence and the progression to more aggressive disease states over time if left unchecked. The management of mHSPC involves controlling the proliferation and spread of cancer cells predominantly driven by androgen signaling.

Current Treatment Landscape  
The current standard of care for managing mHSPC includes androgen deprivation therapy (ADT), which is aimed at reducing levels of male hormones that stimulate the growth of prostate cancer cells. ADT can be achieved through medical castration using gonadotropin-releasing hormone (GnRH) analogs, such as leuprolide, or via surgical castration. While effective in the short term, many patients eventually develop resistance to ADT alone, leading to disease progression. Additional treatments may include chemotherapy with agents like docetaxel, particularly in patients with high-volume disease, as well as radiation therapy and surgery in select cases. However, there remains an unmet need for treatment strategies that extend survival and improve the quality of life without significantly increasing adverse events.

Product Background  
Apalutamide (JNJ-56021927) is an innovative second-generation non-steroidal anti-androgen designed to selectively inhibit the androgen receptor (AR). It works by blocking the effects of androgens, thereby inhibiting the growth of prostate cancer cells that rely on these hormones. Apalutamide is orally administered and has shown promise in clinical trials by extending progression-free survival in various stages of prostate cancer. By targeting the androgen receptor more effectively than earlier generation anti-androgens, apalutamide has potential advantages in managing advanced prostate cancer, making it a candidate for combination with ADT in treating mHSPC.

Study Rationale  
The rationale for this study stems from the need to improve outcomes in patients with mHSPC by enhancing the efficacy of standard treatment approaches. The combination of apalutamide with traditional ADT aims to provide superior control over disease progression, potentially delaying the transition to castration-resistant prostate cancer and extending overall survival. The hypothesis underlying this study is that dual therapy with apalutamide and ADT will lead to better clinical outcomes compared to ADT alone, while maintaining an acceptable safety profile. This study seeks to establish whether such a regimen can significantly improve radiographic progression-free survival and overall survival among men with mHSPC, meeting an unmet clinical need in the oncological community.

# 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), defined as the time from randomization to first documentation of radiographic progression or death due to 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, skeletal-related events (SREs), and the need for 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 subpopulations of subjects with low-volume or high-volume mHSPC.

Secondary Endpoint(s)  
1. Time to pain progression.  
2. Time to the first use of chronic opioids.  
3. Time to first occurrence of skeletal-related events (SREs).  
4. Time to initiation of cytotoxic chemotherapy.  
5. Incidence and nature of safety outcomes and adverse events.  
6. PK parameters such as trough levels of apalutamide and its metabolite.  
7. Testosterone concentrations and percentage of subjects with testosterone levels <50 ng/dL under treatment.

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 associations with clinical response or time-to-event endpoints.  
2. Patient-reported outcomes including change from baseline in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) subscales, EuroQol EQ-5D-5L Visual Analog Scale (VAS), Brief Pain Inventory-Short Form (BPI-SF) interference subscale, and Brief Fatigue Inventory (BFI).  
3. Time to symptomatic local progression and PSA progression.  
4. Collection and analysis of medical resource utilization data during the Treatment Phase.

# Study Design

Study Design

Overall Design  
This is a Phase 3 randomized, double-blind, placebo-controlled, multinational, and multicenter study that aims 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 enrolled and will undergo stratification based on Gleason score at diagnosis (≤7 versus >7), geographical region (North America and European Union versus other countries), and prior use of docetaxel (yes versus no). Subjects will be randomly assigned in a 1:1 ratio to either the treatment group receiving apalutamide plus ADT or the placebo group receiving ADT alone.

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| **Study Schema** |
| Screening |
| Establish eligibility for participationTreatment |
| Up to 28 days28-day cycles of apalutamide plus ADT vs. placebo plus ADTFollow-up |
| Until progression or toxicityData collection for survival and secondary endpoints |

Study Duration  
The anticipated total duration of the study is approximately 54 months, encompassing approximately 30 months of enrollment and follow-up to capture the necessary number of events for the primary endpoints. The study will continue to collect follow-up data on survival, secondary endpoints, and subsequent therapy until the subject's death, withdrawal, loss to follow-up, or study termination by the sponsor.

Treatment Groups  
Subjects will be divided into two treatment arms:

1. 1. Apalutamide plus ADT Group: Subjects will receive 240 mg of apalutamide (4 x 60-mg tablets) orally once daily, plus standard of care ADT, which includes either medical or surgical castration.
2. 2. Placebo plus ADT Group: Subjects will receive matching placebo tablets daily in addition to standard of care ADT, similar to the apalutamide group.

Both groups will continue treatment until disease progression, unacceptable toxicity, or study termination by the sponsor.

Study Schema

# Population

Study Population

Overview of Study Population  
The study population consists of subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). Subjects must 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 and able to carry out light work. All eligible subjects must have distant metastatic disease, confirmed by positive bone scans or additional imaging for single bone lesions.

Inclusion Criteria  
1. Male subjects aged 18 years or older.  
2. Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma.  
3. Documented metastatic disease with one or more bone lesions on a Technetium 99m bone scan.  
4. ECOG performance status of 0 or 1.  
5. Subjects may have received up to 6 cycles of docetaxel for mHSPC, with the final dose administered ≤2 months before randomization.  
6. Prior ADT is allowed for up to 6 months prior to randomization.  
7. May have received one course of radiation therapy or surgical intervention for mHSPC.  
8. For previously localized prostate cancer, subjects may have received ≤3 years of ADT and other prior therapies completed ≥1 year before randomization.  
9. Adequate organ function confirmed by clinical laboratory tests.

Exclusion Criteria  
1. Presence of brain metastases or leptomeningeal disease.  
2. Any prior systemic anti-cancer therapy for prostate cancer outside the specified intervention limits, including chemotherapy (besides docetaxel as noted), immunotherapy, or investigational agents.  
3. More than one prior course of radiation for mHSPC within a year before randomization.  
4. Documented history of another malignancy within the past 3 years, except in situ non-melanoma skin cancer.  
5. Significant concurrent medical condition or laboratory abnormality that would, in the opinion of the investigator, make participation in the study unsafe.  
6. Known severe hypersensitivity to apalutamide or any of its excipients.  
7. Inability to swallow oral medications or significant gastrointestinal conditions affecting drug absorption.  
8. Active or recent (within 6 months) cardiovascular disease including severe or unstable angina, myocardial infarction, or heart failure.

Withdrawal Criteria  
1. Subject withdrawal of consent.  
2. Occurrence of an adverse event deemed unacceptable by the investigator.  
3. Documented disease progression according to protocol-specified criteria including clinical symptoms.  
4. Initiation of an alternate anti-cancer therapy.  
5. Inability to comply with protocol requirements.

Replacement Policy  
Subjects who withdraw from the study before receiving any study medication and before randomization completion may be replaced to achieve the target enrollment of 1,000 subjects. Subjects who discontinue after treatment initiation will not be replaced, ensuring that subject attrition does not skew study outcomes.

# Procedures

Study Procedures

Study Procedures Overview  
This section outlines the detailed procedures to be conducted throughout the study, structured into screening, treatment, and follow-up phases. Each procedure includes specific requirements, designated timing, and personnel responsibilities.

Screening/Baseline Procedures  
1. \*\*Informed Consent\*\*  
 - Timing: Prior to any study-specific procedures.  
 - Specific Requirements: Obtain signed informed consent from each subject.  
 - Responsible Personnel: Research Coordinator or Investigator.  
   
2. \*\*Demographics and Medical History\*\*  
 - Timing: Initial visit.  
 - Specific Requirements: Collect comprehensive demographic data and detailed medical history.  
 - Responsible Personnel: Research Nurse or Study Coordinator.  
   
3. \*\*Physical Examination\*\*  
 - Timing: Initial visit.  
 - Specific Requirements: Conduct a complete physical examination.  
 - Responsible Personnel: Qualified Physician or Investigator.  
   
4. \*\*Vital Signs\*\*  
 - Timing: At initial visit and as required.  
 - Specific Requirements: Measure and record blood pressure, temperature, heart rate, and respiratory rate.  
 - Responsible Personnel: Clinical Staff or Study Nurse.  
   
5. \*\*Laboratory Assessments\*\*  
 - Timing: Initial visit.  
 - Specific Requirements: Conduct hematology and clinical chemistry tests.  
 - Responsible Personnel: Lab Technician or Research Nurse.  
   
6. \*\*Disease Assessment\*\*  
 - Timing: Initial visit.  
 - Specific Requirements: Confirm metastatic hormone-sensitive prostate cancer (mHSPC) status via imaging.  
 - Responsible Personnel: Oncologist or Radiologist.  
   
7. \*\*Inclusion/Exclusion Criteria Review\*\*  
 - Timing: During the initial assessment and prior to randomization.  
 - Specific Requirements: Review eligibility based on study inclusion and exclusion criteria.  
 - Responsible Personnel: Investigator or Study Coordinator.

Treatment Phase Procedures  
1. \*\*Drug Administration\*\*  
 - Timing: Daily, starting from Cycle 1, Day 1.  
 - Specific Requirements: Administer apalutamide or matching placebo as per randomization.  
 - Responsible Personnel: Pharmacist and Research Nurse.  
   
2. \*\*Safety Monitoring\*\*  
 - Timing: Throughout treatment phase in each cycle (28 days).  
 - Specific Requirements: Monitor adverse events and adjust dosing per protocol.  
 - Responsible Personnel: Investigator and Study Nurse.  
   
3. \*\*Efficacy Assessments\*\*  
 - Timing: Every 12 weeks or as specified.  
 - Specific Requirements: Conduct radiographic assessments and evaluate progression.  
 - Responsible Personnel: Investigator and Radiologist.  
   
4. \*\*Laboratory Tests\*\*  
 - Timing: Pre-dose on Day 1 of Cycles 2, 3, 4, 5, and 6.  
 - Specific Requirements: Assess hematology and chemistry profiles.  
 - Responsible Personnel: Lab Technician.  
   
5. \*\*Quality of Life Assessments\*\*  
 - Timing: Every 12 weeks.  
 - Specific Requirements: Utilize BPI-SF, BFI, and EQ-5D-5L tools.  
 - Responsible Personnel: Research Nurse.  
   
6. \*\*Adverse Event Monitoring\*\*  
 - Timing: Continuous during treatment.  
 - Specific Requirements: Capture any treatment-emergent events.  
 - Responsible Personnel: Investigator and Research Nurse.  
   
7. \*\*Concomitant Medication Review\*\*  
 - Timing: Each visit.  
 - Specific Requirements: Document any medications taken by the subject.  
 - Responsible Personnel: Study Coordinator.

Follow-up Procedures  
1. \*\*Safety Follow-up\*\*  
 - Timing: At end-of-treatment and every 4 months during follow-up.  
 - Specific Requirements: Monitor ongoing safety post-treatment.  
 - Responsible Personnel: Investigator.  
   
2. \*\*Disease Assessment\*\*  
 - Timing: Every 4 months during follow-up.  
 - Specific Requirements: Assess for disease progression or relapse.  
 - Responsible Personnel: Oncologist.  
   
3. \*\*Survival Status\*\*  
 - Timing: Every 4 months during follow-up until study end.  
 - Specific Requirements: Record survival status.  
 - Responsible Personnel: Study Coordinator.  
   
4. \*\*Subsequent Therapy Documentation\*\*  
 - Timing: As applicable during follow-up.  
 - Specific Requirements: Document any additional therapies initiated.  
 - Responsible Personnel: Study Coordinator or Investigator.

Safety Assessments  
- Perform regular physical examinations and vital sign checks.  
- Conduct laboratory tests to monitor clinical chemistry and hematology.  
- Record and assess all adverse events utilizing NCI-CTCAE criteria.  
- ECG monitoring if clinically indicated.

Efficacy Assessments  
- Undertake disease-specific assessments utilizing radiographic imaging.  
- Collect patient-reported outcomes on symptoms and quality of life.  
- Evaluate treatment responses and compare apalutamide plus ADT to ADT alone.

Laboratory Assessments  
- Include regular hematology and clinical chemistry panels.  
- Utilize biomarker sampling and analyze trough PK samples.  
- Ensure proper handling and storage of samples for integrity.

Other Assessments  
- Conduct biomarker analyses for treatment response and resistance.  
- Gather medical resource utilization data for future economic modeling.  
- Additional assessments on specific patient-relevant outcomes like pain and fatigue.

# Statistical

Statistical Analysis

Statistical Hypotheses  
The primary efficacy hypotheses of this study are to test whether apalutamide plus androgen deprivation therapy (ADT) significantly improves radiographic progression-free survival (rPFS) and overall survival (OS) compared to ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). The null hypotheses are that there is no difference between apalutamide plus ADT and ADT alone in terms of rPFS and OS. The alternative hypotheses are that apalutamide plus ADT is superior to ADT alone in at least one of the dual-primary endpoints.

Sample Size Determination  
This study is designed with an overall type I error rate of 5%. The dual-primary endpoints of rPFS and OS guide the sample size determination. It is estimated that approximately 368 events of rPFS are required to achieve at least 85% power to detect a hazard ratio (HR) of 0.67 at a significance level of 0.005 for rPFS. Simultaneously, approximately 410 deaths are needed to ensure 80% power to detect an HR of 0.75 for OS at a two-tailed significance level of 0.045. This calculation assumes a median rPFS of 20 months for the control group (ADT) compared to 30 months for the treatment group (apalutamide plus ADT) and a median OS of 44 months for the control group.

Analysis Populations  
The efficacy analysis will be conducted on the Intent-to-Treat (ITT) population, which includes all randomized subjects. Safety analyses will be performed on the Safety Population, comprising all subjects who receive at least one dose of the study drug according to the actual treatment received.

Statistical Methods  
Time-to-event endpoints, rPFS and OS, will be analyzed using the Kaplan-Meier method to estimate survival functions. A Cox proportional hazards model will provide estimates of the hazard ratios and their associated 95% confidence intervals. For testing the primary hypotheses, a stratified log-rank test will be used, stratified by Gleason score, geographical region, and prior docetaxel use. Secondary endpoints such as time to pain progression, time to SRE occurrence, and time to chronic opioid use will also be analyzed using similar methods. Descriptive statistics will summarize distribution of continuous and categorical variables. Multiplicity adjustments will be considered using the Hochberg procedure to maintain type I error across multiple comparisons.

Interim Analyses  
Two interim analyses are planned for the OS endpoint: one after approximately 50% (~205 events) of the required events have occurred, and another after approximately 70% (~287 events). The interim analyses will use an O'Brien-Fleming type spending function for maintaining the type I error rate across the analyses. No interim analysis is planned for the rPFS endpoint.

Missing Data Handling  
Data missing for primary and key secondary endpoints will be handled using the method of censoring at the last available date of assessment or by utilizing multiple imputation techniques where appropriate. Sensitivity analyses will be conducted to assess the robustness of the primary analysis results to different assumptions about the missing data.

Significance Levels  
A 0.005 level of significance is allocated for the rPFS endpoint, while 0.045 is allocated for the OS endpoint. The study will be considered successful if at least one of the dual-primary endpoints is statistically significant at its respective significance level.

In conclusion, this statistical analysis plan is designed to robustly evaluate the efficacy and safety of apalutamide plus ADT compared to ADT alone in improving outcomes for subjects with mHSPC, ensuring accurate and reliable data interpretation while minimizing type I error through well-structured hypothesis testing and interim analysis plans.

# Safety

Safety

Safety Parameters  
The safety parameters for this study include monitoring for any adverse events (AEs), significant changes in vital signs (such as blood pressure), physical examination findings, performance status assessed through the Eastern Cooperative Oncology Group (ECOG) scale, and laboratory tests covering a range of hematology and clinical chemistry parameters. The frequency and nature of these assessments are designed to identify clinical or subclinical adverse effects of the study medication promptly.

Adverse Event Definitions  
Adverse events are defined following the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. AEs will be categorized based on severity from Grade 1 (mild) to Grade 5 (death related to AE). A treatment-emergent adverse event (TEAE) is any unfavorable or unintended sign, symptom, or disease temporally associated with the use of the investigational drug, irrespective of whether it is considered related to the drug.

Adverse Event Reporting  
All AEs that occur after the signing of informed consent until 30 days following the last dose of the study drug will be meticulously documented. Investigators are required to record both the severity and the assessed relationship of the AE to the study drug. Serious adverse events (SAEs), including those resulting in death, life-threatening situations, hospitalization, or significant disability/incapacity, are to be reported within 24 hours to the sponsor.

Safety Monitoring  
Safety monitoring involves regular evaluations, including routine laboratory tests, assessments of ECOG performance status, and physical examinations. These evaluations are conducted at baseline and at defined intervals throughout the study. In addition to routine checks, ECOG status is reassessed periodically to monitor any deterioration in physical performance. The study includes continuous oversight for early detection of any safety concerns mandating protocol amendments or interventions.

Risk Management  
Risk management strategies are crucial to safeguarding participant well-being and maintaining data integrity. The protocol outlines measures to manage expected and unforeseen risks, such as pre-defined dose modifications in response to observed AEs. Immediate action is required should a subject experience a Grade 3 or higher adverse event, potentially including dose reduction or temporary discontinuation of treatment based on specific protocol guidance.

Data Monitoring Committee  
The Independent Data Monitoring Committee (IDMC) is assigned to regularly review accumulating data and ensure the safety of study participants. The IDMC will provide recommendations on whether to continue, modify, or stop the study based on interim safety analyses. Their oversight is critical to maintain the balance between scientific objectives and participant safety.

Stopping Rules  
Stopping rules are embedded into the protocol to pause or terminate the study under certain conditions, such as the occurrence of unexpected adverse events that suggest a greater risk than benefit. The IDMC will review these situations and advise on study continuation or cessation based on the observed safety profiles and efficacy outcomes. Specific rules include the suspension of recruitment or treatment in case of disproportionate SAEs compared to expected rates.

In summary, this study employs comprehensive safety oversight structures to ensure participants' safety, promote diligent AE reporting, and integrate continuous safety monitoring with an independent committee's support. The guidelines set forth aim to efficiently identify and mitigate risks while ensuring all regulatory and ethical standards are upheld throughout the study.