Clinical Trial Protocol

# Background

Background

Disease Background  
Metastatic hormone-sensitive prostate cancer (mHSPC) is a stage of prostate cancer where the disease has spread beyond the prostate gland and still responds to hormonal therapy. This stage of prostate cancer is significant as it often indicates a more aggressive disease course, leading to decreased survival rates and quality of life for affected individuals. Androgens, such as testosterone, promote the growth of prostate cancer cells, making the management of hormone levels a pivotal aspect of treatment. The burden of mHSPC on patients is substantial, often involving skeletal-related events, pain, and impaired physical function. Understanding the progression and management of mHSPC is crucial, as it directly influences treatment strategies aimed at improving survival and quality of life.

Current Treatment Landscape  
The mainstay of treatment for mHSPC has traditionally been androgen deprivation therapy (ADT), which reduces androgen levels to deprive cancer cells of the growth stimuli they require. ADT can be achieved through surgical castration or the use of gonadotropin-releasing hormone (GnRH) analogs. While effective initially, many patients eventually develop castration-resistant prostate cancer, highlighting the need for additional therapeutic strategies. Recent advancements in prostate cancer treatment have introduced the use of combination therapies, including docetaxel, which has shown to further improve survival over ADT alone. Nevertheless, there remains a compelling need for new treatment paradigms that can extend radiographic progression-free survival (rPFS) and overall survival (OS) for patients with mHSPC.

Product Background  
Apalutamide, also known by its research name JNJ-56021927, is a novel, orally administered, non-steroidal anti-androgen currently under development for the treatment of prostate cancer. It functions as a potent and selective antagonist of the androgen receptor (AR), effectively inhibiting the proliferation of prostate cancer cells by blocking androgen signaling. Apalutamide's unique mechanism of action distinguishes it from traditional ADT, offering a potential improvement in therapeutic outcomes when used in combination with ADT. Previous clinical evaluations suggest that apalutamide has a favorable safety profile and demonstrates efficacy in delaying disease progression, making it a promising candidate for further investigation in the context of mHSPC.

Study Rationale  
The rationale for this study is to assess whether the combination of apalutamide with standard ADT improves outcomes for patients with mHSPC compared to ADT alone. Apalutamide's ability to target androgen receptors more effectively could potentially enhance radiographic progression-free survival and overall survival, improving the standard of care for mHSPC. This study intends to address key clinical questions, such as the impact of apalutamide on delaying pain progression and skeletal-related events, while also evaluating the safety and pharmacokinetics of the drug in this patient population. By exploring these outcomes, the study aims to provide robust data that could lead to a shift in the treatment paradigm, ultimately offering patients with mHSPC a more effective therapeutic option.

# 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 the first documentation of radiographic progressive disease 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 for prostate cancer, 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 its PD effect 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 defined as the time from randomization to the first increase in pain scores.  
2. Time to skeletal-related events (SREs) defined as the time from randomization to the occurrence of any SRE.  
3. Time to chronic opioid use defined as the time from randomization to the start of consistent opioid use.  
4. Time to initiation of cytotoxic chemotherapy defined as the time from randomization to the start of such treatment.  
5. Incidence and severity of adverse events (AEs) as per NCI-CTCAE Version 4.03.  
6. Concentration of apalutamide and its metabolite in plasma.  
7. Concentration of leuprolide and percentage of subjects with testosterone levels <50 ng/dL.  
8. Measure of treatment effectiveness in defined subpopulations.

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.

# Study Design

Study Design

Overall Design  
This study is a Phase 3 randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of combining apalutamide with androgen deprivation therapy (ADT) in participants with metastatic hormone-sensitive prostate cancer (mHSPC). Approximately 1,000 participants will be enrolled and equally randomized into one of two treatment arms: apalutamide plus ADT or placebo plus ADT. The randomization will be stratified 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). The study will be conducted across multiple international sites and is structured to include several phases: Screening, Treatment, Follow-up, Open-label Extension, and Long-Term Extension if applicable.

Study Schema  
The study will proceed with initial screening of participants over a period of up to 28 days to establish eligibility. After screening, participants who meet all criteria will enter the treatment phase, receiving either apalutamide or placebo in addition to ADT in 28-day cycles. Treatment will continue until documented disease progression, unacceptable toxicity, or sponsor decision to terminate the study. Following treatment discontinuation, participants will undergo an End-of-Treatment visit within 30 days. Subsequently, they will enter a Follow-up Phase with data collection every four months to record survival and other relevant endpoints until death, withdrawal, or study termination.

Study Duration  
The total study duration is anticipated to be approximately 54 months. Recruitment is planned to take around 30 months, with participants being followed for primary survival outcomes over an additional 24 months. Two interim analyses are planned to assess the dual-primary endpoint of overall survival, with the final analysis scheduled after the necessary number of events is reached.

Treatment Groups  
Participants will be assigned to one of the following treatment groups:

* \*\*Apalutamide plus ADT Group:\*\* Participants in this group will receive oral apalutamide 240 mg (four 60-mg tablets) once daily, in combination with standard of care ADT. ADT includes either medical castration via GnRH analogs or surgical castration, at the investigator’s discretion.
* \*\*Placebo plus ADT Group:\*\* Participants in this group will receive matching placebo tablets once daily, in addition to standard of care ADT.

Monitoring for safety will be ongoing throughout the study, starting at the signing of informed consent and continuing until 30 days post-final dose. Safety parameters include adverse events, laboratory tests, vital signs, and physical examinations. An Independent Data Monitoring Committee will oversee interim analyses and safety evaluations.

Study Schema

```mermaid  
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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# Population

Study Population

Overview of Study Population  
The population for this study consists of adult male subjects with metastatic hormone-sensitive prostate cancer (mHSPC). All subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, which indicates they are fully active or have some symptoms but do not require bed rest. These individuals should possess documented evidence of distant metastatic disease through imaging techniques such as a positive bone scan. Subjects may have received limited prior systemic therapy aimed at controlling their cancer.

Inclusion Criteria  
1. \*\*Diagnosis and Performance Status\*\*  
 - Subjects must have a confirmed diagnosis of prostate cancer.  
 - An ECOG performance status grade of 0 or 1 is required.

2. \*\*Disease Characteristics\*\*  
 - Documented distant metastatic disease by a positive bone scan with one or more bone lesions.  
 - Subjects with a single bone lesion require confirmation via CT or MRI.

3. \*\*Prior Treatment\*\*  
 - Up to 6 cycles of docetaxel for mHSPC, with the last dose administered within 2 months prior to randomization, is allowed.  
 - ≤6 months of ADT is permissible prior to randomization.  
 - A maximum of one course of radiation or surgical intervention for mHSPC is allowed.  
 - For localized prostate cancer, subjects may have had ≤3 years of ADT and other treatments completed at least one year before randomization.

Exclusion Criteria  
1. \*\*Concurrent Illnesses\*\*  
 - Any concurrent illness or condition that, in the opinion of the investigator, would pose an increased risk to the participant.

2. \*\*Prior Therapies\*\*  
 - More than 6 cycles of docetaxel or its administration beyond 2 months prior to randomization is not allowed.  
 - Any history of treatment with androgen signaling inhibitors other than those specified in the protocol.

3. \*\*Medical Conditions\*\*  
 - Severe or uncontrolled medical conditions or any other disease that could confound the study results or endanger the subject’s well-being.  
 - Participants who have a history of seizure or conditions that could predispose to seizure are excluded.

Withdrawal Criteria  
Subjects must be withdrawn from the study under the following conditions:  
1. Documented symptomatic disease progression as per protocol criteria.  
2. Occurrence of unacceptable treatment-related toxicity.  
3. Withdrawal of consent by the subject.  
4. Determination by the investigator or sponsor that continued participation is not in the subject's best interest.

Replacement Policy  
Subjects who withdraw or are withdrawn from the study will not be replaced to maintain the integrity of the intention-to-treat analysis. However, replacements may be considered under specific circumstances dictated by the sponsor, such as inadequate number of enrolled subjects due to early withdrawals. The decision to replace a subject will be made at the sponsor’s discretion.

# Procedures

Study Procedures Overview  
This section outlines the study procedures, detailing specific activities and assessments to be conducted during the Screening/Baseline, Treatment, and Follow-up Phases. Responsibilities for each procedure are indicated.

Screening/Baseline Procedures  
- \*\*Timing\*\*: Up to 28 days before randomization  
- \*\*Procedures\*\*:  
 - Acquisition of informed consent  
 - Collection of demographics and comprehensive medical history  
 - Comprehensive physical examination  
 - Recording of vital signs (blood pressure, heart rate, temperature, respiratory rate)  
 - Laboratory assessments including complete blood count and metabolic panel  
 - Disease assessment through imaging (CT/MRI and bone scan)  
 - Review against inclusion/exclusion criteria  
- \*\*Responsible Personnel\*\*: Clinical research coordinators, investigators, radiologists for imaging

Treatment Phase Procedures  
- \*\*Timing\*\*: 28-day treatment cycles until disease progression, unacceptable toxicity, or study termination  
- \*\*Procedures\*\*:  
 - Daily administration of apalutamide 240 mg or matching placebo  
 - Concurrent androgen deprivation therapy administration as SOC  
 - Regular safety monitoring including adverse event documentation  
 - Efficacy assessments through imaging and PSA measurements per cycle  
 - Assessments of quality of life using PRO measures (BPI-SF, BFI, EQ-5D-5L)  
 - Routine laboratory tests per cycle  
 - Monitoring for concomitant medications  
- \*\*Responsible Personnel\*\*: Investigators, clinical research coordinators, nursing staff

Follow-up Procedures  
- \*\*Timing\*\*: Every 4 months post-treatment discontinuation  
- \*\*Procedures\*\*:  
 - Collection of survival data and documentation of subsequent therapies  
 - Routine laboratory and disease assessments  
 - Continuation of PRO measures up to 12 months after study drug discontinuation  
- \*\*Responsible Personnel\*\*: Clinical research coordinators, investigators

Safety Assessments  
- \*\*Components\*\*:  
 - Regular physical examinations throughout the study  
 - Vital signs assessed at each visit  
 - Laboratory tests for clinical chemistry and hematology  
 - Monitoring and grading of adverse events using NCI-CTCAE (Version 4.03)  
 - ECG monitoring if clinically indicated  
- \*\*Responsible Personnel\*\*: Investigators, clinical staff

Efficacy Assessments  
- \*\*Components\*\*:  
 - Radiographic progression assessed through CT/MRI and bone scans based on RECIST 1.1 criteria  
 - PSA progression evaluations per PCWG2 criteria  
 - Collection of time-to-event efficacy endpoints including rPFS and OS  
 - Regular assessment of pain progression and SREs  
- \*\*Responsible Personnel\*\*: Investigators, radiologists, laboratory staff

Laboratory Assessments  
- \*\*Components\*\*:  
 - Regular hematology and clinical chemistry panels  
 - Trough PK samples for apalutamide and its metabolite at designated cycles  
 - Optional PK and PD sampling for leuprolide sub-study participants  
 - Biomarker sampling, including circulating DNA and tumor tissue analyses  
- \*\*Responsible Personnel\*\*: Laboratory technicians, investigators

Other Assessments  
- \*\*Components\*\*:  
 - Collection and analysis of medical resource utilization data to inform future economic modeling  
 - Biomarker evaluations for exploratory analysis of treatment response and resistance  
- \*\*Responsible Personnel\*\*: Health economists, research scientists

Special handling of any biological samples will follow outlined protocols to ensure proper storage and transport, maintaining sample integrity.

# Statistical

Statistical Analysis

Statistical Hypotheses  
The primary objectives of this study are to evaluate the efficacy of apalutamide in combination with androgen deprivation therapy (ADT) compared to placebo plus ADT in improving radiographic progression-free survival (rPFS) and overall survival (OS) in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). The hypotheses are as follows:  
- Null Hypothesis (H0): There is no difference in rPFS and OS between the apalutamide plus ADT group and the placebo plus ADT group.  
- Alternative Hypothesis (H1): The apalutamide plus ADT group shows a statistically significant improvement in rPFS and/or OS compared to the placebo plus ADT group.

Sample Size Determination  
The study is designed with an overall type I error rate of 5%, allocating a significance level of 0.005 to rPFS and 0.045 to OS. The sample size calculation is based on detecting a hazard ratio (HR) of 0.67 for rPFS with 85% power and a HR of 0.75 for OS with 80% power. This requires 368 rPFS events and 410 death events for OS, with a total enrollment of approximately 1,000 subjects over about 30 months, and a study duration of approximately 54 months.

Analysis Populations  
- \*\*Intent-to-Treat (ITT) Population\*\*: Includes all randomized subjects and will be used for efficacy analyses.  
- \*\*Safety Population\*\*: Includes all subjects who receive at least one dose of study drug and will be used for safety analyses.

Statistical Methods  
Efficacy analyses will utilize the Kaplan-Meier method to estimate survival functions, with comparisons between treatment groups made using the Cox proportional hazards model to calculate the hazard ratio and 95% confidence intervals. The significance of the dual-primary endpoints, rPFS and OS, will be assessed using stratified log-rank tests considering stratification factors applied at randomization.

Secondary and exploratory endpoints, such as time to pain progression and time to the initiation of cytotoxic chemotherapy, will be analyzed using similar time-to-event methodologies.

For biomarker analysis, associations with clinical outcomes will be explored using models appropriate to the data type, such as ANOVA for continuous measures and logistic regression for categorical outcomes.

Interim Analyses  
Two interim analyses for OS are planned after approximately 50% (205 events) and 70% (287 events) of the total death events have occurred. An alpha spending function will be applied to maintain the overall type I error rate, using methods such as O’Brien-Fleming boundaries to determine significance at interim analyses. The first interim analysis will coincide with the final analysis of the rPFS endpoint.

Missing Data Handling  
Missing data will be addressed using multiple imputation methods where appropriate, particularly for continuous variables like quality of life measures. Sensitivity analyses will be conducted to assess the robustness of the primary endpoint results to different missing data assumptions. For time-to-event data, censoring will be appropriately handled when subjects are lost to follow-up or withdraw.

Multiplicity Adjustments  
A Bonferroni correction or similar approach will be applied to control for multiplicity across the dual-primary endpoints, maintaining an overall alpha level of 0.05. Separate significance levels have been pre-specified for rPFS (0.005) and OS (0.045) to address multiple hypothesis testing concerns.

With these statistical methodologies, the study aims to rigorously and comprehensively assess the efficacy and safety of apalutamide added to ADT in the specified patient population.

# Safety

Safety

Safety Parameters  
The safety parameters for this study encompass the monitoring and assessment of adverse events (AEs), vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, and clinical laboratory tests. Adverse events will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

Adverse Event Definitions  
Adverse events are defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, regardless of whether it is considered related to the investigational product. Treatment-emergent adverse events (TEAEs) refer to events that occur from the first dose of study drug until 30 days after the last dose.

Severity Grades  
The severity of AEs will be classified using the NCI-CTCAE criteria, which range from Grade 1 (Mild) to Grade 5 (Death related to AE). This ensures uniform reporting and assessment of AE severity across all study sites.

Adverse Event Reporting  
All AEs will be recorded from the time of informed consent until 30 days post-final dose of study drug. Investigators must document each AE for all study participants, noting its timing, intensity, duration, and any required interventions. Serious adverse events (SAEs) must be reported to the sponsor within 24 hours of awareness, followed by a comprehensive report within five business days.

Safety Monitoring  
Safety monitoring will include routine collection of clinical laboratory tests, and vital signs at each study visit, and physical examinations as indicated. Specific criteria for dose modifications in response to AEs will be provided in the protocol. Continuous safety monitoring is crucial to ensure participant welfare and manage potential study-related risks effectively.

Risk Management  
Risk mitigation strategies include close monitoring of participants for signs of known side effects associated with apalutamide, such as skin rash, hypothyroidism, hypertension, and fracture risk. Dose adjustments or treatment discontinuation will be performed per protocol guidelines if AEs reach unacceptable levels of severity or frequency.

Data Monitoring Committee  
An Independent Data Monitoring Committee (IDMC) will oversee the study, providing an objective review of the safety data at regular intervals and during planned interim efficacy analyses. The IDMC will have the authority to recommend modifications to the study, including early termination based on safety or efficacy findings.

Stopping Rules  
Stopping rules are in place to ensure participant safety and are based on the identification of unexpected, severe, or life-threatening adverse events, as well as lack of efficacy or other significant findings that impact the overall benefit-risk profile of the investigational drug. The study may be paused or stopped following these criteria, based on IDMC recommendations, if the safety profile becomes unacceptable or if predefined safety thresholds are surpassed.

Through these comprehensive safety procedures and oversight mechanisms, we aim to ensure rigorous safety assessment and management throughout the course of the study.