Clinical Trial Protocol

# Background

Background

Disease Background  
Prostate cancer is a significant health concern and is one of the most common malignancies affecting men worldwide. Metastatic hormone-sensitive prostate cancer (mHSPC) is a stage of the disease where cancer cells have spread beyond the prostate gland but still respond to hormone therapy aimed at lowering androgen levels. This stage of prostate cancer is associated with a high burden of disease and impacts overall survival and quality of life. Despite initial hormonal treatment responses, most patients eventually progress to a castration-resistant state.

Current Treatment Landscape  
The current standard of care for mHSPC involves androgen deprivation therapy (ADT), which aims to reduce the levels of androgens that fuel the growth of prostate cancer cells. ADT can be achieved through surgical castration or medical castration using gonadotropin-releasing hormone (GnRH) analogs. Despite the efficacy of ADT in controlling disease progression, many patients eventually develop resistance, leading to disease progression. As such, there is a demonstrated need for novel therapeutic strategies that can improve outcomes and delay the progression to castration-resistant prostate cancer.

Product Background  
Apalutamide, also known as JNJ-56021927 and ARN-509, is a non-steroidal, orally administered, potent, and selective antagonist of the androgen receptor. It functions by blocking androgen receptor signaling pathways, which play a critical role in the development and progression of prostate cancer. Apalutamide has shown promising results in earlier-phase studies, suggesting its potential efficacy in extending radiographic progression-free survival and overall survival in patients with mHSPC when used in combination with ADT.

Study Rationale  
The rationale behind this Phase 3 study is to evaluate whether the addition of apalutamide to standard ADT can provide improved therapeutic benefits for patients with mHSPC. There is a significant clinical need to enhance outcomes in this patient population by delaying disease progression and extending overall survival. This study aims to determine if the combination of apalutamide and ADT will offer superior efficacy compared to ADT alone by improving radiographic progression-free survival and overall survival. Additionally, this study seeks to assess the safety profile of the combination therapy, further characterizing pharmacokinetics and pharmacodynamics, and evaluating patient-relevant outcomes, including quality of life and function.

# 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 date of 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, 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 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. Safety profile characterized by incidence and severity of adverse events (AEs).  
6. Population PK data of apalutamide concentrations.  
7. Leuprolide concentration and testosterone suppression levels.  
8. Efficacy outcomes for low-volume versus high-volume mHSPC populations.

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 data that may be used in future economic modeling.

Other Endpoint(s)  
1. Associations of biomarkers with clinical response or time-to-event endpoints.  
2. Changes from baseline in patient-reported outcomes using tools like FACT-P and EQ-5D-5L.  
3. Various clinically relevant endpoints measuring treatment impact beyond rPFS and OS.  
4. Data on medical resource utilization for potential economic analysis.

# Study Design

Study Design

Overall Design  
This Phase 3 study will be a randomized, double-blind, placebo-controlled, multinational, and multicenter trial designed to assess the efficacy of apalutamide in combination with androgen deprivation therapy (ADT) compared to placebo plus ADT in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). Approximately 1,000 eligible subjects will be enrolled and stratified based on Gleason score at diagnosis, geographical region, and prior docetaxel use. Subjects will then be randomized in a 1:1 ratio to receive either apalutamide plus ADT or matching placebo plus ADT. The treatment will continue in 28-day cycles until disease progression, unacceptable toxicity, or study termination.

Study Schema  
The study consists of several phases:

1. 1. Screening Phase (up to 28 days): Establishes study eligibility.
2. 2. Treatment Phase (28-day cycles): Subjects receive either apalutamide plus ADT or placebo plus ADT.
3. 3. End-of-Treatment Visit: Conducted within 30 days after the last dose of study drug.
4. 4. Follow-up Phase: Collects data on survival and efficacy endpoints every 4 months until death, withdrawal, loss to follow-up, or study termination.
5. 5. Open-label Extension Phase (optional): Provided in case of positive interim or final results, allowing access to apalutamide for approximately 3 years.
6. 6. Long-Term Extension Phase (optional): Continues apalutamide if assessed beneficial post-final analysis.

Study Duration  
The overall study duration will be approximately 54 months. The enrollment period is estimated to last around 30 months, allowing for sufficient observation of required events to assess the primary endpoints of radiographic progression-free survival and overall survival.

Treatment Groups  
Subjects will be randomly assigned to one of the following two treatment groups:

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| **Treatment Group** | **Intervention** | **Administration Detail** |
| Group 1 | Apalutamide + ADT | 240-mg apalutamide (4 x 60-mg tablets) taken orally once daily with or without food, alongside standard ADT as medical or surgical castration. |
| Group 2 | Placebo + ADT | Matching placebo (4 tablets) taken orally once daily with or without food, coupled with standard ADT as defined by medical or surgical castration. |

Dose modifications will occur in accordance with protocol-specified rules, and subjects will be monitored for safety from the point of informed consent through 30 days post-treatment. The study will utilize an Independent Data Monitoring Committee (IDMC) for safety and interim efficacy assessments.

# Population

Study Population

Overview of Study Population  
The study will involve male subjects who have been diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, which indicates that they are fully active (0) or ambulatory and capable of all self-care but unable to carry out any work activities (1). The study aims to include both subjects with low-volume and high-volume metastatic disease, as evidenced by positive bone scans.

Inclusion Criteria  
1. Male subjects with a confirmed diagnosis of metastatic hormone-sensitive prostate cancer (mHSPC).  
2. ECOG performance status of 0 or 1.  
3. Confirmation of distant metastatic disease with:  
 - At least one bone lesion documented by a bone scan.  
 - For those with a single bone lesion, confirmation of metastasis via CT or MRI.  
4. Subjects may have received:  
 - Up to 6 cycles of docetaxel for mHSPC, with the last dose administered no more than 2 months before randomization.  
 - Up to 6 months of androgen deprivation therapy (ADT) prior to randomization.  
 - A maximum of one course of radiation or surgical intervention for mHSPC.  
5. For prior localized prostate cancer, subjects may have received ADT for a total of up to 3 years, with all other forms of prior therapy completed at least 1 year prior to randomization.

Exclusion Criteria  
1. Known castration-resistant prostate cancer.  
2. Prior treatment with androgen receptor inhibitors or CYP17 inhibitors for prostate cancer.  
3. Any other condition or abnormal finding that, in the opinion of the investigator, would preclude the subject's safe participation in and completion of the study.  
4. Clinically significant cardiovascular concerns, including but not limited to:  
 - A recent myocardial infarction (within 6 months prior to randomization).  
 - Uncontrolled hypertension or arrhythmias.  
5. Prior malignancy, except for prostate cancer or adequately treated basal cell or squamous cell skin cancer, with no recurrence within 5 years.

Withdrawal Criteria  
Subjects may be withdrawn from the study under the following circumstances:  
1. Development of clinical progression of the disease.  
2. Occurrence of unacceptable treatment-related toxicity.  
3. Voluntary withdrawal of consent by the subject.  
4. Investigator's judgment that continued participation in the study does not serve the best interest of the subject.

Replacement Policy  
Subjects who withdraw or are removed from the study prior to completion will not be replaced. The study aims for a robust sample size to account for attrition and still provide sufficient data validity and reliability for the primary and secondary endpoints.

# Procedures

Study Procedures

Study Procedures Overview  
This section outlines the procedures to be conducted throughout the study, detailing activities during the screening, treatment, and follow-up phases.

Screening/Baseline Procedures  
1. \*\*Informed Consent:\*\* Obtain from each participant prior to any study-related activities.   
2. \*\*Demographics and Medical History:\*\* Collect information regarding the participant's age, sex, race, medical history, and previous treatments.  
3. \*\*Physical Examination:\*\* Conduct a comprehensive assessment of the participant's general health status.  
4. \*\*Vital Signs:\*\* Record blood pressure, heart rate, respiratory rate, and temperature.  
5. \*\*ECOG Performance Status:\*\* Evaluate to determine baseline functioning (performed by the study investigator).  
6. \*\*Laboratory Assessments:\*\* Perform baseline hematology and clinical chemistry tests.  
7. \*\*Disease Assessment Imaging:\*\* Conduct bone scans and confirm bone lesions via CT or MRI as required.  
8. \*\*ECG:\*\* Perform to assess cardiac baseline.  
9. \*\*Inclusion/Exclusion Criteria Review:\*\* Confirm eligibility based on protocol criteria.

Treatment Phase Procedures  
1. \*\*Drug Administration:\*\* Administer JNJ-56021927 (apalutamide) 240 mg or matching placebo orally once daily; ensure documentation of concurrent GnRHa when applicable.  
2. \*\*Safety Monitoring:\*\* Regularly conduct physical exams and vital signs assessments.  
3. \*\*Efficacy Assessments:\*\* Monitor radiographic progression regularly as per protocol schedule.  
4. \*\*Laboratory Tests:\*\* Conduct routine blood sampling for PSA, testosterone, and other parameters.  
5. \*\*Quality of Life Assessments:\*\* Administer BPI-SF, BFI, and EQ-5D-5L at designated visits.  
6. \*\*Adverse Event Monitoring:\*\* Continuously assess and record any treatment-emergent adverse events.  
7. \*\*Concomitant Medication Review:\*\* Document any additional medications taken by participants during the study.

Follow-up Procedures  
1. \*\*Safety Follow-up:\*\* Maintain surveillance for adverse events 30 days post-treatment cessation.  
2. \*\*Disease Assessment:\*\* Regularly update participant's disease progression status at scheduled follow-up intervals.  
3. \*\*Survival Status:\*\* Assess and record participant survival status every 4 months.  
4. \*\*Subsequent Therapy Documentation:\*\* Keep detailed records of any subsequent prostate cancer therapies initiated post-study treatment.

Safety Assessments  
- Perform comprehensive physical examinations and measure vital signs regularly throughout the study.  
- Conduct periodic laboratory tests for hematology and chemistry.  
- Continuously monitor for and document any adverse events, graded per NCI-CTCAE criteria.

Efficacy Assessments  
- Carry out radiographic assessments to measure rPFS per protocol schedule.  
- Monitor PSA levels and evaluate clinical progression using PCWG2 criteria.  
- Conduct pain assessments and administer quality of life questionnaires periodically.

Laboratory Assessments  
- Conduct hematology, clinical chemistry, PSA, and testosterone testing at specified intervals throughout the study.  
- Perform pharmacokinetic sampling for apalutamide and its metabolites during Cycles 2 to 6.  
- Participants in the leuprolide PK sub-study will provide additional blood samples as outlined.

Other Assessments  
- Collect and analyze patient-reported outcomes on symptoms and function using standardized questionnaires.  
- Gather data on medical resource utilization for future economic analyses.  
- Perform biomarker sampling for exploratory analysis of predictive and resistance markers.

All procedures will be conducted by qualified clinical staff trained in study protocol specifics, ensuring compliance with all regulatory requirements and study guidelines. Special care will be taken in handling and processing biological samples to maintain integrity and accuracy.

# Statistical

Statistical Analysis

Statistical Hypotheses  
The primary hypothesis is that apalutamide plus androgen deprivation therapy (ADT) will 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 dual-primary endpoints are rPFS and OS, with the study considered successful if at least one endpoint is statistically significant.

Sample Size Determination  
The trial is designed to control the overall type I error rate at 5%. A significance level of 0.005 will be used for the rPFS endpoint, while 0.045 is allocated to the OS endpoint. To achieve sufficient power, approximately 368 rPFS events are required for 85% power to detect a hazard ratio (HR) of 0.67. For OS, approximately 410 death events are needed to provide 80% power to detect an HR of 0.75. Thus, a total of 1,000 subjects will be enrolled over approximately 30 months, with the study duration estimated at 54 months.

Analysis Populations  
- \*\*Intent-to-Treat (ITT) Population:\*\* All randomized subjects, used for efficacy analysis.  
- \*\*Safety Population:\*\* Includes all subjects who receive at least one dose of the study drug, analyzed based on treatment received.

Statistical Methods  
Efficacy analyses will evaluate the dual-primary endpoints of rPFS and OS using the ITT population. Kaplan-Meier estimations will be applied to determine time-to-event distributions. Cox proportional hazards models will calculate hazard ratios and 95% confidence intervals for rPFS and OS. Adjustments for multiplicity due to dual-primary endpoints will utilize the pre-specified significance levels for rPFS and OS.

Secondary endpoints, such as time to pain progression, time to skeletal-related events (SREs), and other time-to-event secondary outcomes, will also be analyzed using the Cox model. Changes in patient-reported outcomes will be assessed through mixed-model repeated measures or analysis of covariance (ANCOVA), as appropriate.

Interim Analyses  
Two interim analyses will be conducted to evaluate the dual-primary endpoint of OS. These are scheduled after approximately 50% (205 events) and 70% (287 events) of the required deaths have occurred. The interim analysis of rPFS will take place at the first interim analysis of OS. There is no planned interim analysis for rPFS alone. All interim analyses will consider alpha spending to preserve the overall type I error rate, using O’Brien-Fleming-type boundaries.

Missing Data Handling  
Missing data for primary and secondary endpoints will be addressed using multiple imputation methods or sensitivity analyses to assess the robustness of the results. Time-to-event analyses such as rPFS and OS will consider censoring at the last available assessment where applicable, according to the predefined rules in the statistical analysis plan.

The proposed statistical methodologies ensure rigorous assessment of efficacy and safety profiles, alongside explorations into biomarkers and pharmacokinetics to enhance understanding of treatment effects.

# Safety

Safety

Safety Parameters  
The primary safety parameters for this study include the incidence and severity of treatment-emergent adverse events (AEs), clinically significant changes in vital signs (blood pressure), physical examination findings, ECOG performance status, and clinical laboratory results. Safety assessments will be conducted at regular intervals from the initiation of treatment until 30 days following the final dose of the study drug.

Adverse Event Definitions  
Adverse events are defined as any untoward medical occurrence in a study subject who has received the investigational product, regardless of its relation to the investigational product. AEs will be classified by severity in accordance with the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

Severity Grades  
- 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  
The reporting of adverse events and serious adverse events (SAEs) must comply with regulatory requirements and be documented in the electronic case report form (eCRF). Any SAEs, including those deemed related to the study drug, must be reported to the sponsor within 24 hours of awareness. Regular summaries of AEs will be provided at each data safety review.

Safety Monitoring  
Safety monitoring will involve continuous AE surveillance, periodic review of laboratory results, and scheduled assessments of vital signs and physical examinations. The investigators are responsible for monitoring subjects between scheduled visits and reporting any clinically relevant findings that may affect subject safety.

Risk Management  
Risk management strategies will include the implementation of predefined dose modification guidelines in response to specific AEs or laboratory abnormalities. Regular communication with the clinical team will ensure rapid response to mitigate any identified risks. Subjects will receive guidelines on recognizing symptoms that may indicate potential adverse events or toxicities.

Data Monitoring Committee  
An Independent Data Monitoring Committee (IDMC) will be established to monitor and review safety data at regular intervals. The IDMC will conduct planned interim safety analyses and provide recommendations on the continuation, modification, or termination of the study based on its findings.

Stopping Rules  
Stopping rules have been incorporated to ensure participant safety. The study may be halted if a significant imminent risk to participant health is identified, if unexpected and severe adverse events related to the investigational product occur at a higher-than-anticipated frequency, or upon recommendations from the IDMC. Stopping criteria are detailed in the protocol and are to be evaluated against adverse event trends, efficacy data, and external information pertinent to subject safety.

All safety oversight procedures are designed to protect the well-being of study participants while maintaining the scientific integrity of the study results. These procedures will be consistently enforced through all phases of the study.