Clinical Trial Protocol

# Background

Background

Disease Background  
Prostate cancer is among the most common malignancies affecting men, and its progression to metastatic hormone-sensitive prostate cancer (mHSPC) marks a critical advancement in the disease's severity and complexity. Metastasis typically involves the spread of cancer cells to areas such as the bones and can significantly impact a patient's quality of life and overall survival. The standard clinical indication of metastatic involvement is typically verified through imaging studies, including bone scans, CT, or MRI, suggesting the presence of disease beyond the prostate gland. The disease burden of mHSPC can vary significantly, with distinctions often made between cases with high-volume and low-volume disease based on the extent and pattern of metastasis. Management of mHSPC is particularly challenging due to the heterogeneity in clinical presentation and disease trajectory.

Current Treatment Landscape  
The primary strategy for treating mHSPC involves androgen deprivation therapy (ADT), which can be achieved through surgical castration or medical castration with gonadotropin-releasing hormone (GnRH) analogs. ADT endeavors to lower androgen levels, which are crucial for prostate cancer cell growth, thereby limiting disease progression. The introduction of chemotherapy with agents like docetaxel has demonstrated increased survival in certain mHSPC patient populations, albeit with significant toxicity profiles. Despite the proven benefits of these treatments, there remains a substantial need to delay progression and improve survival outcomes. Increasing attention is being given to combination therapies that integrate novel androgen receptor antagonists to enhance therapeutic efficacy without unmanageable side effects.

Product Background  
Apalutamide (JNJ-56021927; ARN-509) is an orally administered, small molecule, non-steroidal anti-androgen that functions as a potent and selective antagonist of the androgen receptor. Apalutamide has demonstrated promising preclinical and early clinical trial results in terms of effectively inhibiting androgen receptor signaling, a key driver in prostate cancer pathogenesis. Its non-steroidal structure allows it to exhibit anti-androgen effects without the steroid-associated side effects seen with some other classes of chemotherapy. The development of apalutamide is integral to potentially extending the benefits of ADT in mHSPC patients through a mechanism of action that combines blockade of androgen receptor signaling with existing androgen suppression strategies.

Study Rationale  
The rationale for this study emerges from the hypothesis that combining apalutamide with ADT may significantly improve clinical outcomes in patients with mHSPC compared to ADT alone. The goal is to determine whether this combination can effectively extend radiographic progression-free survival (rPFS) and overall survival (OS), thus providing a more robust therapeutic strategy against mHSPC. Additionally, the study seeks to uncover potentially favorable effects on secondary clinical endpoints such as delays in pain progression, reduction in skeletal-related events, and postponement of cytotoxic chemotherapy initiation. Furthermore, evaluating the safety profile of apalutamide in combination with ADT is an essential component in determining its viability as a treatment option. By addressing these objectives, the study aims to deliver meaningful insights that could inform future treatment paradigms for mHSPC patients and ultimately enhance patient quality of life and survival.

# 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 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, 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 the subpopulations of subjects with low-volume or high-volume mHSPC.

Secondary Endpoints  
1. Time to pain progression.  
2. Time to first use of opioids for prostate cancer pain.  
3. Time to first skeletal-related event (SRE).  
4. Time to initiation of cytotoxic chemotherapy.  
5. Incidence and severity of adverse events (AEs) associated with apalutamide plus ADT.  
6. Population PK and PD parameters of apalutamide.  
7. Leuprolide concentration and testosterone suppression with and without apalutamide.

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), 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 that may be used in future economic modeling.

Other Endpoints  
1. Biomarkers predictive of response and resistance.  
2. Changes from baseline in patient-reported outcomes measures related to symptoms and quality of life.  
3. Additional clinical endpoints of interest beyond the primary and secondary objectives.  
4. Data related to medical resource utilization during the study.

# Study Design

Study Design

Overall Design  
This Phase 3 study is designed as a randomized, double-blind, placebo-controlled trial conducted across multiple international centers 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 be stratified based on Gleason score, geographic region, and prior docetaxel use. Eligible subjects will be randomly assigned in a 1:1 ratio to either the apalutamide plus ADT group or a placebo plus ADT group. The primary focus of this design is to assess the improvement in radiographic progression-free survival (rPFS) and overall survival (OS).

Study Schema

|  |  |
| --- | --- |
| **Phase** | **Description** |
| Screening Phase | Up to 28 days to establish subject eligibility for the study. |
| Treatment Phase | 28-day cycles of treatment until disease progression, unacceptable toxicity, or study termination. |
| Follow-up Phase | Data collection every 4 months post-treatment discontinuation for survival and secondary endpoints. |
| Open-label Extension Phase | Subjects can receive apalutamide post-study termination based on study results. |
| Long-Term Extension Phase | Continuation of apalutamide for subjects deriving benefit. |

Study Duration  
The study plans for an enrollment period of approximately 30 months, with an estimated total study duration of about 54 months. This timeline accounts for the anticipated duration required to observe the necessary number of primary endpoint events (rPFS and OS), including interim assessments and follow-up.

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

1. 1. \*\*Apalutamide Plus ADT Group\*\*: Participants will receive a daily oral dose of 240 mg apalutamide (4 x 60 mg tablets), combined with androgen deprivation therapy as a standard care regimen. ADT can be administered either through medical castration using GnRHa or surgical castration at the investigator’s discretion.

2. \*\*Placebo Plus ADT Group\*\*: Participants will receive a daily oral placebo (matching tablets to apalutamide) in conjunction with the standard ADT regimen as described above.

Both groups will continue their respective treatments in cycles until criteria for discontinuation are met, including disease progression, unacceptable toxicity levels, or withdrawal of consent.

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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# Population

Study Population

Overview of Study Population  
The study population comprises male subjects with a diagnosis of metastatic hormone-sensitive prostate cancer (mHSPC). Eligible subjects must have a documented distant metastatic disease, verified via imaging studies such as bone scans showing one or more lesions. The clinical status of these subjects must align with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 or 1, reflecting their ability to carry out daily living activities without substantial restrictions.

Inclusion Criteria  
1. Male subjects with a confirmed diagnosis of prostate cancer.  
2. ECOG performance status of 0 or 1.  
3. Presence of distant metastatic disease as confirmed by a positive bone scan; subjects with a single bone lesion must have this confirmed by CT or MRI.  
4. May have received up to 6 cycles of docetaxel for mHSPC, with the last dose given no more than 2 months prior to randomization.  
5. Prior ADT is allowed if administered for up to 6 months before randomization for mHSPC.  
6. Subjects might have had a maximum of 1 course of radiation or surgical intervention for mHSPC.  
7. For localized prostate cancer history, subjects may have undergone ≤3 years of ADT and other treatments (e.g., radiation therapy, prostatectomy) must be completed at least 1 year before randomization.

Exclusion Criteria  
1. Previous treatment with androgen receptor inhibitors such as apalutamide.  
2. History of another malignancy within the last 5 years, except adequately treated non-melanoma skin cancer or superficial bladder cancer.  
3. Significant cardiovascular conditions, including recent myocardial infarction or stroke.  
4. Active infection or other medical conditions that could interfere with study participation or outcomes.  
5. Prior participation in any clinical trial involving apalutamide.

Withdrawal Criteria  
1. Subjects may voluntarily withdraw consent at any time.  
2. Investigator decision based on the subject’s best interest due to adverse effects or other medical conditions.  
3. Disease progression as defined by radiographic or clinical assessments under protocol criteria.  
4. Sponsor’s decision to halt the study based on interim analysis results or other considerations.

Replacement Policy  
Subjects who withdraw or are removed from the study will not be replaced to maintain the statistical integrity of the trial's sample size and power calculations. Data from withdrawn subjects will be included in the intention-to-treat (ITT) analysis set, wherever feasible, to ensure comprehensive statistical analysis.

# Procedures

Study Procedures Overview  
This section provides detailed procedures for the study, structured into screening/baseline, treatment, and follow-up phases, and includes safety, efficacy, laboratory, and other assessments.

Screening/Baseline Procedures  
These procedures will be conducted up to 28 days before randomization to determine eligibility and baseline characteristics of participants.

1. 1. \*\*Informed Consent\*\*

* Timing: Prior to any screening activities
* Requirement: Obtain signed consent from all participants
* Responsible Personnel: Investigator or delegated research staff

2. \*\*Demographic and Medical History Collection\*\*  
 - Timing: During initial visits  
 - Requirement: Collect detailed demographic data and comprehensive medical and treatment history  
 - Responsible Personnel: Clinical research coordinator

3. \*\*Physical Examination\*\*  
 - Timing: At the screening visit  
 - Requirement: Comprehensive physical evaluation to assess general health  
 - Responsible Personnel: Study physician

4. \*\*Vital Signs Measurement\*\*  
 - Timing: At screening and baseline visits  
 - Requirement: Measure blood pressure, heart rate, respiratory rate, and temperature  
 - Responsible Personnel: Qualified nursing staff

5. \*\*Laboratory Assessments\*\*  
 - Timing: During screening period  
 - Requirement: Perform hematology, chemistry panel, testosterone levels, and confirmatory tests for metastatic disease  
 - Responsible Personnel: Laboratory technician

6. \*\*Disease Assessment\*\*  
 - Timing: Baseline imaging prior to randomization  
 - Requirement: Perform bone scan and CT/MRI where necessary to confirm metastatic disease  
 - Responsible Personnel: Radiologist

7. \*\*Inclusion/Exclusion Criteria Review\*\*  
 - Timing: Before randomization  
 - Requirement: Thorough review to ensure all criteria are met  
 - Responsible Personnel: Investigator

Treatment Phase Procedures  
Participants will be randomized to receive either apalutamide plus ADT or placebo plus ADT, followed by scheduled evaluations in 28-day cycles.

1. 1. \*\*Drug Administration\*\*

* Timing: Daily oral administration of study drug or placebo
* Requirement: Ensure compliance with dosage and record any deviations
* Responsible Personnel: Study nurse

2. \*\*Safety Monitoring\*\*  
 - Timing: At each treatment cycle  
 - Requirement: Regular monitoring for AEs and treatment-related toxicity  
 - Responsible Personnel: Investigator

3. \*\*Efficacy Assessments\*\*  
 - Timing: Scheduled per protocol  
 - Requirement: Radiographic assessments for progression and patient-reported outcomes  
 - Responsible Personnel: Investigator and clinical research team

4. \*\*Laboratory Tests\*\*  
 - Timing: Pre-specified cycles and as clinically indicated  
 - Requirement: Hematology, chemistry panels, and PK/PD samples collection  
 - Responsible Personnel: Laboratory personnel

5. \*\*Quality of Life Assessments\*\*  
 - Timing: Regular intervals during treatment  
 - Requirement: Administer instruments like BPI-SF, BFI, EQ-5D-5L  
 - Responsible Personnel: Trained interviewer

6. \*\*Adverse Event Monitoring\*\*  
 - Timing: Each cycle and unscheduled visits if necessary  
 - Requirement: Document and grade all AEs using NCI-CTCAE  
 - Responsible Personnel: Investigator and study staff

7. \*\*Concomitant Medication Review\*\*  
 - Timing: At each visit  
 - Requirement: Record and review any additional medications being taken  
 - Responsible Personnel: Clinical research staff

Follow-up Procedures  
Post-treatment monitoring to assess long-term outcomes and safety.

1. 1. \*\*Safety Follow-Up\*\*

* Timing: Within 30 days after last dose
* Requirement: Perform comprehensive safety assessments and AE monitoring
* Responsible Personnel: Investigator

2. \*\*Disease Assessment\*\*  
 - Timing: Every 4 months post-treatment discontinuation  
 - Requirement: Radiographic and clinical assessment of disease status  
 - Responsible Personnel: Clinical team

3. \*\*Survival Status\*\*  
 - Timing: Every 4 months during follow-up  
 - Requirement: Document survival status and any cancer-related events  
 - Responsible Personnel: Study coordinator

4. \*\*Subsequent Therapy Documentation\*\*  
 - Timing: As required during follow-up  
 - Requirement: Record details of any new cancer therapy started  
 - Responsible Personnel: Clinical research associate

Safety Assessments  
Comprehensive safety evaluations conducted throughout the study.

1. 1. \*\*Physical Examinations\*\*
2. 2. \*\*Vital Signs Monitoring\*\*
3. 3. \*\*Laboratory Tests and Analysis\*\*
4. 4. \*\*Adverse Event and ECG Monitoring (as indicated)\*\*

Efficacy Assessments  
These assessments will evaluate the treatment's success based on predefined endpoints.

1. 1. \*\*Radiographic Progression-Free Survival (rPFS) and Overall Survival (OS) Assessments\*\*
2. 2. \*\*Patient-Reported Outcomes\*\*
3. 3. \*\*QoL Measures\*\*

Laboratory Assessments  
Laboratory evaluations to monitor health and treatment effects.

1. 1. \*\*Hematology and Clinical Chemistry\*\*
2. 2. \*\*Pharmacokinetic and Pharmacodynamic Samples\*\*
3. 3. \*\*Biomarker Evaluation Samples\*\*

Other Assessments  
Additional assessments to support comprehensive study evaluation.

1. 1. \*\*PK Sub-study (when applicable)\*\*
2. 2. \*\*Biomarker Analysis using biological samples\*\*
3. 3. \*\*Medical Resource Utilization Data Collection\*\*

# Statistical

Statistical Analysis

Statistical Hypotheses  
The primary hypotheses of this study concern the efficacy of apalutamide plus ADT compared to ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). Specifically, the hypotheses are:  
1. Null Hypothesis for rPFS: There is no difference in radiographic progression-free survival (rPFS) between the treatment arms.  
2. Null Hypothesis for OS: There is no difference in overall survival (OS) between the treatment arms.  
3. Alternative Hypothesis for rPFS and OS: The combination of apalutamide and ADT provides superior improvement in rPFS or OS compared to ADT alone.

Sample Size Determination  
The study is designed to enroll approximately 1,000 subjects. An overall type I error rate of 5% is divided between the dual-primary endpoints: 0.005 for rPFS and 0.045 for OS. For rPFS, approximately 368 events are required to achieve 85% power at a hazard ratio (HR) of 0.67. For OS, approximately 410 death events are needed to achieve 80% power to detect a HR of 0.75. The estimated study duration is approximately 54 months.

Analysis Populations  
1. Intent-to-Treat (ITT) Population: All randomized subjects. This population will be used for efficacy analyses, including primary and secondary endpoints.  
2. Safety Population: All subjects who received at least one dose of study drug. This population will be used for safety analyses.  
3. Pharmacokinetic (PK) Sub-study Population: Subjects who consent to participate in the optional PK evaluation of leuprolide.

Statistical Methods  
Time-to-event endpoints, including rPFS and OS, will be analyzed using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios and 95% confidence intervals will be estimated using a Cox proportional hazards model. For secondary endpoints like time to pain progression and time to SREs, similar methods will be used. Continuous variables will be analyzed using analysis of variance (ANOVA) or appropriate statistical tests, and categorical outcomes will be analyzed with chi-square or Fisher's exact test, where applicable.

Interim Analyses  
Two interim analyses are planned solely for the OS dual-primary endpoint after approximately 205 and 287 events, which correspond to 50% and 70% of the required total 410 death events, respectively. The final analysis of rPFS will coincide with the first OS interim analysis. No interim analysis is planned for rPFS.

Missing Data Handling  
Missing data for primary endpoints will be addressed using multiple imputation methods, assuming data are missing at random. Sensitivity analyses will be conducted to assess the impact of different missing data mechanisms on the results. For time-to-event analyses, the last available assessment will be used to censor subjects without events.

Multiplicity Adjustments  
A hierarchical testing approach will be employed to control for type I error across the dual-primary endpoints of rPFS and OS. The significance level of 0.005 will be applied to rPFS first, and if it is statistically significant, testing will proceed to OS utilizing a significance level of 0.045. The allocation of errors ensures that the study will be considered successful if at least one primary endpoint shows a statistically significant result.

This comprehensive statistical analysis plan aims to thoroughly evaluate the efficacy and safety of the addition of apalutamide to ADT in treating mHSPC while rigorously maintaining the integrity of statistical inference through predefined hypotheses testing and appropriate control of type I error rates.

# Safety

Safety

Safety Parameters  
The safety parameters for this study will include the evaluation of adverse events (AEs), laboratory test abnormalities, vital signs (including blood pressure), physical examination findings, and ECOG performance status.

Adverse Event Definitions  
Adverse events are defined as any untoward medical occurrence in a subject administered a pharmaceutical product and may or may not have a causal relationship with the treatment. AEs will be graded and summarized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Severity grades are 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 existing hospitalization indicated; disabling; limiting self-care ADL.  
- Grade 4: Life-threatening consequences; urgent intervention indicated.  
- Grade 5: Death related to adverse event.

Adverse Event Reporting  
All AEs and suspected adverse reactions will be documented from the time of informed consent until 30 days following the last dose of study drug. Serious adverse events (SAEs) must be reported to the sponsor within 24 hours of the investigator becoming aware of the event. Non-serious AEs should be recorded in the case report form within the timeframe specified by the protocol.

Safety Monitoring  
Subjects will be monitored for safety from the signing of informed consent until 30 days after the last dose of study drug. Routine safety evaluations will be conducted at each visit during the treatment phase and at specified intervals during the follow-up phase. These evaluations will include AEs assessment, relevant laboratory tests, vital signs, and physical examinations.

Risk Management  
In case of any severe or life-threatening adverse event related to the study drug, dose modification or discontinuation guidelines outlined in the protocol will be followed to mitigate risks to the subjects. Regular safety data reviews by the IDMC will inform risk management decisions.

Data Monitoring Committee  
An Independent Data Monitoring Committee (IDMC) will be appointed to oversee the conduct of the trial and ensure the safety of the subjects. The IDMC will conduct interim reviews of accumulating safety and efficacy data and provide recommendations on study continuation or modification.

Stopping Rules  
Stopping rules are in place to halt the study early if there is sufficient evidence of treatment efficacy or harm. These include predefined criteria based on interim analysis outcomes, significant safety concerns, or if efficacy boundaries are reached. The IDMC will be responsible for determining if any stopping criteria are met during interim analyses or safety evaluations.

By implementing comprehensive safety oversight procedures, including clear definitions and robust reporting structures for adverse events, this study aims to ensure the highest level of participant safety throughout the trial.