Clinical Trial Protocol

# Background

Background

Disease Background  
Prostate cancer remains one of the most commonly diagnosed cancers among men globally, representing a significant burden on patients and healthcare systems. Metastatic hormone-sensitive prostate cancer (mHSPC) is a subset of prostate cancer where the disease has spread beyond the prostate gland and still responds to androgen deprivation therapy (ADT). Despite initial sensitivity to ADT, most patients eventually progress to a castration-resistant state, necessitating the need for therapies that can delay progression and improve overall survival. The transition from hormone-sensitive disease to castration-resistant prostate cancer poses a substantial challenge, underscoring the need for effective early interventions in the mHSPC stage.

Current Treatment Landscape  
The current mainstay of treatment for mHSPC includes ADT, which works by reducing androgen levels that fuel the growth of prostate cancer cells. ADT can be achieved through surgical castration or more commonly, through medical castration using gonadotropin-releasing hormone analogs (GnRHa). Recently, the addition of chemotherapy with docetaxel and more potent androgen receptor signaling inhibitors like abiraterone acetate has shown improved outcomes in specific patient subgroups. However, there remains a need for therapies that can further improve progression-free survival and overall survival while managing the disease's morbidity.

Product Background  
Apalutamide (JNJ-56021927, ARN-509) is an orally active, non-steroidal anti-androgen that selectively inhibits the androgen receptor. Designed to target androgen receptor signaling more effectively, apalutamide helps in hindering the growth-promoting action of androgens on prostate cancer cells. Demonstrating potent activity in preclinical settings, apalutamide is undergoing clinical evaluation to determine its efficacy and safety profile in various stages of prostate cancer, including mHSPC. The strong selectivity and inhibitory action of apalutamide on the androgen receptor suggest its potential to significantly delay disease progression and enhance survival outcomes.

Study Rationale  
Given the unmet need for improved and well-tolerated treatments in mHSPC, this study aims to evaluate the efficacy of adding apalutamide to ADT compared to ADT alone. The hypothesis driving this research posits that the combination therapy will yield superior results in terms of radiographic progression-free survival (rPFS) and overall survival (OS), with a satisfactory safety profile. By integrating apalutamide, which targets androgen receptor pathways more directly, the study seeks to explore its potential to delay critical endpoints associated with mHSPC progression, thus offering a promising therapeutic avenue for patients. This study will contribute valuable data on the clinical benefits and risks of combining apalutamide with conventional ADT in the early metastatic setting.

# 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).

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 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 of apalutamide when added to ADT.  
6. PK and PD parameters of apalutamide and leuprolide.  
7. Efficacy in subpopulations of low-volume or high-volume mHSPC.

# Study Design

Study Design

Overall Design  
This study is a Phase 3, randomized, double-blind, placebo-controlled, multinational, and multicenter trial aimed at evaluating the efficacy of apalutamide in combination with androgen deprivation therapy (ADT) versus ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). Approximately 1,000 subjects will be enrolled, undergoing a stratified randomization based on Gleason score at diagnosis, geographic region, and prior docetaxel use. Stratified subjects will be assigned in a 1:1 ratio to receive either apalutamide plus ADT or placebo plus ADT.

Following a Screening Phase of up to 28 days, eligible subjects will enter the Treatment Phase, which comprises 28-day cycles until disease progression, the occurrence of unacceptable toxicity, or study termination by the sponsor. The study incorporates an Open-label Extension Phase for subjects achieving positive results during interim analyses, allowing them to receive apalutamide for up to three years, followed by a Long-Term Extension Phase. Safety monitoring will persist from informed consent until 30 days post last study drug dose.

Study Schema  
The study follows a structured sequence starting with a Screening Phase and progressing through Treatment, Follow-up, Open-label Extension, and Long-Term Extension Phases. Randomization will be conducted as follows:

|  |  |  |
| --- | --- | --- |
| **Phase** | **Duration** | **Key Activities** |
| Screening | Up to 28 days | Eligibility assessments |
| Treatment | 28-day cycles, until progression | Apalutamide plus ADT or placebo plus ADT |
| Follow-up | Until death or withdrawal | Ongoing data collection, survival follow-up |
| Open-label Extension | Up to 3 years if applicable | Continued apalutamide treatment for eligible subjects |
| Long-Term Extension | Begins after final study analysis | Continued treatment for subjects deriving benefit |

Study Duration  
The anticipated duration for total study completion is approximately 54 months. This timeline includes an enrollment period of approximately 30 months and an additional follow-up period to accrue the necessary 410 death events required for the final analysis of overall survival (OS).

Treatment Groups  
Subjects will be randomized in a 1:1 ratio to one of the following two study treatment groups:

|  |  |
| --- | --- |
| **Treatment Group** | **Description** |
| Apalutamide plus ADT | Subjects will receive 240 mg of apalutamide (4 x 60 mg tablets) orally daily along with ADT as standard of care. |
| Placebo plus ADT | Subjects will receive matching placebo orally daily along with ADT as standard of care. |

All subjects will receive ADT, which may consist of medical or surgical castration, following the discretion of the investigator regarding the form and administration of the ADT. Randomization and dosing will be meticulously documented and monitored throughout the study.

Study Schema

# Population

Study Population

Overview of Study Population  
The study population consists of subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC) who have a documented Eastern Cooperative Oncology Group (ECOG) performance status of grade 0 or 1. Subjects must present with distant metastatic disease confirmed by a positive bone scan indicating the presence of at least one bone lesion. In cases of a single bone lesion, confirmation through computed tomography (CT) or magnetic resonance imaging (MRI) is required. Participants may have previously received chemotherapy regimens or underwent surgical or radiation interventions under specific conditions as detailed below.

Inclusion Criteria  
1. \*\*Diagnosis and Disease Status\*\*  
 - Subjects must have a confirmed diagnosis of prostate cancer.  
 - Presence of distant metastatic disease documented by a positive bone scan (1 or more bone lesions on Technetium 99m [99mTc] bone scan).  
 - For subjects with a single bone lesion, confirmation by CT or MRI is required.

2. \*\*Performance Status\*\*  
 - ECOG performance status grade of 0 or 1 is mandatory for inclusion.

3. \*\*Prior Treatment\*\*  
 - Up to 6 cycles of docetaxel for mHSPC allowed, with the last dose administered ≤2 months prior to randomization.  
 - ≤6 months of ADT allowed prior to randomization.  
 - Maximum of 1 course of radiation or surgical intervention for mHSPC permitted.  
 - For localized prostate cancer, subjects may have received up to 3 years of ADT and other therapies, including radiation, prostatectomy, or lymph node dissection, provided such therapies were completed ≥1 year prior to randomization.

Exclusion Criteria  
1. \*\*Medical Exclusions\*\*  
 - Any condition that contradicts the study protocol or the safe administration of study drugs.  
 - Subjects with uncontrolled intercurrent illness.

2. \*\*Contraindications and Prior Therapies\*\*  
 - Prior treatment with apalutamide or similar anti-androgen therapies in the metastatic setting.  
 - Any systemic therapies completed less than 1 year prior to randomization unless specified as allowable under inclusion criteria.

3. \*\*Other Exclusions\*\*  
 - Known brain metastasis or leptomeningeal disease.  
 - Known history of or current evidence of thromboembolic events or significant bleeding disorders.

Withdrawal Criteria  
- Subjects must be withdrawn from the study if they exhibit disease progression as defined by protocol criteria, experience unacceptable adverse events related to the study drugs, or withdraw consent from participation.  
- The investigator may also stop participation if deemed necessary for safety concerns or based on a subject's best interest.

Replacement Policy  
- Subjects who withdraw, are lost to follow-up, or discontinued prematurely for any reason may be replaced to ensure adequate study power and data integrity. Replacement will generally be conducted during the initial recruitment and randomization period to maintain the study design's statistical calculations. Specific guidelines for subject replacement will be followed as per the protocol specifications.

# Procedures

Study Procedures

Study Procedures Overview  
This section outlines the detailed procedures to be conducted throughout the study phases, including Screening, Treatment, and Follow-up, alongside specific assessments such as safety, efficacy, laboratory, and others.

Screening/Baseline Procedures  
- \*\*Timing:\*\* Up to 28 days before randomization  
- \*\*Specific Requirements:\*\*  
 - Obtain written informed consent from all subjects.  
 - Record demographics and complete medical history.  
 - Conduct a comprehensive physical examination.  
 - Measure vital signs, including blood pressure.  
 - Perform laboratory assessments, including standard hematology and biochemistry tests.  
 - Conduct disease assessment using bone scan for metastatic disease confirmation.  
 - Review inclusion and exclusion criteria to establish eligibility.  
- \*\*Responsible Personnel:\*\* Study Investigator and Supporting Clinical Staff

Treatment Phase Procedures  
- \*\*Timing:\*\* Every 28-day cycle  
- \*\*Specific Requirements:\*\*  
 - Administer study medication (apalutamide or placebo) orally once daily.  
 - Conduct regular safety monitoring, including adverse event tracking.  
 - Carry out efficacy assessments through imaging and clinical evaluations.  
 - Conduct laboratory tests periodically to assess health status.  
 - Administer and evaluate Quality of Life (QoL) assessments using BPI-SF, BFI, and EQ-5D-5L.  
 - Monitor for adverse events and manage according to protocol-specified dose modifications.  
 - Document the use of any concomitant medications in the electronic case report form (eCRF).  
- \*\*Responsible Personnel:\*\* Study Coordinator, Principal Investigator, and Nursing Staff

Follow-up Procedures  
- \*\*Timing:\*\* Every 4 months after treatment discontinuation  
- \*\*Specific Requirements:\*\*  
 - Conduct safety follow-up to observe long-term health outcomes.  
 - Perform disease assessments to monitor any progression.  
 - Document survival status and any subsequent therapies initiated.  
 - Collect patient-reported outcomes up to 12 months post-treatment discontinuation.  
- \*\*Responsible Personnel:\*\* Study Investigator and Clinical Research Coordinator

Safety Assessments  
- \*\*Components:\*\*  
 - Comprehensive physical examinations at scheduled visits.  
 - Monitoring and recording of vital signs at each visit.  
 - Routine laboratory tests to detect any treatment-emergent abnormalities.  
 - Continuous monitoring for any adverse events, graded using NCI-CTCAE Version 4.03.  
- \*\*Responsible Personnel:\*\* Study Investigator and Clinical Research Staff

Efficacy Assessments  
- \*\*Components:\*\*  
 - Radiographic assessments for progression-free survival using CT/MRI scans following RECIST 1.1 criteria.  
 - Overall survival tracked throughout study duration.  
 - Collection and analysis of patient-reported outcomes.  
- \*\*Responsible Personnel:\*\* Imaging Specialists, Study Investigator, and Clinical Research Team

Laboratory Assessments  
- \*\*Components:\*\*  
 - Routine hematology and clinical chemistry panels.  
 - Biomarker sampling for exploratory endpoints.  
 - Pharmacokinetic sampling for apalutamide and leuprolide analysis.  
- \*\*Specific Handling:\*\* Ensure samples are processed according to standard laboratory protocols to maintain integrity.  
- \*\*Responsible Personnel:\*\* Laboratory Technician and Study Coordinator

Other Assessments  
- \*\*Components:\*\*  
 - Biomarker assessments to explore treatment response and resistance.  
 - Investigate medical resource utilization for economic modeling.  
- \*\*Special Requirements:\*\* Collection and storage of tumor and blood samples as outlined in protocol.  
- \*\*Responsible Personnel:\*\* Study Coordinator, Laboratory Personnel, and Data Analysis Team

This structure ensures consistent implementation and comprehensive monitoring throughout the study, adhering to protocol requirements and maintaining participant safety and data integrity.

# Statistical

Statistical Analysis

Statistical Hypotheses

The primary hypothesis for this phase 3 study is that the addition of apalutamide to androgen deprivation therapy (ADT) will improve radiographic progression-free survival (rPFS) and/or overall survival (OS) compared to ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). For the dual-primary endpoints, the study is considered successful if statistical significance is achieved for at least one of the endpoints: rPFS or OS.

Sample Size Determination

The study is designed with an overall type I error rate of 5%. A significance level of 0.005 is allocated for the rPFS endpoint, and 0.045 is allocated for the OS endpoint. An estimated 368 events for rPFS will provide at least 85% power to detect a hazard ratio (HR) of 0.67 (with assumed median rPFS of 20 months for the control group [ADT] versus 30 months for the treatment group with apalutamide plus ADT). For OS, approximately 410 events are expected to provide 80% power to detect a HR of 0.75, assuming a median OS of 44 months for the control group. The enrollment period is approximately 30 months, with a total study duration of approximately 54 months, allowing time to accrue 410 death events.

Analysis Populations

The primary analysis will be conducted using the intent-to-treat (ITT) population, which includes all subjects randomized in the study. The safety population will consist of all subjects who receive at least one dose of the study drug, and analyses will be conducted 'as treated'.

Statistical Methods

Time-to-event variables, such as rPFS and OS, will be analyzed using the Kaplan-Meier product-limit method. Hazard ratios for treatment effects will be estimated using the Cox proportional hazards model, with corresponding 95% confidence intervals. For secondary and other time-to-event endpoints (e.g., time to pain progression, time to initiation of cytotoxic chemotherapy), similar statistical methodologies will be employed.

Multiplicity Adjustments

To adjust for multiple comparisons for the dual-primary endpoints (rPFS and OS), an alpha-spending approach is applied with separate significance levels pre-allocated (0.005 for rPFS and 0.045 for OS). This approach controls the overall type I error rate to ensure robustness against potential false positive results.

Interim Analyses

Two interim analyses are planned for the OS endpoint, at approximately 50% (205 events) and 70% (287 events) of the total 410 required OS events. These analyses are intended to assess efficacy and guide potential early stopping decisions. The rPFS final analysis will be performed at the first interim analysis of OS. No interim analysis is planned for the rPFS endpoint.

Missing Data Handling

For time-to-event analyses, subjects who have not experienced the event by the cut-off date will be censored at their last known follow-up date. Sensitivity analyses will be conducted to assess the impact of missing data, using imputation methods or other appropriate statistical techniques, to confirm the robustness of the study results.

Overall, these detailed statistical methods will ensure comprehensive and accurate evaluation of study objectives while maintaining scientific rigor and integrity.

# Safety

Safety

Safety Parameters

The safety evaluation in this study will include the monitoring of adverse events (AEs), changes in vital signs, findings from physical examinations, ECOG performance status assessments, and clinical laboratory tests. Specific emphasis will be placed on the incidence and intensity of treatment-emergent adverse events (TEAEs), any clinically significant shifts in laboratory results, and variations in physical examination outcomes.

Adverse Event Definitions

Adverse events are defined as any untoward medical occurrences in subjects enrolled in the study, regardless of their causal relationship to the study drug. Adverse events will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, with severity categorized into five grades:  
- Grade 1: Mild  
- Grade 2: Moderate  
- Grade 3: Severe  
- Grade 4: Life-threatening  
- Grade 5: Death related to the adverse event

Adverse Event Reporting

Adverse events will be collected from the time of informed consent signing through 30 days post-final dose of study drug. All AEs must be documented in the subject's electronic case report form (eCRF), including the onset, duration, severity grade, and possible relationship to the study drug. Serious adverse events (SAEs) will be reported to the sponsor within 24 hours of the principal investigator becoming aware of the event.

Safety Monitoring

Safety monitoring will be ongoing and will include routine assessments during each 28-day treatment cycle. This will involve measuring blood pressure, conducting physical exams, and performing laboratory tests consistent with study protocol timelines. The study monitoring includes steps to ensure any dose modifications required for safety reasons are followed as outlined in protocol-specific guidelines.

Risk Management

To manage risk, the study includes predefined criteria for dose reduction or discontinuation in response to identified AEs. Safety oversight is provided through the implementation of these guidelines, with dose adjustments executed as per the protocol to mitigate adverse effects while maintaining treatment efficacy.

Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will oversee the safety and efficacy data throughout the trial. The IDMC will conduct regular reviews as well as planned interim efficacy analyses. The committee will provide recommendations for the continuation, modification, or termination of the study based on accrued data.

Stopping Rules

Stopping rules for this study include criteria related to safety and efficacy. Any unforeseen significant safety concerns, or instances where interim analyses reveal definitive efficacy benefits, may prompt early study termination. The IDMC will review these outcomes against predefined stopping rules, ensuring participant safety remains the top priority. Furthermore, individual participant withdrawal criteria include instances of confirmed disease progression based on clinical judgment or intolerable toxicity to the study drug.

Overall, these procedures and protocols ensure vigilant safety oversight throughout the study duration, prioritizing participant well-being and the integrity of study findings.