Clinical Trial Protocol

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# 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 remains responsive to hormone therapy. Patients with mHSPC often present with a variety of distant metastases, which can include bone lesions demonstrated by imaging methods such as a bone scan or confirmation through CT or MRI. The management of mHSPC is critical, as it significantly impacts the patient’s prognosis and quality of life. Prostate cancer represents a leading cause of cancer-related mortality in men worldwide, necessitating the development of more effective therapies to delay disease progression and improve survival outcomes.

Current Treatment Landscape  
The current standard treatment for mHSPC involves androgen deprivation therapy (ADT), which can be achieved through medical castration using gonadotropin-releasing hormone (GnRH) analogs or surgical castration such as orchiectomy. ADT effectively lowers serum testosterone levels, thus inhibiting the growth stimulatory effects of androgens on prostate cancer cells. While this approach is initially effective, most patients eventually develop resistance, leading to progression to castration-resistant prostate cancer. In some cases, additional systemic therapies, such as chemotherapy with docetaxel, may also be employed. Despite these interventions, disease progression remains inevitable, signaling a need for improved therapeutic strategies to enhance efficacy and delay resistance.

Product Background  
Apalutamide (JNJ-56021927), also known as ARN-509, is an orally-administered, non-steroidal, potent, and selective antagonist of the androgen receptor. As an anti-androgen, apalutamide interferes with androgen receptor signaling, which is a critical pathway in the development and progression of prostate cancer. Its mechanism of action allows apalutamide to inhibit tumor growth in both androgen-sensitive and castration-resistant prostate cancer models. By blocking the androgen receptor, apalutamide disrupts the signaling cascade crucial for prostate cancer cell survival and proliferation, providing a promising treatment avenue for mHSPC.

Study Rationale  
The rationale for the study is based on the hypothesis that the addition of apalutamide to standard ADT could enhance treatment efficacy in patients with mHSPC compared to ADT alone. This hypothesis is grounded in the need to improve radiographic progression-free survival (rPFS) and overall survival (OS) for individuals diagnosed with mHSPC. Apalutamide has demonstrated potential in halting disease progression due to its targeted action on the androgen receptor pathway. By integrating apalutamide with conventional ADT, this study aims to assess the possibility of yielding superior clinical outcomes, including delay in pain progression, reduction in skeletal-related events, and restraining the need for cytotoxic chemotherapy. Furthermore, the study seeks to evaluate the safety profile of apalutamide combined with ADT, addressing an essential factor in the overall therapeutic strategy for improving patient outcomes in mHSPC.

# 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 from any cause, whichever occurs first.  
2. Overall survival (OS), defined as the time from randomization to 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 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 subpopulations of subjects with low-volume or high-volume mHSPC.

Secondary Endpoint(s)  
1. Time to pain progression.  
2. Time to the use of chronic opioids.  
3. Time to skeletal-related events (SREs).  
4. Time to initiation of cytotoxic chemotherapy.  
5. Incidence and safety profile assessment through adverse events and clinical laboratory tests.  
6. Plasma concentration-time data analysis for apalutamide and its metabolite.  
7. Testosterone concentration analysis and percentage of subjects maintaining testosterone levels below 50 ng/dL.

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), 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 data for future economic modeling.

# Study Design

Study Design

Overall Design  
This Phase 3 study is designed as a randomized, double-blind, placebo-controlled, multinational, and multicenter trial 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, stratified by Gleason score at diagnosis, regional location, and prior docetaxel use. Eligible subjects will be randomized in a 1:1 ratio to receive either apalutamide plus ADT or a matching placebo plus ADT.

Study Schema  
The study will include the following key phases:  
1. \*\*Screening Phase\*\*: Up to 28 days to determine eligibility criteria adherence.  
2. \*\*Treatment Phase\*\*: Subjects will undergo treatment in 28-day cycles until disease progression, unacceptable toxicity, or discontinuation by the sponsor.  
3. \*\*Follow-up Phase\*\*: Collection of survival data and secondary endpoint assessments every four months until withdrawal, death, or study termination.  
4. \*\*Open-label Extension Phase\*\*: Upon a positive outcome, subjects may receive apalutamide for approximately three years.  
5. \*\*Long-Term Extension Phase\*\*: Continuation of apalutamide if beneficial per investigator assessment, post-final analysis cut-off.

Study Duration  
The overall study duration is approximately 54 months, with a 30-month enrollment period expected to gather about 1,000 subjects. Treatment will continue until 410 death events occur for primary endpoint analyses. Subjects in treatment at interim or final positive result will have additional opportunities to enroll in extension phases for continued assessment.

Treatment Groups  
Subjects in the study will be assigned to one of two treatment groups:

|  |  |  |
| --- | --- | --- |
| Treatment Group | ADT Component | Additional Treatment |
| --------------------- | --------------------------------------- | ------------------------------------------ |
| Apalutamide + ADT | Standard of care, GnRHa or orchiectomy | Apalutamide 240 mg orally once daily |
| Placebo + ADT | Standard of care, GnRHa or orchiectomy | Matching placebo orally once daily |

• Apalutamide Group\*\*: Subjects will receive 240 mg of apalutamide in a daily oral dose alongside ADT.

• Placebo Group\*\*: Subjects assigned will receive a matching placebo alongside ADT.

Safety monitoring, dose modifications, and adverse event reporting will be conducted throughout the study following established criteria to ensure comprehensive safety evaluation.

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 consists of adult males diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). These subjects are required to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, indicating fully active or restricted in physically strenuous activities but ambulatory.

Inclusion Criteria  
1. Male subjects with a confirmed diagnosis of prostate cancer.  
2. Evidence of metastatic disease, demonstrated by at least one lesion on a Technetium 99m (99mTc) bone scan.  
 - Subjects with a single bone lesion must have additional confirmation of bone metastasis via CT or MRI.  
3. ECOG performance status of 0 or 1.  
4. Subjects may have received up to six cycles of docetaxel for mHSPC, with the final dose administered no more than two months prior to randomization.  
5. Previous androgen deprivation therapy (ADT) should not exceed six months prior to randomization.  
6. Subjects may have undergone one course of radiation or surgical intervention for mHSPC treatment.  
7. For initially localized prostate cancer, subjects may have received androgen deprivation therapy (ADT) for a total of up to three years, along with other therapies (e.g., radiation, prostatectomy, lymph node dissection) provided these were completed at least one year before randomization.

Exclusion Criteria  
1. History of prior treatment with investigational agents targeting the androgen receptor.  
2. Previous malignancies diagnosed within the last three years, except for non-melanoma skin cancers or adequately treated in situ carcinomas.  
3. Presence of any condition that would compromise the subject's ability to comply with study requirements or give informed consent.

Withdrawal Criteria  
1. Disease progression as defined by the study protocol.  
2. Occurrence of unacceptable treatment-related toxicity.  
3. Withdrawal of consent by the subject.  
4. Significant protocol deviation that may affect the study integrity or subject safety.

Replacement Policy  
Subjects who withdraw from the study or are removed due to protocol-defined withdrawal criteria will not be replaced, as the statistical analysis plan accommodates for attrition within the initially calculated sample size.

# Procedures

Study Procedures

Study Procedures Overview  
This section outlines the study procedures to be conducted during the screening, treatment, and follow-up phases, including safety and efficacy assessments, laboratory evaluations, and other necessary assessments.

Screening/Baseline Procedures  
Screening will occur up to 28 days before randomization. The following procedures will be performed:

• Informed Consent\*\*

• Timing: Prior to any study-specific procedures

• Requirements: Obtain written informed consent from all subjects

• Personnel: Investigators or designated study staff

2. \*\*Demographics and Medical History\*\*  
 - Timing: At initial visit  
 - Requirements: Collect subject demographics and detailed medical history, including prior therapies  
 - Personnel: Investigators or designated study staff

3. \*\*Physical Examination\*\*  
 - Timing: At screening  
 - Requirements: Conduct a comprehensive physical examination  
 - Personnel: Qualified healthcare professionals

4. \*\*Vital Signs\*\*  
 - Timing: At screening  
 - Requirements: Record blood pressure, heart rate, temperature, and respiratory rate  
 - Personnel: Nursing staff or designated personnel

5. \*\*Laboratory Assessments\*\*  
 - Timing: At screening  
 - Requirements: Conduct hematology, clinical chemistry, and urinalysis  
 - Personnel: Laboratory technicians

6. \*\*Disease Assessment\*\*  
 - Timing: At screening  
 - Requirements: Perform imaging studies including bone scan, CT, or MRI as applicable  
 - Personnel: Radiologists or designated imaging personnel

7. \*\*Inclusion/Exclusion Criteria Review\*\*  
 - Timing: Prior to randomization  
 - Requirements: Confirm eligibility based on protocol-defined criteria  
 - Personnel: Investigators

Treatment Phase Procedures  
Once randomized, subjects will undergo repeated assessments and monitoring as outlined below:

• Drug Administration\*\*

• Timing: Daily

• Requirements: Administer JNJ-56021927 (apalutamide) 240 mg orally or matching placebo once daily

• Personnel: Subjects, under supervision and reporting by study staff

2. \*\*Safety Monitoring\*\*  
 - Timing: Ongoing throughout treatment cycles  
 - Requirements: Monitor for adverse events (AEs) and dose modifications as outlined in the protocol  
 - Personnel: Investigators and study staff

3. \*\*Efficacy Assessments\*\*  
 - Timing: At specified intervals during treatment  
 - Requirements: Perform radiographic assessments as per schedule  
 - Personnel: Radiologists or designated imaging personnel

4. \*\*Laboratory Tests\*\*  
 - Timing: Day 1 of Cycles 2, 3, 4, 5, and 6  
 - Requirements: Trough PK blood sampling; collect samples for hematology and clinical chemistry  
 - Personnel: Laboratory technicians

5. \*\*Quality of Life Assessments\*\*  
 - Timing: At specified intervals  
 - Requirements: Administer Brief Pain Inventory-Short Form (BPI-SF), Brief Fatigue Inventory (BFI), EQ-5D-5L  
 - Personnel: Study staff

6. \*\*Adverse Event Monitoring\*\*  
 - Timing: Continually during each cycle  
 - Requirements: Document and review AEs; utilize NCI-CTCAE criteria  
 - Personnel: Investigators and designated study staff

7. \*\*Concomitant Medication Review\*\*  
 - Timing: Each visit  
 - Requirements: Document any changes in concomitant medications  
 - Personnel: Investigators or study staff

Follow-up Procedures  
Upon treatment discontinuation, the following follow-up assessments will be conducted:

• Safety Follow-up\*\*

• Timing: Within 30 days after last dose

• Requirements: Final safety evaluations including laboratory tests and vital signs

• Personnel: Investigators

2. \*\*Disease Assessment\*\*  
 - Timing: Every 4 months post-treatment  
 - Requirements: Collect data on disease status and progression  
 - Personnel: Investigators or designated study staff

3. \*\*Survival Status\*\*  
 - Timing: Every 4 months until study termination  
 - Requirements: Document survival and disease status  
 - Personnel: Study staff

4. \*\*Subsequent Therapy Documentation\*\*  
 - Timing: During the follow-up phase  
 - Requirements: Record any new therapies for prostate cancer  
 - Personnel: Investigators or study staff

Safety Assessments  
- \*\*Physical Examinations\*\*  
 - Timing: Baseline, and according to protocol schedule  
 - Personnel: Qualified healthcare professionals  
- \*\*Vital Signs\*\*  
 - Timing: Regularly during visits  
 - Personnel: Nursing staff or qualified personnel  
- \*\*Laboratory Tests\*\*  
 - Timing: Per protocol schedule  
 - Personnel: Laboratory technicians  
- \*\*Adverse Event Monitoring\*\*  
 - Timing: Continuously  
 - Personnel: Investigators

Efficacy Assessments  
- \*\*Radiographic Assessments\*\*  
 - Timing: Per protocol-defined schedule  
 - Personnel: Radiologists  
- \*\*Patient-reported Outcomes\*\*  
 - Timing: Regular intervals as per protocol  
 - Personnel: Study staff

Laboratory Assessments  
- \*\*Hematology and Clinical Chemistry\*\*  
 - Timing: Screening and during treatment  
 - Personnel: Laboratory technicians  
- \*\*Biomarker Sampling\*\*  
 - Timing: At specified time points   
 - Personnel: Study staff or laboratory technicians  
- \*\*Pharmacokinetic/Pharmacodynamic Assessments\*\*  
 - Timing: Specified cycles for PK trough samples  
 - Personnel: Laboratory technicians

Other Assessments  
- \*\*Biomarker Analysis\*\*  
 - Timing: At baseline and specified times  
 - Personnel: Study staff  
- \*\*Medical Resource Utilization\*\*  
 - Timing: Throughout the treatment phase  
 - Personnel: Study staff

All procedures are to adhere strictly to protocol guidelines and ethical research practices, ensuring all data collection and subject interaction are conducted with subject safety and confidentiality as priorities.

# Statistical

Statistical Analysis

Statistical Hypotheses  
The primary hypothesis of this study is that the addition of apalutamide to androgen deprivation therapy (ADT) will result in a statistically significant improvement in radiographic progression-free survival (rPFS) and/or overall survival (OS) compared to ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). The study will be deemed successful if at least one of the dual-primary endpoints is statistically significant.

Sample Size Determination  
The sample size for this study is determined to ensure sufficient power to detect clinically significant differences in the dual-primary endpoints, rPFS and OS. The allocation of type I error across each endpoint is 0.005 for rPFS and 0.045 for OS, maintaining the overall alpha level at 0.05. Approximately 368 rPFS events are needed to provide at least 85% power for detecting a hazard ratio (HR) of 0.67. For OS, approximately 410 death events are required to detect an HR of 0.75 with 80% power. An estimated 1,000 subjects will be enrolled over approximately 30 months.

Analysis Populations

Intent-to-Treat (ITT) Population  
The ITT population will consist of all randomized subjects and will be used for efficacy analyses, including rPFS and OS.

Safety Population  
The safety population comprises subjects who received at least one dose of study drug, analyzed according to the actual treatment received.

Statistical Methods

Primary Efficacy Analysis  
- \*\*Radiographic Progression-Free Survival (rPFS)\*\* and \*\*Overall Survival (OS)\*\*: The primary endpoint analyses will employ the Kaplan-Meier method to estimate survival functions, and the Cox proportional hazards model will generate hazard ratios and 95% confidence intervals (CIs).  
- \*\*Hypothesis Testing\*\*: A stratified log-rank test will compare rPFS and OS between treatment groups. The significance levels are set at 0.005 for rPFS and 0.045 for OS.

Secondary Efficacy Analyses  
- \*\*Time-to-Event Analyses\*\*: For secondary endpoints (e.g., time to pain progression, time to SREs), similar Kaplan-Meier and Cox model approaches will be used.

Population Pharmacokinetic Analysis  
Population PK analysis of apalutamide concentration-time data will be performed using nonlinear mixed-effects modeling. Separate reports will present detailed results of the PK/PD analyses.

Biomarker Analyses  
For exploratory biomarkers, associations with clinical response or other endpoints will be assessed using analysis of variance, categorical, or survival models. Detailed plans will be outlined in a separate Statistical Analysis Plan.

Interim Analyses  
Two interim analyses are planned for the OS endpoint after approximately 50% and 70% of the planned 410 death events occur. The final analysis for the rPFS endpoint will also be executed at the time of the first OS interim analysis. Statistical significance will be adjusted using the O'Brien-Fleming spending function to control the family-wise error rate.

Missing Data Handling  
Missing efficacy data will be managed using multiple imputation methods, where appropriate, and sensitivity analyses will be performed to evaluate the robustness of the primary results to different assumptions concerning missing data. A detailed strategy will be outlined in the Statistical Analysis Plan.

Multiplicity Adjustments  
Given the dual-primary endpoint design, a hierarchical testing procedure will control the type I error rate. The primary hypothesis testing will first assess rPFS, and if significant, proceed to OS evaluation. If either endpoint reaches statistical significance, the study hypotheses are considered supported.

# Safety

Safety

Safety Parameters

The safety parameters to be evaluated in this study include the incidence and intensity of treatment-emergent adverse events (AEs), clinically significant changes in physical examination findings, vital signs, and clinical laboratory results.

Adverse Event Definitions

Adverse events will be categorized per the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. Severity of AEs will be graded on a scale from Grade 1 (mild) to Grade 5 (death related to an AE).

Adverse Event Reporting

All AEs, whether related to the study drug or not, must be reported from the time of informed consent signing until 30 days after the last dose of study drug. Serious adverse events (SAEs) must be reported within 24 hours of the investigator becoming aware of the event. AEs will be recorded in the electronic case report form (eCRF).

Safety Monitoring

Safety monitoring will be conducted continuously throughout the study. This includes periodic assessment of vital signs, physical examinations, and laboratory tests. In particular, hematological and biochemical monitoring will be performed at each scheduled visit to identify any clinically significant changes that might suggest treatment-emergent toxicities.

Risk Management

The protocol includes predefined dose modifications and interruptions in response to AEs to mitigate risks and manage toxicities. Detailed instructions for dose adjustments based on AE severity are provided within the protocol. Close monitoring and proactive AE management strategies are integral to minimizing risk.

Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will oversee the safety data regularly to ensure the well-being of study participants. The IDMC will include independent experts in clinical research and oncology. The committee will meet at predetermined intervals to evaluate cumulative safety data and provide recommendations regarding study continuation or modification.

Stopping Rules

Stopping rules are in place for both safety and efficacy endpoints. For safety, if a specific AE exceeds a predetermined incidence rate threshold, or if any unforeseen safety concerns arise, the study may be paused or terminated upon IDMC recommendation. For efficacy, interim analyses will guide potential early stopping for benefit if significant improvements in primary endpoints are observed, preserving ethical considerations for participant well-being.

Consistent adherence to these safety procedures ensures rigorous assessment and swift responsiveness to any safety issues, optimizing participant safety while maintaining study integrity.