Clinical Trial Protocol

# Background

Background

Disease Background  
Prostate cancer is one of the most commonly diagnosed malignancies in men worldwide, often resulting in significant morbidity and mortality. Metastatic hormone-sensitive prostate cancer (mHSPC) is a stage of the disease where cancer has spread beyond the prostate gland but remains responsive to therapies that suppress androgen hormones, which fuel the cancer's growth. Despite initial responsiveness to androgen deprivation therapy (ADT), the majority of patients eventually progress to a castration-resistant state, leading to advanced disease and decreased survival. Understanding the mechanisms that drive disease progression in mHSPC is critical for developing new therapeutic strategies to enhance survival and quality of life in affected patients.

Current Treatment Landscape  
The standard treatment for mHSPC involves androgen deprivation therapy (ADT), which aims to reduce levels of male hormones that assist in the growth and spread of prostate cancer cells. ADT can be achieved through surgical castration or the use of gonadotropin-releasing hormone (GnRH) analogs. While ADT effectively manages the disease initially, many patients ultimately develop resistance, necessitating additional therapeutic options. Recently, the addition of docetaxel, a cytotoxic chemotherapy, to ADT has shown an improvement in survival for certain subgroups of mHSPC patients. However, the need persists for novel treatment combinations that can delay progression and improve overall survival outcomes.

Product Background  
Apalutamide (JNJ-56021927) is an innovative, orally administered, small molecule that functions as a potent and selective antagonist of the androgen receptor (AR). By inhibiting the AR, apalutamide disrupts the androgen signaling pathway, which is crucial for the proliferation and survival of prostate cancer cells. It is a non-steroidal anti-androgen that has shown promise in preclinical studies and early-phase clinical trials. Apalutamide offers a potential new mechanism of action for treating mHSPC, aiming to improve outcomes in patients by delaying disease progression and ultimately enhancing survival when combined with standard ADT.

Study Rationale  
The rationale behind this Phase 3 study of apalutamide plus ADT compared to ADT alone in subjects with mHSPC stems from the encouraging results from preliminary studies and the pressing need for more advanced treatment regimens. By investigating the efficacy and safety of apalutamide in conjunction with ADT, the study seeks to ascertain whether this combination can provide superior radiographic progression-free survival (rPFS) and overall survival (OS) compared to ADT alone. Additionally, the study will explore secondary outcomes such as pain progression, opioid use, and skeletal-related events, while also providing insights into the pharmacokinetics, pharmacodynamics, and potential biomarkers associated with response and resistance to treatment. Understanding these variables is crucial for identifying patient populations that can benefit most from apalutamide and optimizing therapeutic strategies for 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) as assessed by investigator evaluation.  
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 subpopulations of subjects with low-volume or high-volume mHSPC.

Secondary Endpoints  
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 assessed through incidence and intensity of treatment-emergent adverse events (AEs).  
6. Plasma concentration-time data analysis for population PK.  
7. Change in testosterone concentrations in leuprolide PK sub-study.  
8. Evaluation of treatment effectiveness in subjects with low-volume or high-volume mHSPC.

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, multicenter, multinational, randomized, double-blind, placebo-controlled trial designed to assess 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 eligible subjects will be enrolled and stratified based on Gleason score at diagnosis, geographic region, and prior docetaxel use. Subjects will then be randomized in a 1:1 ratio to receive either apalutamide plus ADT or a matching placebo plus ADT. The study aims to determine if apalutamide provides superior radiographic progression-free survival (rPFS) and overall survival (OS).

Study Schema  
The study follows a structured progression through several phases:  
1. Screening Phase: Lasts up to 28 days to confirm eligibility.  
2. Treatment Phase: Subjects receive study treatment in 28-day cycles until disease progression, unacceptable toxicity, or sponsor termination of the study.  
3. Follow-up Phase: Post-treatment data collection every 4 months to gather data on survival, secondary endpoints, and progression events until death, withdrawal of consent, or study termination.  
4. Open-label Extension Phase: Initiated upon a positive study result to allow continued apalutamide treatment.  
5. Long-Term Extension Phase: For subjects benefiting from apalutamide beyond the study’s final analysis.

Study Duration  
The total study duration is anticipated to be approximately 54 months. Enrollment is estimated to complete within 30 months, and the study will continue until 410 death events are observed to meet the required statistical power for analyzing overall survival.

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

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| --- | --- | --- |
| **Treatment Group** | **Description** | **Administration** |
| Apalutamide plus ADT | Apalutamide 240 mg (4 tablets) orally once daily | Standard ADT administered concurrently |
| Placebo plus ADT | Matching placebo (4 tablets) orally once daily | Standard ADT administered concurrently |

Androgen deprivation therapy will be carried out as per standard of care, using either medical or surgical castration. The choice of GnRH analog is at the investigator’s discretion, adhering to prescribed dosing protocols. Monitoring for safety will persist from the signing of informed consent to 30 days post-study drug discontinuation, with an Independent Data Monitoring Committee (IDMC) overseeing interim analyses and safety reviews.

Study Schema

# Population

Study Population

Overview of Study Population  
The study will include adult male subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, indicating full activity or some symptoms but ambulatory. The presence of distant metastatic disease must be confirmed through imaging, such as a positive bone scan or additional validation via computed tomography (CT) or magnetic resonance imaging (MRI) for those with a single bone lesion.

Inclusion Criteria  
1. Male subjects aged 18 years or older.  
2. Histologically or cytologically confirmed adenocarcinoma of the prostate.  
3. Evidence of metastatic disease, specifically:   
 - At least one bone metastasis as documented by a positive Technetium 99m bone scan.  
 - Confirmation by CT or MRI is required for subjects with a solitary bone lesion.  
4. ECOG performance status of 0 or 1.  
5. Candidates may have received up to 6 cycles of docetaxel for mHSPC, provided that the last dose was administered ≤2 months prior to randomization.  
6. Up to 6 months of prior androgen deprivation therapy (ADT) for mHSPC is allowed.  
7. Patients may have undergone 1 course of radiation therapy or surgical procedure for mHSPC.  
8. For previously localized prostate cancer, no more than 3 years of total ADT, with completion of all prior therapies, including surgeries and systemic treatments, at least 1 year before randomization.

Exclusion Criteria  
1. Known central nervous system (CNS) metastases.  
2. Another active malignancy requiring systemic therapy within the last 5 years, excluding certain non-melanoma skin cancers.  
3. Clinically significant cardiac disease or unstable cardiac conditions.  
4. Prior use of investigational drugs for prostate cancer within 4 weeks of randomization or 5 half-lives of the drug, whichever is longer.  
5. Any contraindication to receiving study drug components or treatments.  
6. Severe liver or renal impairment.  
7. Known hypersensitivity to any component of the study treatments.

Withdrawal Criteria  
Subjects may be withdrawn from the study for any of the following reasons:  
1. Significant non-compliance with study procedures.  
2. Adverse events or toxicities that necessitate the discontinuation of treatment.  
3. Subject's decision to withdraw consent.  
4. Disease progression based on clinical judgment or imaging results that require alternative treatment.  
5. Investigator or sponsor decision based on emerging safety or efficacy data.

Replacement Policy  
Subjects withdrawn from the study prior to completing at least one cycle of treatment (28 days) without a recorded efficacy endpoint, and those who voluntarily withdraw consent during the Screening Phase, will be replaced to ensure the study achieves its target sample size of approximately 1,000 evaluable participants. Replacement will occur in accordance with stratification guidelines used during initial randomization to maintain balanced treatment arms.

# Procedures

Study Procedures

Study Procedures Overview  
This section provides a detailed account of the procedures conducted during the study, including the phases of screening, treatment, and follow-up.

Screening/Baseline Procedures  
1. \*\*Informed Consent\*\*  
 - Timing: Prior to any study-specific procedures.  
 - Requirements: Obtain written consent from each participant.  
 - Responsible Personnel: Investigator or designated study staff.  
   
2. \*\*Demographics and Medical History\*\*  
 - Timing: During the initial screening visit.  
 - Requirements: Record demographic details and comprehensive medical history.  
 - Responsible Personnel: Investigator or study coordinator.

3. \*\*Physical Examination\*\*  
 - Timing: During the screening period, up to 28 days prior to randomization.  
 - Requirements: Conduct a complete physical examination.  
 - Responsible Personnel: Qualified healthcare professional.

4. \*\*Vital Signs\*\*  
 - Timing: Collected during screening.  
 - Requirements: Measure blood pressure, heart rate, respiratory rate, and temperature.  
 - Responsible Personnel: Study nurse or medical staff.

5. \*\*Laboratory Assessments\*\*  
 - Timing: During the screening phase.  
 - Requirements: Conduct hematology, clinical chemistry tests, and PSA levels.  
 - Responsible Personnel: Laboratory technician.

6. \*\*Disease Assessment\*\*  
 - Timing: At screening/baseline.  
 - Requirements: Conduct bone scans and CT/MRI to confirm metastatic disease.  
 - Responsible Personnel: Radiologist or trained technician.

7. \*\*Inclusion/Exclusion Criteria Review\*\*  
 - Timing: Prior to randomization.  
 - Requirements: Ensure all inclusion/exclusion criteria are met.  
 - Responsible Personnel: Investigator.

Treatment Phase Procedures  
1. \*\*Drug Administration\*\*  
 - Timing: Daily during the treatment phase.  
 - Requirements: Administer 240 mg of apalutamide or placebo orally once daily with or without food.  
 - Responsible Personnel: Participant under supervision.

2. \*\*Safety Monitoring\*\*  
 - Timing: Regularly during each treatment cycle.  
 - Requirements: Monitor for adverse events and conduct necessary tests.  
 - Responsible Personnel: Study staff.

3. \*\*Efficacy Assessments\*\*  
 - Timing: Assess at the end of each cycle.  
 - Requirements: Perform imaging studies to evaluate rPFS and collect data for other secondary endpoints.  
 - Responsible Personnel: Radiologist or investigator.

4. \*\*Laboratory Tests\*\*  
 - Timing: At the start of every cycle and as needed.  
 - Requirements: Regular blood tests including pharmacokinetic samples.  
 - Responsible Personnel: Laboratory technician.

5. \*\*Quality of Life Assessments\*\*  
 - Timing: At specified intervals during the treatment phase.  
 - Requirements: Utilize questionnaires like BPI-SF, BFI, and EQ-5D-5L.  
 - Responsible Personnel: Study coordinator.

6. \*\*Adverse Event Monitoring\*\*  
 - Timing: Continuously throughout the treatment phase.  
 - Requirements: Document and grade adverse events per NCI-CTCAE.  
 - Responsible Personnel: Investigator or designee.

7. \*\*Concomitant Medication Review\*\*  
 - Timing: At each study visit.  
 - Requirements: Record all medications taken by subjects during the study.  
 - Responsible Personnel: Study staff.

Follow-up Procedures  
1. \*\*Safety Follow-up\*\*  
 - Timing: 30 days post-treatment discontinuation.  
 - Requirements: Conduct a follow-up visit to assess safety and manage ongoing AEs.  
 - Responsible Personnel: Investigator.

2. \*\*Disease Assessment\*\*  
 - Timing: Every 4 months during follow-up.  
 - Requirements: Capture data on disease progression and treatments.  
 - Responsible Personnel: Study personnel.

3. \*\*Survival Status\*\*  
 - Timing: At each follow-up point.  
 - Requirements: Record survival status and document any deaths.  
 - Responsible Personnel: Study coordinator.

4. \*\*Subsequent Therapy Documentation\*\*  
 - Timing: During the follow-up phase.  
 - Requirements: Document therapies initiated after study treatment.  
 - Responsible Personnel: Investigator or study team.

Safety Assessments  
- \*\*Physical Examinations\*\*  
 - Regular examinations scheduled throughout the study.  
- \*\*Vital Signs\*\*  
 - Monitored at each study visit.  
- \*\*Laboratory Tests\*\*  
 - Include hematology and clinical chemistry panels.  
- \*\*Adverse Event Monitoring\*\*  
 - Continuous assessment for adverse events.

Efficacy Assessments  
- \*\*Radiographic Assessments\*\*  
 - Conduct imaging as per modified RECIST 1.1.  
- \*\*Patient-Reported Outcomes\*\*  
 - Use validated questionnaires for symptoms and QoL assessments.

Laboratory Assessments  
- \*\*Hematology and Chemistry Tests\*\*  
 - Conducted at specified intervals.  
- \*\*Biomarker Sampling\*\*  
 - Collect circulating DNA to assess resistance markers.  
- \*\*PK/PD Assessments\*\*  
 - Trough plasma levels of apalutamide and leuprolide PK sample collection.

Other Assessments  
- \*\*Biomarker Analysis\*\*  
 - Assess predictive markers via molecular analyses.  
- \*\*Medical Resource Utilization\*\*  
 - Collect data related to healthcare encounters for economic modeling.

Ensure all procedures are followed diligently and any special handling instructions or deviations are documented according to protocol.

# Statistical

STATISTICAL ANALYSIS

Statistical Hypotheses  
The primary hypotheses for this study are that the addition of apalutamide to androgen deprivation therapy (ADT) will significantly improve radiographic progression-free survival (rPFS) and overall survival (OS) compared to ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). These hypotheses will be tested using a 5% overall type I error rate, with 0.005 allocated to rPFS and 0.045 to OS to address dual-primary endpoints.

Sample Size Determination  
The study is designed to achieve a high statistical power for detecting differences in efficacy between treatment groups. Approximately 368 rPFS events are required to provide at least 85% power to detect a hazard ratio (HR) of 0.67 (rPFS of 20 months for control vs. 30 months for apalutamide plus ADT) at a significance level of 0.005. For OS, approximately 410 death events will provide an 80% power to detect an HR of 0.75, assuming a median OS of 44 months for the control group, with a significance level of 0.045.

Analysis Populations  
- Intent-to-Treat (ITT) Population: Comprises all randomized subjects and serves as the primary population for efficacy analyses, ensuring that treatment assignment reflects original randomization.  
- Safety Population: Includes all subjects who receive at least one dose of the study drug, used predominantly for safety analyses.

Statistical Methods  
Time-to-event variables such as rPFS and OS will be evaluated using the Kaplan-Meier method, and the Cox proportional hazards model will estimate HRs with associated confidence intervals. Categorical data will be summarized using chi-square or Fisher's exact test as appropriate. Change from baseline for continuous variables will be assessed using repeated measures ANOVA or mixed-models for repeated measures.

Multiplicity Adjustments  
Due to dual-primary endpoints, adjustments for multiplicity will be made using pre-specified alpha allocations: 0.005 for rPFS and 0.045 for OS. The study will declare success if at least one of the primary endpoints reaches statistical significance.

Interim Analyses  
Two interim analyses are pre-planned to assess OS; the first will occur after approximately 50% of death events (around 205 events), and the second after approximately 70% (~287 events). The final analysis of rPFS will also be conducted during the first interim analysis of OS.

Missing Data Handling  
Missing data for time-to-event endpoints will be censored at the last known contact date. Sensitivity analyses will be conducted to evaluate the impact of missing data, employing multiple imputation techniques where necessary to ensure robustness of conclusions.

This structured statistical analysis framework ensures rigorous evaluation of the treatment's impact on mHSPC, with considerations for the handling of multiplicity and missing data, thereby ensuring the validity and reliability of the study's findings.

# Safety

Safety

Safety Parameters  
The safety parameters to be evaluated in this study include:  
- Incidence and intensity of treatment-emergent adverse events (AEs).  
- Clinically significant changes in physical examination findings.  
- Vital signs measurements, including blood pressure, heart rate, and temperature.  
- Clinical laboratory test results encompassing hematology and clinical chemistry.

Adverse Event Definitions  
Adverse events (AEs) will be defined and graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Severity grades are classified as:  
- \*\*Grade 1:\*\* Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.  
- \*\*Grade 2:\*\* Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental 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 adverse event.

Adverse Event Reporting  
All adverse events will be documented from the time of informed consent until 30 days following the last dose of the study drug. Serious adverse events (SAEs) must be reported to the sponsor within 24 hours of the study site becoming aware of the event. Non-serious AEs should be reported according to scheduled study visits unless warranted earlier by intensity or a change in clinical status.

Safety Monitoring  
Safety monitoring will involve regular assessments through scheduled medical examinations, laboratory testing, and review of any concurrent medications. Regular monitoring will occur at each treatment cycle and during follow-up visits. Safety data will be collected and uploaded into electronic case report forms (eCRFs) promptly to enable ongoing analysis.

Risk Management  
Risk management strategies will include predefined dose modifications based on specific toxicity criteria to manage AEs effectively. Detailed guidelines describing dose interruption, reduction, or discontinuation due to toxicity will be provided in the study protocol. Participants at high risk of adverse reactions will be closely monitored, with appropriate interventions implemented as required.

Data Monitoring Committee  
An Independent Data Monitoring Committee (IDMC) will oversee the trial's conduct with particular emphasis on safety. The IDMC will review accumulated safety data at regular intervals and during planned interim analyses to ensure participant safety and make recommendations regarding study continuation or modification, if necessary.

Stopping Rules  
The study will be stopped or modified if new evidence indicates that risks outweigh the benefits of continuing the trial. Specific stopping criteria based on the frequency and severity of adverse events across treatment groups are outlined in the protocol. The IDMC has the authority to recommend halting the study for safety concerns at any point.

These safety procedures are designed to ensure patient safety and data integrity throughout the duration of the trial while allowing for swift action and communication of any concerning findings.