Clinical Trial Protocol

Background

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Disease Background  
Prostate cancer remains one of the most prevalent malignancies among men worldwide, characterized by its dependence on androgen stimulation for growth and progression. Metastatic hormone-sensitive prostate cancer (mHSPC) is a stage of the disease where the cancer has spread beyond the prostate gland and remains sensitive to hormonal manipulation. Despite the initial effectiveness of androgen deprivation therapy (ADT), which aims to decrease testosterone levels, mHSPC can eventually progress to a castration-resistant state, posing significant treatment challenges. The management of mHSPC is critical given its substantial impact on patient quality of life and overall survival outcomes.

Current Treatment Landscape  
The current standard treatment for mHSPC primarily involves androgen deprivation therapy, either through surgical castration (bilateral orchiectomy) or medical castration using gonadotropin-releasing hormone (GnRH) analogs. While ADT is effective in reducing androgen levels and controlling disease progression, approximately all patients with mHSPC will eventually experience progression to a castration-resistant form of prostate cancer. In an effort to improve outcomes, recent therapeutic strategies have included the addition of traditional chemotherapy agents such as docetaxel, particularly in patients with high-volume disease. However, there is an ongoing need for treatments that provide better control of the disease, delay progression, and improve overall survival while maintaining a tolerable safety profile.

Product Background  
Apalutamide, known chemically as JNJ-56021927, is a next-generation non-steroidal anti-androgen developed specifically to inhibit the androgen receptor pathway, which is crucial in the pathogenesis of prostate cancer. It acts as a potent and selective antagonist of the androgen receptor, thereby blocking the effects of androgens at the receptor level. Apalutamide is orally bioavailable, offering a convenient administration route for long-term therapy. Pre-clinical studies and early-phase clinical trials have demonstrated its efficacy in reducing prostate cancer cell proliferation and effectively delaying disease progression in prostate cancer models, including patients with mHSPC.

Study Rationale  
The rationale for conducting this Phase 3 study is grounded in the hypothesis that the addition of apalutamide to standard ADT may enhance therapeutic outcomes for patients with mHSPC. By further inhibiting the androgen receptor signaling pathway that ADT alone cannot fully suppress, apalutamide has the potential to substantially delay radiographic progression and improve overall survival. This study builds on promising preliminary evidence suggesting that apalutamide, as an adjunct to ADT, could offer significant improvements in clinically relevant endpoints such as pain progression, opioid use, and the occurrence of skeletal-related events. Furthermore, apalutamide's safety profile needs to be thoroughly characterized in combination with ADT to ensure it is both effective and well-tolerated by patients with mHSPC.

Objectives

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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 from the date of randomization to the date of first documentation of radiographic progressive disease or death due to any cause.
2. Overall survival (OS) 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 subpopulations of subjects with low-volume or high-volume mHSPC.

Secondary Endpoints

1. Time to pain progression.
2. Time to first use of chronic opioids.
3. Time to the first occurrence of skeletal-related events (SREs).
4. Time to initiation of cytotoxic chemotherapy.
5. Safety profile as assessed by the incidence of treatment-emergent adverse events (AEs), changes in laboratory test results, physical examination findings, and vital signs.
6. Pharmacokinetic and pharmacodynamic parameters of apalutamide and leuprolide.
7. Time to prostate cancer-specific antigen (PSA) progression.
8. Changes in health-related quality of life and patient-reported outcomes.

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 with apalutamide plus ADT compared to ADT alone.
4. To collect medical resource utilization (MRU) data for potential future economic modeling.

Study Design

Study Design

Overall Design

This study is a Phase 3, randomized, double-blind, placebo-controlled clinical trial designed to assess the efficacy and safety of adding apalutamide to androgen deprivation therapy (ADT) in patients with metastatic hormone-sensitive prostate cancer (mHSPC). Approximately 1,000 subjects will be enrolled across multiple international sites. Participants will be stratified based on Gleason score at diagnosis (≤7 versus >7), geographic region (North America and European Union versus other regions), and prior usage of docetaxel (yes versus no). Subjects will then be randomly assigned in a 1:1 ratio to receive apalutamide plus ADT or a placebo plus ADT.

Following a Screening Phase of up to 28 days, eligible subjects will enter the Treatment Phase, during which they will receive study treatment in 28-day cycles. Treatment will continue until disease progression, unacceptable toxicity, or study termination by the sponsor. Subjects experiencing radiographic progression without clinical progression may continue treatment until clinical progression occurs. An End-of-Treatment Visit will be scheduled within 30 days after the final dose of study drug.

During the Follow-up Phase, data collection will occur every 4 months, focusing on survival, secondary endpoints, and progression details. Additionally, patient-reported outcomes will be collected up to 12 months post-treatment. An Open-label Extension Phase will be offered to eligible participants in case of positive study outcomes, allowing for continued access to apalutamide. An Independent Data Monitoring Committee (IDMC) will oversee interim analyses and safety reviews throughout the study.

Study Schema

| Phase | Description | Duration |  
|-----------------------|-------------------------------------------------------|---------------------------|  
| Screening Phase | Establish study eligibility | Up to 28 days |  
| Treatment Phase | Randomized treatment with apalutamide or placebo plus ADT | 28-day cycles until progression or unacceptable toxicity |  
| Follow-up Phase | Data collection on survival and progression | Every 4 months |  
| Open-label Extension | Access to apalutamide post-positive study outcomes | Approximately 3 years |

Study Duration

The anticipated duration of this study is approximately 54 months. This encompasses an estimated 30 months for patient enrollment and an additional 24 months for follow-up to capture the required number of events for primary endpoints.

Treatment Groups

Subjects will be divided into two treatment groups:

1. The experimental group will receive apalutamide 240 mg (four 60 mg tablets) orally once daily, in addition to standard ADT. ADT consists of either medical castration via gonadotropin-releasing hormone analogs or surgical castration.
2. The control group will receive a matching placebo orally once daily, plus standard ADT as defined in the experimental group.

Study Schema

Population

Study Population

Overview of Study Population

This study targets subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC) and who exhibit an Eastern Cooperative Oncology Group (ECOG) performance status of grade 0 or 1. These participants must have documented distant metastatic disease, as confirmed by positive findings on a bone scan (one or more bone lesions on Technetium 99m [99mTc]) and confirmed with a computed tomography (CT) or magnetic resonance imaging (MRI) scan in cases of a single bone lesion. Participants may have received prior treatments, including up to six cycles of docetaxel for mHSPC and up to six months of androgen deprivation therapy (ADT) before randomization.

Inclusion Criteria

1. Male subjects aged 18 years or older.
2. Diagnosis of prostate cancer with histological confirmation.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Evidence of distant metastatic disease documented by a positive bone scan with at least one bone lesion.
5. For those with a single bone lesion, additional confirmation of bone metastasis via CT or MRI is required.
6. Up to six cycles of prior docetaxel treatment for mHSPC are permitted, with the last dose administered no more than two months before randomization.
7. Up to six months of ADT use prior to randomization is allowed.
8. One course of radiation or surgical intervention for mHSPC is permitted.
9. For localized prostate cancer, subjects may have received up to three years of ADT and other therapies such as radiation therapy, prostatectomy, or systemic therapies, provided these were completed at least one year before randomization.

Exclusion Criteria

1. Known hypersensitivity to apalutamide or any of the components used in the study drug formulation.
2. Diagnosis of another active malignancy requiring hormone therapy or chemotherapy.
3. Evidence of castration-resistant prostate cancer at study entry.
4. Uncontrolled concurrent illness, including significant cardiac, hepatic, renal, or psychiatric conditions.
5. History of seizure or condition predisposing to epilepsy.
6. Participation in another clinical study with an investigational product within 30 days prior to randomization.
7. Use of medications with potential drug-drug interactions with apalutamide.
8. Known brain metastases or leptomeningeal disease.

Withdrawal Criteria

Subjects must withdraw from the study under the following circumstances:  
1. Evidence of disease progression as per protocol-specified criteria accompanied by clinical progression.  
2. Occurrence of unacceptable treatment-related toxicity.  
3. Withdrawal of informed consent by the subject.  
4. Decision by the investigator that participation is not in the subject's best interest.

Replacement Policy

Subjects who withdraw or are withdrawn from the study before the completion of the initial screening phase will be replaced to meet the targeted enrollment number. Participants who discontinue treatment during the treatment phase due to progression, toxicity, or other reasons will not be replaced.

Procedures

Study Procedures

Study Procedures Overview  
This section outlines the procedures to be conducted throughout the study, including those during the screening, treatment, and follow-up phases. These procedures will be administered by qualified healthcare professionals and study personnel as specified.

Screening/Baseline Procedures  
Screening procedures are to be conducted up to 28 days prior to randomization to determine eligibility and gather baseline data.  
- Informed Consent: Obtain and document informed consent from each participant.  
- Demographics and Medical History: Record baseline demographics and comprehensive medical history.  
- Physical Examination: Conduct a detailed physical examination, including an evaluation of the Eastern Cooperative Oncology Group (ECOG) performance status.  
- Vital Signs: Measure and record blood pressure, heart rate, temperature, and respiratory rate.  
- Laboratory Assessments: Perform baseline laboratory tests including hematology, clinical chemistry, and prostate-specific antigen (PSA) levels.  
- Disease Assessment: Confirm metastatic disease status using imaging techniques like bone scans, computed tomography (CT), or magnetic resonance imaging (MRI).  
- Eligibility Assessment: Review inclusion/exclusion criteria to confirm study eligibility.

Treatment Phase Procedures  
These procedures are repeated in 28-day cycles during the treatment phase until disease progression, unacceptable toxicity, or study termination.  
- Drug Administration: Administer apalutamide or placebo orally once daily. ADT will be administered per standard of care, documented in the eCRF.  
- Safety Monitoring: Continuously monitor for adverse events (AEs), and document any AE occurrence following the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE).  
- Efficacy Assessments: Conduct efficacy evaluations using imaging studies (CT/MRI), monitor PSA levels, and document clinically relevant outcomes such as time to pain progression.  
- Laboratory Tests: Conduct routine blood tests to monitor the treatment impact on hematology and clinical chemistry.  
- Quality of Life Assessment: Collect data using the Functional Assessment of Cancer Therapy-Prostate (FACT-P), EQ-5D-5L, Brief Pain Inventory-Short Form (BPI-SF), and Brief Fatigue Inventory (BFI).  
- Concomitant Medication Review: Document all concurrent medications at each visit.

Follow-up Procedures  
These procedures are conducted every 4 months after treatment discontinuation until the study concludes or the subject's withdrawal.  
- Safety Follow-up: Monitor for delayed AEs up to 30 days post-final dose.  
- Survival Status: Record survival status and document any subsequent treatments for prostate cancer.  
- Disease Assessment: Continue monitoring disease progression, including radiographic, PSA, and clinical progressions.  
- Patient-Reported Outcomes: Continue collecting quality of life data for up to 12 months post-treatment.

Safety Assessments  
- Adverse Event Monitoring: Track and manage AEs throughout the study duration, with severity and causal relationship evaluated by study personnel.  
- Physical Examinations: Conduct regularly scheduled physical exams.  
- Vital Signs and ECOG PS: Regularly monitor vital signs and update ECOG performance status.  
- Clinical Laboratory Tests: Routine lab tests for safety monitoring.

Efficacy Assessments  
- Radiographic Assessments: Conduct CT/MRI scans to track disease progression.  
- PSA Monitoring: Regularly check PSA levels to assess disease status.  
- Patient-Reported Outcomes: Evaluate symptoms and quality of life using standardized questionnaires.

Laboratory Assessments  
- Hematology and Clinical Chemistry: Perform routine bloodwork.  
- Biomarker Sampling: Collect and analyze plasma and DNA samples to investigate biomarkers associated with treatment response and resistance.  
- PK/PD Assessments: Assess pharmacokinetics and pharmacodynamics for apalutamide and its active metabolites.

Other Assessments  
- Medical Resource Utilization: Collect data on healthcare utilization for cost-effectiveness analysis.  
- Leuprolide PK Sub-study: An optional pharmacokinetic sub-study for subjects receiving leuprolide, executed at designated time points.  
- Biomarker Analysis: Evaluate potential biomarkers using plasma DNA and archival tumor samples for treatment response prediction.

All procedures and assessments shall be performed per protocol specifications by trained study personnel, ensuring all data is accurately recorded in the electronic case report form (eCRF).

Statistical

Statistical Analysis

Statistical Hypotheses  
The primary objective is to assess whether the combination of apalutamide plus ADT improves radiographic progression-free survival (rPFS) or overall survival (OS) compared to ADT alone. The null hypothesis for each endpoint is that there is no difference between the treatment groups in rPFS and OS. The alternative hypothesis is that the combination of apalutamide and ADT will result in a statistically significant improvement in either rPFS, OS, or both.

Sample Size Determination  
The study is designed with an overall type I error rate of 5%, split into 0.005 significance level for the rPFS endpoint and 0.045 for the OS endpoint. A total of approximately 1,000 subjects are expected to be enrolled to achieve at least 85% power to detect a hazard ratio (HR) of 0.67 for rPFS and approximately 80% power to detect a HR of 0.75 for OS. The power calculations are based on the projected median rPFS of 20 months for the control group and 30 months for the treatment group, and a median OS of 44 months for the control group. The trial will continue until approximately 368 rPFS events and 410 OS events have been observed.

Analysis Populations  
The primary analysis will utilize the intent-to-treat (ITT) population, which includes all randomized participants. Efficacy analyses, including those for rPFS and OS, will be based on the ITT population. The safety population will consist of all participants who receive at least one dose of the study drug, analyzed according to the treatment received.

Statistical Methods  
Time-to-event endpoints, including rPFS and OS, will be analyzed using the Kaplan-Meier method and compared between treatment groups using the Cox proportional hazards model to estimate hazard ratios and corresponding 95% confidence intervals. The log-rank test will be employed for hypothesis testing at each endpoint's significance level. Secondary endpoints will be evaluated using similar time-to-event analysis techniques, as applicable. Descriptive statistics will summarize continuous variables, and frequency distributions will present categorical variables.

Interim Analyses  
Two interim analyses are planned for the OS endpoint, occurring after approximately 50% (205) and 70% (287) of the 410 total required events have occurred. The first interim analysis will also serve as the final analysis for rPFS. Decisions regarding continuation, modification, or termination of the study will be guided by the Independent Data Monitoring Committee (IDMC) based on efficacy and safety findings from these analyses.

Missing Data Handling  
For time-to-event analyses, participants without observed events will be censored at their last follow-up date. Missing covariate data will be addressed using appropriate imputation methods if necessary. Sensitivity analyses will be conducted to assess the impact of the missing data on study conclusions.

Multiplicity Adjustments  
The study addresses multiplicity by allocating distinct significance levels to each primary endpoint: 0.005 for rPFS and 0.045 for OS. This approach controls the overall type I error rate across the dual-primary endpoints, ensuring a robust conclusion if one or both outcomes reach statistical significance.

The above statistical methodology is designed to rigorously evaluate the efficacy and safety of apalutamide combined with ADT, ensuring reliable results that address the study's primary objectives while maintaining transparency and integrity in data interpretation.

Safety

Safety

Safety Parameters

Safety will be comprehensively assessed through the monitoring of treatment-emergent adverse events (AEs), vital signs, physical examinations, ECOG performance status, and clinical laboratory test results. Safety data will be collected from the point of informed consent until 30 days post-final administration of the study drug.

Adverse Event Definitions

Adverse events are defined per the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. They include any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, regardless of a causal relationship.

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 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 required.  
- Grade 5: Death related to AE.

Adverse Event Reporting

All AEs will be documented in the electronic case report form (eCRF) and reported in line with regulatory requirements. Investigators will assess and document the severity, relationship to the study drug, and expectedness of each AE.

Reporting Requirements  
- Serious adverse events (SAEs) must be reported to the sponsor within 24 hours of awareness.  
- Non-serious AEs should be documented and reported per routine data collection at study visits.

Safety Monitoring

Safety assessments will be conducted at each study visit. They include a physical examination, monitoring of vital signs, laboratory tests, and ECOG performance status evaluation. Immediate medical attention and appropriate documentation will be provided for any treatment-related adverse events.

Risk Management

To minimize risks associated with apalutamide, the study will implement dose modifications per protocol specifications for managing treatment-related toxicities. Continuous education and training will be provided to study personnel on risk management procedures.

Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will oversee the study, conducting interim analyses to review safety data and efficacy results. Recommendations for study continuation, modification, or termination will be based on these independent evaluations.

Stopping Rules

The IDMC will recommend halting the study if there is clear evidence of harm outweighing the potential benefits or if a statistically significant improvement in the dual-primary endpoints is observed in interim analyses, warranting early study termination for ethical considerations.

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In summary, the safety monitoring of this trial involves a systematic approach to identifying, reporting, and managing AEs, supported by the oversight of an independent committee, ensuring participant safety remains the utmost priority throughout the study.