Study Protocol

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# Background

Study Background

*Disease/Condition Overview*

Metastatic hormone-sensitive prostate cancer (mHSPC) is a stage of prostate cancer characterized by the spread of cancer cells beyond the prostate gland to distant sites, such as bones, lymph nodes, or other organs, while still responding to hormonal therapy. Prostate cancer is one of the most common malignancies affecting men worldwide, and its progression to a metastatic state significantly impacts patient prognosis and quality of life. The disease is often initially managed with androgen deprivation therapy (ADT), which reduces levels of male hormones that fuel cancer growth. However, despite initial responsiveness, many patients eventually develop resistance to ADT, leading to castration-resistant prostate cancer (CRPC), which is associated with a poorer prognosis and limited treatment options.

*Current Treatment Landscape*

The standard of care for mHSPC involves the use of ADT, which can be achieved through medical castration using gonadotropin-releasing hormone (GnRH) analogs or surgical castration via bilateral orchiectomy. Recent advancements in the treatment landscape have introduced the use of combination therapies, such as the addition of docetaxel or novel hormonal agents like abiraterone acetate, to ADT, which have demonstrated improved survival outcomes in patients with mHSPC. Despite these advancements, there remains a need for therapies that can further delay disease progression and improve overall survival while maintaining an acceptable safety profile.

*Rationale for Study*

The rationale for this Phase 3 study is based on the potential therapeutic benefit of apalutamide, a non-steroidal anti-androgen, in combination with ADT for the treatment of mHSPC. Apalutamide acts as a potent and selective antagonist of the androgen receptor (AR), thereby inhibiting the signaling pathways that drive prostate cancer cell growth. Preclinical studies and early-phase clinical trials have shown promising results in terms of efficacy and safety, suggesting that apalutamide could enhance the therapeutic effects of ADT in mHSPC.

This study aims to evaluate whether the addition of apalutamide to ADT provides superior efficacy in improving radiographic progression-free survival (rPFS) and overall survival (OS) compared to ADT alone. The study also seeks to assess secondary endpoints, including the delay in pain progression, opioid use, and skeletal-related events, as well as the safety profile of the combination therapy. By exploring these outcomes, the study intends to provide robust evidence on the clinical benefits of apalutamide in this patient population, potentially establishing a new standard of care for mHSPC.

[PLACEHOLDER:*Additional context on emerging therapies and ongoing research in mHSPC could be beneficial to further substantiate the study rationale.*]

[RECOMMENDED:*Incorporate recent data from relevant clinical trials or meta-analyses to strengthen the discussion on the current treatment landscape and the potential impact of apalutamide.*]

# Objectives

Study Objectives

*Primary Objective*

The primary objective of this Phase 3 study is to determine whether the addition of apalutamide to androgen deprivation therapy (ADT) provides superior efficacy in improving radiographic progression-free survival (rPFS) or overall survival (OS) in subjects with metastatic hormone-sensitive prostate cancer (mHSPC).

*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 profile of adding apalutamide to ADT in 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.

*Exploratory Objectives*

1. To evaluate exploratory biomarkers predictive of response and resistance to treatment.

2. To assess 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 (MRU) data that may be used in future economic modeling. [RECOMMENDED: Specify the types of MRU data to be collected for clarity.]

[PLACEHOLDER:*Consider including additional exploratory objectives if relevant to the study's broader scientific goals.*]

# Study Design

Study Design

Study Type and Methodology

This study is a Phase 3, randomized, double-blind, placebo-controlled, multinational, and multicenter clinical trial. It aims 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). The study is designed to enroll approximately 1,000 subjects who will be randomly assigned in a 1:1 ratio to receive either apalutamide plus ADT or a matching placebo plus ADT. The randomization will be stratified by Gleason score at diagnosis (≤7 versus >7), geographic region (North America and European Union versus other countries), and prior docetaxel use (yes versus no).

The study will consist of several phases: a Screening Phase of up to 28 days to establish eligibility, a Treatment Phase with 28-day cycles until disease progression or unacceptable toxicity, and a Follow-up Phase for data collection every four months. An Open-label Extension Phase will be available for subjects in the Treatment Phase if positive results are observed at interim or final analyses. A Long-Term Extension (LTE) Phase will follow for subjects continuing to benefit from apalutamide treatment.

Population Characteristics

The study population includes male subjects with a confirmed diagnosis of prostate cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of grade 0 or 1. Eligible subjects must have documented distant metastatic disease, as evidenced by a positive bone scan with one or more bone lesions. Confirmation of a single bone lesion must be obtained via computed tomography (CT) or magnetic resonance imaging (MRI). Subjects may have received up to six cycles of docetaxel for mHSPC, with the last dose administered no more than two months prior to randomization. Additionally, subjects may have received up to six months of ADT prior to randomization and a maximum of one course of radiation or surgical intervention for mHSPC. For localized prostate cancer, subjects may have received up to three years of ADT and other prior therapies, provided these were completed at least one year before randomization.

Key Procedures and Assessments

Subjects will receive ADT as the standard of care, defined as either medical castration using a gonadotropin-releasing hormone analog (GnRHa) or surgical castration (bilateral orchiectomy). The choice of GnRHa and dosing will be at the investigator's discretion, consistent with prescribing information. Apalutamide or matching placebo will be administered orally at a dose of 240 mg (four 60-mg tablets) once daily, with or without food.

Efficacy Evaluations/Endpoints

The dual-primary endpoints are radiographic progression-free survival (rPFS) and overall survival (OS). Secondary endpoints include time to pain progression, time to skeletal-related events (SREs), time to chronic opioid use, and time to initiation of cytotoxic chemotherapy. Other endpoints involve time to symptomatic local progression, time to prostate cancer-specific antigen (PSA) progression, and various quality of life measures.

Safety Evaluations

Safety assessments will include monitoring adverse events (AEs), vital signs, physical examinations, ECOG performance status, and clinical laboratory tests. AEs will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE; Version 4.03). An Independent Data Monitoring Committee (IDMC) will oversee interim efficacy analyses and regular safety reviews.

Statistical Methods

The primary analysis will use the intent-to-treat (ITT) population for efficacy evaluations. The study is powered to detect a hazard ratio (HR) of 0.67 for rPFS and 0.75 for OS, with a type I error rate of 5%. Kaplan-Meier and Cox proportional hazards models will be employed for time-to-event analyses. Interim analyses for OS are planned after approximately 50% and 70% of the required events are observed.

[PLACEHOLDER:*Additional statistical methods, if applicable*]

[RECOMMENDED:*Consider including a detailed Statistical Analysis Plan to guide exploratory biomarker studies and medical resource utilization analyses.*]

# Population

*Target Population*

The target population for this study comprises subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). Eligible participants should exhibit an Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 or 1, indicating that they are fully active or restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. The study specifically targets individuals with documented distant metastatic disease, confirmed by a positive bone scan showing one or more bone lesions using Technetium 99m (99mTc). In cases where a single bone lesion is present, confirmation of the bone metastasis by computed tomography (CT) or magnetic resonance imaging (MRI) is required.

*Inclusion/Exclusion Criteria*

Inclusion criteria for this study mandate that subjects may have received up to six cycles of docetaxel for mHSPC, with the last dose administered no more than two months prior to randomization. Additionally, subjects may have undergone androgen deprivation therapy (ADT) for a duration of up to six months prior to randomization. A maximum of one course of radiation or surgical intervention for mHSPC is permissible. For those with localized prostate cancer, subjects may have received up to three years of ADT and other prior therapies, including radiation therapy, prostatectomy, lymph node dissection, and systemic therapies, provided these were completed at least one year before randomization.

Exclusion criteria include any conditions or treatments that might confound the study results or pose undue risk to the participants. Specific exclusion criteria are not detailed in the synopsis and should be referenced from the full protocol document. [PLACEHOLDER:*Detailed exclusion criteria*]

*Sample Size Justification*

The study plans to enroll approximately 1,000 subjects to ensure robust statistical power for detecting significant differences in the dual-primary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS). The sample size determination is based on an overall type I error rate of 5%, with 0.005 significance allocated for the rPFS endpoint and 0.045 for OS. The study is designed to achieve at least 85% power to detect a hazard ratio (HR) of 0.67 for rPFS, assuming a median rPFS of 20 months for the control group (ADT) versus 30 months for the treatment group (apalutamide plus ADT). Additionally, the study aims to provide approximately 80% power to detect an HR of 0.75 for OS, with an assumed median OS of 44 months for the control group. Approximately 368 rPFS events and 410 death events are required to achieve these power calculations. The estimated enrollment duration is approximately 30 months, with a total study duration of approximately 54 months to capture the necessary events.

# Procedures

Study Procedures

Study Assessments

The study assessments are designed to comprehensively evaluate the efficacy, safety, and pharmacokinetics of apalutamide in combination with androgen deprivation therapy (ADT) in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). Key assessments include:

1.Efficacy Assessments:

- Radiographic progression-free survival (rPFS) will be assessed by the investigator using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for soft tissue lesions and bone scans for bone lesions.

- Overall survival (OS) will be monitored from the date of randomization to the date of death from any cause.

- Secondary endpoints such as time to pain progression, time to skeletal-related events (SREs), time to chronic opioid use, and time to initiation of cytotoxic chemotherapy will be evaluated.

2.Safety Assessments:

- Adverse events (AEs) will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE; Version 4.03).

- Vital signs, including blood pressure, will be measured regularly.

- Physical examinations and Eastern Cooperative Oncology Group (ECOG) performance status evaluations will be conducted.

- Clinical laboratory tests will be performed to monitor safety parameters.

3.Pharmacokinetic and Pharmacodynamic Assessments:

- Trough plasma samples for apalutamide and its active metabolite (JNJ-56142060) will be collected on Day 1 of Cycles 2, 3, 4, 5, and 6.

- Optional pharmacokinetic samples for leuprolide and testosterone concentrations will be collected from consenting subjects.

4.Biomarker Assessments:

- Plasma-based circulating DNA will be analyzed for the presence of the ARF876L mutation and other resistance markers.

- Archival formalin-fixed paraffin-embedded (FFPE) tumor blocks or slides will be collected for mRNA expression analysis of genes related to androgen receptor signaling and immune markers.

Treatment Procedures

1.Randomization and Stratification:

- Subjects will be randomly assigned in a 1:1 ratio to receive either apalutamide plus ADT or a matching placebo plus ADT.

- Stratification factors include Gleason score at diagnosis (≤7 versus >7), region (North America and European Union versus other countries), and prior docetaxel use (yes versus no).

2.Administration of Study Drug:

- Apalutamide 240 mg (4 x 60 mg tablets) or matching placebo will be administered orally once daily, with or without food.

- All subjects will receive ADT as standard of care, defined as medical or surgical castration. The choice of gonadotropin-releasing hormone analog (GnRHa) will be at the investigator's discretion.

3.Treatment Cycles:

- Subjects will receive treatment in 28-day cycles during the Treatment Phase until disease progression, unacceptable toxicity, or study termination by the sponsor.

Follow-up Procedures

1.End-of-Treatment Visit:

- An End-of-Treatment Visit will occur within 30 days after the last dose of the study drug to assess safety and collect relevant data.

2.Follow-up Phase:

- Data collection will occur every 4 months, including survival data, secondary endpoints, disease progression, and subsequent therapy for prostate cancer.

- Patient-reported outcome measures, such as the Brief Pain Inventory-Short Form (BPI-SF), Brief Fatigue Inventory (BFI), and EQ-5D-5L, will continue up to 12 months after treatment discontinuation.

3.Open-label and Long-Term Extension Phases:

- In the event of a positive study result, subjects in the Treatment Phase may enroll in an Open-label Extension Phase to receive apalutamide for approximately 3 years.

- Subjects benefiting from apalutamide may continue treatment in a Long-Term Extension Phase based on investigator assessment.

4.Safety Monitoring:

- Safety monitoring will continue from the signing of informed consent until 30 days after the last dose of the study drug, with regular safety reviews conducted by an Independent Data Monitoring Committee (IDMC).

[PLACEHOLDER:*Additional specific procedures or assessments not detailed in the synopsis*]

[RECOMMENDED:*Consider including detailed timelines for each phase and specific criteria for clinical progression to enhance clarity*]

# Statistical Analysis

*Statistical Methods*

*Analysis Populations*

The primary analysis population for this study is the intent-to-treat (ITT) population, which encompasses all randomized subjects. The ITT population will be utilized for analyzing subject disposition and efficacy outcomes. In addition, the safety population will include all subjects who have received at least one dose of the study drug, and analyses will be conducted based on the treatment received.

*Primary Analyses*

The study employs dual-primary endpoints: radiographic progression-free survival (rPFS) and overall survival (OS). The Kaplan-Meier product limit method will be used to estimate time-to-event variables, while the Cox proportional hazards model will be applied to obtain hazard ratios (HR) along with their associated confidence intervals. An overall type I error rate of 5% is allocated, with 0.005 significance level for the rPFS endpoint and 0.045 for the OS endpoint. The study is deemed successful if at least one of the dual-primary endpoints achieves statistical significance.

For the rPFS endpoint, approximately 368 events are required to achieve at least 85% power in detecting an HR of 0.67, assuming a median rPFS of 20 months for the control group (ADT) versus 30 months for the treatment group (apalutamide plus ADT). For the OS endpoint, approximately 410 death events are necessary to detect an HR of 0.75, assuming a median OS of 44 months for the control group, with approximately 80% power.

*Secondary Analyses*

Secondary endpoints include time to pain progression, time to skeletal-related events (SREs), time to chronic opioid use, and time to initiation of cytotoxic chemotherapy. Additional analyses will explore time to symptomatic local progression, time to prostate cancer-specific antigen (PSA) progression, and time to Eastern Cooperative Oncology Group (ECOG) performance status deterioration. Prostate cancer-specific survival and progression-free survival on subsequent therapy (PFS2) will also be evaluated.

The analysis of secondary endpoints will employ similar statistical methodologies as the primary analyses, including Kaplan-Meier estimates and Cox proportional hazards models, to assess time-to-event outcomes. Exploratory analyses may involve response markers for apalutamide, androgen receptor (AR) gene anomalies, and other markers associated with resistance to treatment. The detailed statistical methods for these exploratory analyses will be outlined in a separate Statistical Analysis Plan.

*Interim Analysis*

Two interim analyses are planned for the OS endpoint after approximately 50% (~205 events) and 70% (~287 events) of the total required events (410) have occurred. The final analysis of the rPFS endpoint will coincide with the first interim analysis of OS. No interim analysis is planned for the rPFS endpoint.

*Recommendations*

[RECOMMENDED: Ensure that the Statistical Analysis Plan includes detailed methodologies for handling missing data and sensitivity analyses to assess the robustness of the findings. Additionally, consider including subgroup analyses to explore treatment effects across different demographic and clinical characteristics.]

# Safety

Safety Considerations

Safety Monitoring

Safety monitoring in this study will be conducted rigorously from the signing of informed consent until 30 days after the last dose of the study drug. Subjects will be monitored for adverse events (AEs), vital signs measurements (including blood pressure), physical examinations, and Eastern Cooperative Oncology Group (ECOG) performance status (PS). Clinical laboratory tests will also be performed to ensure comprehensive safety assessments. An Independent Data Monitoring Committee (IDMC) will be commissioned to provide recommendations during planned interim efficacy analyses and regular safety reviews. The IDMC will play a critical role in overseeing the safety of the subjects and ensuring the integrity of the study data.

Adverse Event Reporting

Adverse events, including laboratory AEs, will be graded and summarized using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE; Version 4.03). The reporting of AEs will be systematic and detailed, capturing the incidence, severity, and potential relationship to the study drug. Dose modifications will be made according to the dose modification rules outlined in the protocol to manage any treatment-related toxicities effectively. The safety population, which includes all subjects who received at least one dose of the study drug, will be utilized for the analysis of AEs.

Risk Management

Risk management strategies will be implemented to minimize potential risks associated with the study drug, apalutamide, and its combination with androgen deprivation therapy (ADT). These strategies will include predefined criteria for dose modifications and discontinuation of the study drug in cases of unacceptable treatment-related toxicity. The protocol will specify criteria for clinical progression, which will necessitate the discontinuation of the study drug. Additionally, the study design includes a robust monitoring plan and the involvement of the IDMC to ensure that any emerging safety concerns are promptly addressed.

[PLACEHOLDER:*Specific risk mitigation strategies for identified risks associated with apalutamide*] should be detailed in the protocol, including monitoring for known side effects such as [PLACEHOLDER:*common side effects of apalutamide*].

[RECOMMENDED:*Consideration of additional safety measures, such as regular ECG monitoring if cardiac risks are identified, or specific laboratory tests if hepatotoxicity or nephrotoxicity is a concern.*]

Overall, the safety considerations in this study are designed to ensure the well-being of the subjects while maintaining the scientific integrity of the study.

# Endpoints

Study Endpoints

*Primary Endpoints:*

The primary endpoints of this Phase 3 study are radiographic progression-free survival (rPFS) and overall survival (OS). Radiographic progression-free survival is defined as the time from the date of randomization to the first documentation of radiographic progressive disease or death due to any cause, whichever occurs first. Radiographic progression will be assessed via soft tissue lesions using computed tomography (CT) or magnetic resonance imaging (MRI) per modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) or by bone lesion progression on bone scans. Overall survival is defined as the time from randomization to the date of death from any cause.

*Secondary Endpoints:*

The secondary endpoints include:

- Time to pain progression

- Time to skeletal-related events (SREs)

- Time to chronic opioid use

- Time to initiation of cytotoxic chemotherapy

- Time to symptomatic local progression

- Time to prostate cancer-specific antigen (PSA) progression based on Prostate Cancer Working Group 2 (PCWG2) criteria

- Time to Eastern Cooperative Oncology Group (ECOG) performance status deterioration

- Prostate cancer-specific survival

- Progression-free survival 2 (PFS2), defined as the time from the date of randomization to the date of disease progression on first subsequent therapy for prostate cancer or death, whichever occurs first

- Change from baseline over time in each of the subscales of Functional Assessment of Cancer Therapy-Prostate (FACT-P), EuroQol EQ-5D-5L Visual Analog Scale (VAS), Brief Pain Inventory-Short Form (BPI-SF) interference subscale, and Brief Fatigue Inventory (BFI)

*Safety Endpoints:*

Safety endpoints will be evaluated through the incidence and intensity of treatment-emergent adverse events (AEs), clinically significant changes in physical examination findings, vital signs measurements, and clinical laboratory results. The exposure to the study drug and the reasons for discontinuation of study treatment will also be tabulated. Adverse events will be graded and summarized using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE; Version 4.03).

[RECOMMENDED: Consider including additional exploratory endpoints to assess long-term safety and quality of life outcomes, if applicable.]