Clinical Trial Protocol

Background

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Disease Background  
Metastatic hormone-sensitive prostate cancer (mHSPC) is a significant clinical condition characterized by the spread of prostate cancer cells to distant sites while retaining sensitivity to hormonal therapies. Prostate cancer is one of the most prevalent malignancies among men worldwide, and its metastatic form marks an advanced stage where cancer cells have disseminated beyond the prostate gland. This stage of the disease poses a substantial threat to patient health and life expectancy, necessitating effective therapeutic strategies to manage disease progression and improve overall survival rates. Despite advances in treatment, mHSPC remains a challenging condition that requires continued research to develop therapies that address the complexities of this disease.

Current Treatment Landscape  
The primary treatment approach for metastatic hormone-sensitive prostate cancer revolves around androgen deprivation therapy (ADT), which aims to reduce the effects of androgens, the hormones driving prostate cancer growth. ADT can be achieved through surgical castration (bilateral orchiectomy) or medical castration using gonadotropin-releasing hormone (GnRH) analogs. While ADT is initially effective in managing mHSPC, resistance often develops, leading to castration-resistant prostate cancer and necessitating further therapeutic intervention. In recent years, combination therapies involving ADT and chemotherapy, particularly docetaxel, have been employed for certain high-risk groups within the mHSPC population to enhance survival outcomes. However, given the heterogeneous nature of prostate cancer and the complexity of its treatment, there is a critical need for novel therapeutic agents that can extend control over the disease and delay progression.

Product Background  
Apalutamide (JNJ-56021927) is a promising therapeutic agent under development for the treatment of prostate cancer, particularly in the context of mHSPC. It is an orally administered, small molecule, non-steroidal antagonist of the androgen receptor. As a potent and selective anti-androgen, apalutamide functions by binding to the androgen receptor, inhibiting its activation, and thereby preventing androgen-driven proliferation of prostate cancer cells. Existing preclinical and clinical evaluations have shown apalutamide to exhibit significant efficacy profiles, which have led to its investigation in advanced stages of prostate cancer. Its pharmacological profile makes it a potential addition to standard ADT regimens, with the aim of enhancing treatment outcomes in patients with mHSPC.

Study Rationale  
The rationale for conducting a Phase 3 study of apalutamide in combination with ADT compared to ADT alone in subjects with mHSPC stems from the hypothesis that this combination could provide superior efficacy in improving radiographic progression-free survival (rPFS) and overall survival (OS). While ADT remains a cornerstone of treatment for mHSPC, the addition of apalutamide could potentially delay disease progression, reduce the onset of pain and skeletal-related events, decrease the need for opioid analgesics, and delay the initiation of cytotoxic chemotherapy. Additionally, this combination therapy could offer a favorable safety profile, enhance patient quality of life, and address the unmet medical needs in this patient population. The study aims to provide robust clinical evidence to support the incorporation of apalutamide into therapeutic regimens for mHSPC, thus contributing to the evolving landscape of prostate cancer treatment.

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

Secondary Endpoint(s)  
1. Time to pain progression, time to SREs, time to chronic opioid use, and time to initiation of cytotoxic chemotherapy.  
2. Adverse events (AEs) and safety profile assessment.  
3. PK and PD profiles of apalutamide and its active metabolite, JNJ-56142060.  
4. Concentrations of leuprolide and testosterone levels in subjects.  
5. Efficacy measures in low-volume versus high-volume mHSPC subpopulations.

Other Objective(s)  
1. To evaluate exploratory biomarkers predictive of response and resistance to treatment.  
2. To evaluate patient-relevant outcomes, including symptoms (pain, fatigue, urination) and function (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.

Other Endpoint(s)  
1. Biomarker assessment results correlated with clinical response.  
2. Changes in patient-reported outcomes related to symptoms, function, and quality of life.  
3. Clinically relevant endpoints beyond primary and secondary endpoints.  
4. Data collection on medical resource utilization during the study.

Study Design

Study Design

Overall Design  
This study is a Phase 3 randomized, double-blind, placebo-controlled trial aimed at evaluating the efficacy and safety of apalutamide in combination with androgen deprivation therapy (ADT) in subjects with metastatic hormone-sensitive prostate cancer (mHSPC) compared to ADT alone. Approximately 1,000 subjects will be enrolled and randomized in a 1:1 ratio to receive either apalutamide plus ADT or a matching placebo plus ADT. Stratification will occur based on Gleason score at diagnosis, geographic region, and prior docetaxel use. The study will consist of a Screening Phase, Treatment Phase, Follow-up Phase, Open-label Extension Phase, and Long-Term Extension Phase, ensuring comprehensive data collection on efficacy, safety, and exploratory biomarkers.

Study Schema  
| Phase | Duration | Activities |  
|---------------------------|------------------------|-----------------------------------------------------------------------|  
| Screening Phase | Up to 28 days | Establish eligibility, stratification |  
| Treatment Phase | 28-day cycles | Randomized treatment with apalutamide or placebo until disease progression or unacceptable toxicity |  
| Follow-up Phase | Every 4 months | Data collection on survival, disease progression, and subsequent therapies |  
| Open-label Extension Phase| Up to approximately 3 years | Active drug administration following positive interim or final analysis |  
| Long-Term Extension Phase | Begins at the study's final analysis cut-off | Continued administration of apalutamide for subjects benefiting from treatment |

Study Duration  
The anticipated total study duration is approximately 54 months. Recruitment and randomization will occur over approximately 30 months, followed by treatment and follow-up phases to collect required data, including endpoints related to radiographic progression-free survival (rPFS) and overall survival (OS).

Treatment Groups  
1. Apalutamide Plus ADT Group: Subjects will receive apalutamide 240 mg orally (4 x 60 mg tablets) daily in combination with standard ADT.  
2. Placebo Plus ADT Group: Subjects will receive matching placebo orally (4 tablets) daily along with standard ADT.

Both groups will continue treatment in 28-day cycles until disease progression, unacceptable toxicity, or conclusion by the sponsor. Subjects may enter an Open-label Extension Phase pending evidence of benefit, with further continuation in the Long-Term Extension Phase based on investigator’s assessment of ongoing therapeutic benefit.

Study Schema

Population

Study Population

Overview of Study Population  
The study will include subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC), exhibiting an Eastern Cooperative Oncology Group (ECOG) performance status of either grade 0 or 1, and documented evidence of distant metastatic disease.

Inclusion Criteria  
1. Male subjects with a confirmed diagnosis of prostate cancer.  
2. ECOG performance status grade of 0 or 1.  
3. Evidence of distant metastatic disease confirmed by a positive bone scan showing one or more bone lesions (Technetium 99m).  
4. Confirmation of bone metastasis by computed tomography (CT) or magnetic resonance imaging (MRI) for subjects with a single bone lesion.  
5. Receipt of up to 6 cycles of docetaxel for mHSPC, with the last dose administered within ≤2 months prior to randomization.  
6. Receipt of ≤6 months of androgen deprivation therapy (ADT) prior to randomization.  
7. Receipt of a maximum of one course of radiation or surgical intervention for mHSPC.  
8. For localized prostate cancer, receipt of ≤3 years of total ADT and completion of any prior therapies (including radiation therapy, prostatectomy, lymph node dissection, and systemic therapies) ≥1 year prior to randomization.

Exclusion Criteria  
1. Evidence of castration-resistant prostate cancer.  
2. Previous treatment with apalutamide or any other anti-androgen.  
3. Known hypersensitivity to apalutamide or any of its excipients.  
4. Enrollment in another clinical study involving an investigational agent.  
5. Any condition that, in the opinion of the investigator, may affect subject compliance.

Withdrawal Criteria  
1. Subjects can be withdrawn at any time if they choose to do so or if deemed necessary by the investigator due to adverse events, lack of efficacy, or protocol deviation.  
2. Subjects should be withdrawn from the study drug upon confirmed clinical progression of prostate cancer as per protocol-specified criteria.

Replacement Policy  
Subjects who withdraw from the study prior to randomization may be replaced to meet target enrollment. However, subjects who withdraw after randomization will not be replaced.

Procedures

Study Procedures

Study Procedures Overview  
This section outlines the procedures to be conducted during the study, categorized into screening, treatment, and follow-up phases.

Screening/Baseline Procedures  
1. Informed Consent: Obtain signed informed consent from subjects prior to any study-related activities. Responsible Personnel: Study Coordinator.  
2. Demographics and Medical History: Collect demographic data and detailed medical history. Responsible Personnel: Study Nurse.  
3. Physical Examination: Conduct comprehensive physical examination. Responsible Personnel: Investigator.  
4. Vital Signs: Record baseline vital signs, including blood pressure and heart rate. Responsible Personnel: Study Nurse.  
5. Laboratory Assessments: Conduct initial laboratory evaluations, including hematology and clinical chemistry. Responsible Personnel: Laboratory Technician.  
6. Disease Assessment: Confirm diagnosis of metastatic prostate cancer and assess disease extent through imaging studies. Responsible Personnel: Investigator.  
7. Inclusion/Exclusion Criteria Review: Verify eligibility based on protocol criteria. Responsible Personnel: Investigator.

Treatment Phase Procedures  
1. Drug Administration: Administer apalutamide or placebo and ADT in 28-day cycles. Document administration in the electronic case report form (eCRF). Responsible Personnel: Study Nurse.  
2. Safety Monitoring: Perform scheduled safety evaluations, including monitoring of vital signs and adverse events. Responsible Personnel: Investigator.  
3. Efficacy Assessments: Conduct efficacy evaluations per schedule, including imaging studies for radiographic progression. Responsible Personnel: Radiologist/Investigator.  
4. Laboratory Tests: Perform routine laboratory tests, including PK/PD sampling, as per schedule. Responsible Personnel: Laboratory Technician.  
5. Quality of Life Assessments: Collect patient-reported outcomes via validated tools like BPI-SF, BFI, and EQ-5D-5L. Responsible Personnel: Study Coordinator.  
6. Adverse Event Monitoring: Monitor and document adverse events continuously. Responsible Personnel: Investigator.  
7. Concomitant Medication Review: Review and document any concomitant medications at each visit. Responsible Personnel: Study Nurse.

Follow-up Procedures  
1. Safety Follow-up: Conduct safety assessments 30 days post last dose. Responsible Personnel: Investigator.  
2. Disease Assessment: Document radiographic and clinical progression, if any, during follow-ups. Responsible Personnel: Investigator.  
3. Survival Status: Collect data on survival status every 4 months. Responsible Personnel: Study Coordinator.  
4. Subsequent Therapy Documentation: Record details of any subsequent therapy for prostate cancer. Responsible Personnel: Study Coordinator.

Safety Assessments  
- Physical Examinations: Conduct regular physical assessments to monitor changes. Responsible Personnel: Investigator.  
- Vital Signs: Measure and record vital signs during each visit. Responsible Personnel: Study Nurse.  
- Laboratory Tests: Review laboratory results to identify safety concerns. Responsible Personnel: Laboratory Technician.  
- Adverse Event Monitoring: Continuously assess and document adverse events. Responsible Personnel: Investigator.  
- ECG Monitoring: Perform ECG monitoring as needed based on clinical judgment. Responsible Personnel: Cardiology Technician.

Efficacy Assessments  
- Disease-Specific Assessments: Evaluate disease progression using imaging techniques like CT/MRI and bone scans. Responsible Personnel: Radiologist.  
- Response Evaluation: Assess tumor response using RECIST 1.1 criteria. Responsible Personnel: Radiologist.  
- Patient-Reported Outcomes: Evaluate patient-reported outcomes using validated questionnaires. Responsible Personnel: Study Coordinator.  
- Quality of Life Measures: Continuously monitor quality of life through designated tools. Responsible Personnel: Study Coordinator.

Laboratory Assessments  
- Hematology: Conduct routine blood count analyses. Responsible Personnel: Laboratory Technician.  
- Clinical Chemistry: Assess key chemistry parameters. Responsible Personnel: Laboratory Technician.  
- Biomarker Sampling: Collect samples for exploratory biomarker analysis. Special Handling Instructions: Follow specified handling and storage protocols. Responsible Personnel: Laboratory Technician.  
- PK/PD Assessments: Collect samples for PK/PD analysis of apalutamide and leuprolide. Responsible Personnel: Laboratory Technician.

Other Assessments  
- Medical Resource Utilization: Collect data on medical resource usage during the treatment phase. Responsible Personnel: Study Coordinator.  
- Biomarker Analysis: Explore associations of biomarkers with clinical outcomes as per the statistical analysis plan. Responsible Personnel: Investigator.

Statistical

Statistical Analysis

Statistical Hypotheses  
The primary hypothesis is that apalutamide plus androgen deprivation therapy (ADT) is superior in improving radiographic progression-free survival (rPFS) or overall survival (OS) compared with ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). For rPFS, the hypothesis tests if the hazard ratio (HR) is less than 1 (HR < 1). Similarly, for OS, the hypothesis aims to show a reduction in the risk of death with apalutamide plus ADT relative to placebo plus ADT, gauged by HR < 1.

Sample Size Determination  
The sample size was calculated to ensure adequate power for detecting significant differences in the dual-primary endpoints of rPFS and OS. Approximately 1,000 subjects will be randomized to attain at least 368 rPFS events, giving at least 85% power to detect a HR of 0.67 for rPFS at a significance level of 0.005. Additionally, the study is powered to detect a HR of 0.75 for OS, requiring approximately 410 death events, providing 80% power at a two-sided significance level of 0.045, ensuring sufficient sensitivity to discern treatment effects.

Analysis Populations  
1. Intent-to-Treat (ITT) Population: Includes all randomized subjects and will be used for all efficacy analyses. This population ensures that all subjects are analyzed in the groups to which they were originally assigned, maintaining the integrity of randomization.  
   
2. Safety Population: Comprises all subjects who receive at least one dose of study medication and will be utilized for all safety evaluations. This ensures that all participants who started the intervention are analyzed for any potential adverse events.

Statistical Methods  
Efficacy endpoints will be analyzed using the Kaplan-Meier method to estimate survival functions, and the log-rank test will be employed to compare survival distributions between treatment groups. The Cox proportional hazards model will be used to estimate hazard ratios and their 95% confidence intervals for time-to-event outcomes. Secondary endpoints like time to pain progression and time to skeletal-related events (SREs) will be analyzed similarly.

Multiplicity Adjustments  
The significance levels for dual-primary endpoints will be adjusted using a prespecified alpha spending approach: 0.005 for rPFS and 0.045 for OS. This partitioning shields against inflated type I error rates due to multiple testing.

Interim Analyses  
Two interim analyses for OS, conducted after approximately 50% and 70% of expected 410 deaths, will employ a Haybittle-Peto boundary to preserve the integrity of the final analysis. The first interim is synchronized with the rPFS final analysis. The IDMC will review interim data and recommend the continuation or modification of the study.

Missing Data Handling  
Efforts will be made to minimize missing data. Sensitivity analyses will handle missing data through multiple imputation methods and other approaches like last observation carried forward (LOCF) and worst-case/best-case scenarios to evaluate the robustness of the findings. Dropouts, loss to follow-up, and missing covariate data will be addressed through these techniques to ensure unbiased estimations.

This statistical strategy ensures that legitimate conclusions about the efficacy and safety of apalutamide plus ADT in subjects with mHSPC are reached, maintaining scientific integrity even amidst challenges like missing data and multiplicity.

Safety

Safety

Safety Parameters  
The safety parameters evaluated in this study include the incidence, severity, and seriousness of treatment-emergent adverse events (AEs), vital signs changes, physical examination findings, Eastern Cooperative Oncology Group (ECOG) performance status, and clinical laboratory test results. Safety data will be collected from the signing of informed consent to 30 days after the last dose of the study drug.

Adverse Event Definitions  
Adverse events (AEs) will be defined according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. An AE is considered any untoward medical occurrence in a participant administered with the study drug, which does not necessarily have a causal relationship with this treatment.

Severity Grades  
Each AE will be graded on a scale from 1 to 5:  
- Grade 1: Mild  
- Grade 2: Moderate  
- Grade 3: Severe  
- Grade 4: Life-threatening  
- Grade 5: Death

Adverse Event Reporting  
All adverse events will be documented and reported according to institutional and regulatory guidelines. This includes any changes in the participant's condition, abnormal lab results, or any other atypical findings noted during the study. Serious adverse events (SAEs) must be reported immediately to the sponsor and the relevant regulatory bodies, following local law requirements.

Safety Monitoring  
Safety monitoring will be ongoing throughout the study, with scheduled evaluations for AEs, vital signs, physical exams, and laboratory tests. Investigators are responsible for assessing the severity and potential relationship of AEs to the study drug, with guidance from the protocol. Participants may have their doses adjusted or treatment paused based on predefined dose modification criteria.

Risk Management  
The protocol includes risk management strategies focusing on early identification of adverse safety signals through vigilant monitoring and predefined criteria for dose adjustment or interruption. Participants experiencing unacceptable toxicity levels may have their treatment suspended or dose adjusted per protocol guidelines.

Data Monitoring Committee  
An Independent Data Monitoring Committee (IDMC) has been established for this study to provide independent assessments of safety data and interim analysis results. The IDMC will regularly review accumulating safety data and provide recommendations regarding the continuation, modification, or termination of the study based on risk-benefit assessments.

Stopping Rules  
If at any time during the study the IDMC identifies a significant safety concern, the committee may recommend halting further enrollment or treatment. Stopping rules encompass considerations for unacceptable adverse events frequency or severity that outweigh the benefits of continuing the study drug administration. Additionally, protocol-specific criteria requiring the cessation of treatment in response to marked clinical progression or adverse reactions that contravene patient health are predefined. Decisions to stop treatment will also factor in interim analysis results emphasizing unmanageable safety issues.

Safety oversight procedures, together with comprehensive reporting structures, ensure that any potential risks are promptly and adequately addressed, maintaining adherence to ethical standards and participant welfare.