Clinical Trial Protocol

# Background

Background

Disease Background  
Prostate cancer is one of the most common malignancies affecting men worldwide. It can progress to a metastatic hormone-sensitive state (mHSPC), where the cancer cells have spread beyond the prostate gland and continue to grow in response to androgenic hormonal stimulation. The standard measure for controlling disease progression in mHSPC is through androgen deprivation therapy (ADT), which targets these hormones. Despite initial responsiveness to ADT, the disease eventually progresses in most patients. Therefore, the need for effective treatments that can extend progression-free periods and improve overall survival remains critical.

Current Treatment Landscape  
The current standard treatment for mHSPC involves either medical or surgical castration to reduce androgen levels, commonly through the use of GnRH analogs or orchiectomy. ADT alone, however, is often not sufficient to halt long-term disease progression. Recent advancements have focused on improving outcomes by combining ADT with additional therapies. Docetaxel, a chemotherapeutic agent, has shown improved survival benefits when added to ADT in some cases. Nonetheless, this treatment is associated with significant toxicity and not suitable for every patient. Therefore, there is a continuous search for more tolerable and effective therapeutic combinations to treat mHSPC.

Product Background  
Apalutamide is a novel, orally administered, non-steroidal anti-androgen that functions as a selective antagonist of the androgen receptor. It is designed to inhibit androgen receptor signaling, which is pivotal for the growth and survival of prostate cancer cells. Apalutamide uniquely binds directly to the ligand-binding domain of the androgen receptor, preventing its activation. This mechanism of action makes it a promising candidate for combination therapy with ADT, potentially leading to improved outcomes in patients with mHSPC by both delaying disease progression and extending survival times.

Study Rationale  
The rationale for this Phase 3 study stems from the need to assess whether the addition of apalutamide to standard ADT regimens could provide superior efficacy compared to ADT alone in patients with mHSPC. The study aims to establish benefits not just in clinical endpoints such as radiographic progression-free survival and overall survival, but also in quality of life measures such as pain and function. By exploring the pharmacokinetic and pharmacodynamic profile of apalutamide in conjunction with ADT, the study will contribute to a better understanding of its therapeutic potential and safety profile. Additionally, evaluating subpopulations based on disease volume and prior docetaxel use may provide insights into tailoring treatment strategies further, ensuring more personalized and effective therapeutic approaches for managing 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).  
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 the 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 as assessed by incidence and intensity of treatment-emergent adverse events (AEs), clinically significant changes in physical examination findings, vital signs, and laboratory results.  
6. Pharmacokinetic and pharmacodynamic parameters of apalutamide.  
7. Leuprolide concentration and its PD effect on testosterone levels.  
8. Response in subpopulations with low-volume or high-volume mHSPC.

# Study Design

Study Design

Overall Design

This Phase 3 study is a randomized, double-blind, placebo-controlled, multinational, and multicenter trial designed to evaluate the efficacy and safety of adding apalutamide to androgen deprivation therapy (ADT) in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). Approximately 1,000 subjects will be enrolled. Participants will be stratified by Gleason score at diagnosis, region, and prior docetaxel use, then randomized in a 1:1 ratio to receive either apalutamide plus ADT or a matching placebo plus ADT. The study will include a Screening Phase, Treatment Phase with 28-day cycles, Follow-up Phase, Open-label Extension Phase, and Long-Term Extension (LTE) Phase.

Study Schema

The study schema involves the following phases:

1. 1. Screening Phase: Up to 28 days for eligibility determination.
2. 2. Treatment Phase: Subjects will receive treatment in 28-day cycles until disease progression, unacceptable toxicity, or study termination.
3. 3. End-of-Treatment Visit: Conducted within 30 days after the last dose.
4. 4. Follow-up Phase: Every 4 months data collection for survival and secondary endpoints until death, consent withdrawal, or study termination.
5. 5. Open-label Extension Phase: For subjects in the Treatment Phase if interim analyses show positive results.
6. 6. Long-Term Extension Phase: Begins after final analysis cut-off or upon Amendment 5 approval at site, allowing continued apalutamide treatment if beneficial.

Study Duration

The total study duration will be approximately 54 months, including up to 30 months for enrollment and to achieve the required number of events for statistical purposes.

Treatment Groups

|  |  |  |
| --- | --- | --- |
| **Group** | **Treatment** | **Dose/Frequency** |
| Apalutamide + ADT | Apalutamide (240 mg daily) + ADT | Orally, with or without food |
| Placebo + ADT | Matching placebo + ADT | Orally, with or without food |

All subjects will receive ADT as standard of care, defined as medical or surgical castration. The choice of GnRH analog for ADT is at the investigator’s discretion, adhering to prescribing information.

Study Schema

# Population

Study Population

Overview of Study Population  
The study population will consist of male subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC), characterized by the presence of distant metastatic disease as documented by a positive bone scan with one or more bone lesions. Eligible participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of grade 0 or 1, indicating they are fully active or restricted in physically strenuous activity but ambulatory.

Inclusion Criteria  
1. Male subjects aged 18 years or older.  
2. Histologically or cytologically confirmed diagnosis of prostate cancer.  
3. Documented metastatic disease with one or more bone lesions identified on a Technetium 99m (99mTc) bone scan. In cases of a single bone lesion, confirmation via computed tomography (CT) or magnetic resonance imaging (MRI) is required.  
4. ECOG performance status of 0 or 1.  
5. Subjects may have received up to 6 cycles of docetaxel for mHSPC, with the last dose administered no more than 2 months prior to randomization.  
6. Subjects may have received androgen deprivation therapy (ADT) for a duration of 6 months or less prior to randomization.  
7. Participants may have had a maximum of 1 course of radiation or surgical intervention for mHSPC.  
8. For localized prostate cancer, subjects may have been treated with ADT and other therapies (radiation, prostatectomy, lymph node dissection, systemic therapies) completed at least 1 year prior to randomization.

Exclusion Criteria  
1. Subjects with known brain metastases or leptomeningeal disease.  
2. History of seizure or any condition that may predispose to seizure (e.g., stroke, brain injury, concussion).  
3. Any condition that, in the investigator’s opinion, would interfere with the evaluation of the study drug or interpretation of subject safety or study results.  
4. Prior treatment with apalutamide or other investigational agents for prostate cancer.  
5. Subjects with serious uncontrolled concomitant diseases, including but not limited to heart failure, myocardial infarction within the last 6 months, or significant liver disease.  
6. Other malignancies diagnosed within the last 5 years, with exceptions for adequately treated basal cell or squamous cell carcinoma of the skin.

Withdrawal Criteria  
1. Subjects may withdraw from the study at any time without prejudice.  
2. Withdrawal of consent by the subject.  
3. Investigator determines it is in the best interest of the subject to discontinue participation.  
4. Significant protocol violation.  
5. Adverse events that, per the investigator's judgment, warrant withdrawal.

Replacement Policy  
Subjects who withdraw or are discontinued from the study, will not be replaced to ensure the integrity of the randomization. Enrollment will continue until the target number of approximately 1,000 subjects is achieved.

# Procedures

Study Procedures

Study Procedures Overview  
This section outlines the detailed procedures to be conducted during the study, covering the screening, treatment, and follow-up phases, as well as the safety and efficacy assessments, and other study-related evaluations.

Screening/Baseline Procedures  
Screening procedures will be conducted within 28 days prior to randomization to ensure eligibility based on the inclusion and exclusion criteria.

1. 1. \*\*Informed Consent\*\*

* Timing: Prior to any study-specific procedure.
* Requirements: Subjects must provide written consent.
* Responsible Personnel: Research staff.

2. \*\*Demographics and Medical History\*\*   
 - Timing: During initial screening visit.   
 - Requirements: Collect subject's age, gender, ethnicity, prior medical history, including any previous cancer therapies.   
 - Responsible Personnel: Investigator or designated research staff.

3. \*\*Physical Examination\*\*   
 - Timing: Performed during screening visit.   
 - Requirements: Comprehensive physical exam, including evaluation of ECOG performance status.   
 - Responsible Personnel: Investigator or qualified healthcare professional.

4. \*\*Vital Signs Measurement\*\*   
 - Timing: At screening visit.   
 - Requirements: Includes blood pressure, heart rate, and temperature.   
 - Responsible Personnel: Qualified healthcare staff.

5. \*\*Laboratory Assessments\*\*   
 - Timing: Screening phase.   
 - Requirements: Blood samples for hematology, clinical chemistry, and PSA levels.   
 - Responsible Personnel: Laboratory technician.

6. \*\*Disease Assessment\*\*   
 - Timing: At baseline.   
 - Requirements: Imaging studies (CT/MRI and bone scans) to confirm metastatic disease.   
 - Responsible Personnel: Radiologist or investigator.

7. \*\*Inclusion/Exclusion Criteria Review\*\*   
 - Timing: Prior to randomization.   
 - Requirements: Confirm eligibility against criteria.   
 - Responsible Personnel: Investigator.

Treatment Phase Procedures  
Subjects will be randomized to commence treatment with apalutamide plus ADT or placebo plus ADT in 28-day cycles.

1. 1. \*\*Drug Administration\*\*

* Timing: Daily, post-randomization.
* Requirements: Apalutamide 240 mg (or matching placebo) taken orally once daily, with or without food.
* Responsible Personnel: Subject under supervision of research staff.

2. \*\*Safety Monitoring\*\*   
 - Timing: Ongoing during treatment cycle.   
 - Requirements: Monitor adverse events, perform physical exams and lab tests as needed.   
 - Responsible Personnel: Healthcare staff.

3. \*\*Efficacy Assessments\*\*   
 - Timing: At regular pre-specified intervals.   
 - Requirements: Evaluate radiographic and clinical progression.   
 - Responsible Personnel: Investigator.

4. \*\*Laboratory Tests\*\*   
 - Timing: On Day 1 of select cycles (2, 3, 4, 5, and 6).   
 - Requirements: Blood samples for PK analysis of apalutamide and its active metabolite.   
 - Responsible Personnel: Laboratory staff.

5. \*\*Quality of Life Assessments\*\*   
 - Timing: During treatment at specified visits.   
 - Requirements: Completion of BPI-SF, BFI, and EQ-5D-5L questionnaires.   
 - Responsible Personnel: Subject, assisted by research staff if necessary.

6. \*\*Adverse Event Monitoring\*\*   
 - Timing: Continuous.   
 - Requirements: Document all AEs per NCI-CTCAE criteria.   
 - Responsible Personnel: Investigator or designated staff.

7. \*\*Concomitant Medication Review\*\*   
 - Timing: Each treatment cycle.   
 - Requirements: Record any medications taken by subjects.   
 - Responsible Personnel: Investigator.

Follow-up Procedures  
After treatment discontinuation, subjects will transition to the follow-up phase, where evaluations continue every 4 months.

1. 1. \*\*Safety Follow-up\*\*

* Timing: 30 days post last dose of study drug.
* Requirements: Monitor delayed drug-related AEs.
* Responsible Personnel: Investigator.

2. \*\*Disease Assessment\*\*   
 - Timing: During follow-up visits.   
 - Requirements: Update disease progression status.   
 - Responsible Personnel: Investigator.

3. \*\*Survival Status\*\*   
 - Timing: Every follow-up visit.   
 - Requirements: Record subject survival and any subsequent therapies started.   
 - Responsible Personnel: Research staff.

4. \*\*Subsequent Therapy Documentation\*\*   
 - Timing: As applicable during follow-up.   
 - Requirements: Details of new cancer treatments.   
 - Responsible Personnel: Research staff.

Safety Assessments  
- \*\*Physical Examinations:\*\* Conducted throughout the study to monitor general health.  
- \*\*Vital Signs:\*\* Regular recording at each visit.  
- \*\*Laboratory Tests:\*\* Routine blood tests to monitor for any treatment effects.  
- \*\*Adverse Event Monitoring:\*\* Continuous documentation of adverse events as per NCI-CTCAE.

Efficacy Assessments  
- \*\*Radiographic and Clinical Progression Assessments:\*\* Evaluating rPFS and OS.  
- \*\*Patient-Reported Outcomes:\*\* Collected using BPI-SF, BFI, and EQ-5D-5L questionnaires.  
- \*\*Quality of Life Measures:\*\* Assessed periodically during treatment and follow-up phases.

Laboratory Assessments  
- \*\*Hematology and Clinical Chemistry:\*\* Baseline and periodic blood analyses.  
- \*\*Biomarker Sampling:\*\* For exploratory research on resistance and predictive markers.  
- \*\*PK/PD Assessments:\*\* Pre-dose PK samples on specific cycle days.

Other Assessments  
- \*\*Biomarker Evaluations:\*\* Analysis of circulating DNA and tumor samples for AR mutations and immune markers.  
- \*\*Medical Resource Utilization Data:\*\* Collected during treatment to inform future economic modeling.

# Statistical

Statistical Analysis

Statistical Hypotheses

The primary hypothesis of this study is that apalutamide plus ADT will improve radiographic progression-free survival (rPFS) or overall survival (OS), or both, compared to ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). This study will be considered successful if at least one of the dual-primary endpoints is statistically significant. The significance level for rPFS is set at 0.005, and for OS, it is set at 0.045, ensuring a cumulative type I error rate of 5%.

Sample Size Determination

The study aims to randomize approximately 1,000 subjects to ensure adequate power for detecting differences in the dual-primary endpoints. For rPFS, the study requires approximately 368 progression events to achieve at least 85% power to detect a hazard ratio (HR) of 0.67, assuming a median rPFS of 20 months for the control group (ADT) and 30 months for the treatment group (apalutamide plus ADT), with a two-tailed significance level of 0.005. For OS, approximately 410 death events are needed to achieve 80% power to detect a HR of 0.75, with an assumed median OS of 44 months in the control group, at a two-tailed significance level of 0.045. The study duration is anticipated to be approximately 54 months, including an enrollment period of about 30 months.

Analysis Populations

The Intent-to-Treat (ITT) population, consisting of all randomized subjects, will be used for primary efficacy analyses and subject disposition. The Safety Population, defined as all subjects who received at least one dose of study drug, will be employed for safety assessments. Separate analyses will be performed for subpopulations defined by disease volume and prior docetaxel use.

Statistical Methods

Time-to-event endpoints such as rPFS and OS will be analyzed using the Kaplan-Meier method, with comparisons between treatment groups conducted using the log-rank test. Hazard ratios and corresponding 95% confidence intervals will be estimated using Cox proportional hazards models. For secondary endpoints, similar survival analysis techniques will be applied. The analysis of covariance (ANCOVA) will be used for continuous variables like quality of life measures. Multiplicity adjustments for the dual-primary endpoint analyses will be managed by allocating different significance levels for rPFS and OS (0.005 and 0.045 respectively).

Interim Analyses

Two interim analyses are planned for assessing the OS endpoint, occurring after approximately 50% (~205 events) and 70% (~287 events) of the 410 required death events. An independent data monitoring committee (IDMC) will oversee these analyses to make recommendations based on safety and efficacy data. The final analysis of the rPFS will coincide with the first interim analysis of OS. No interim analysis is planned for rPFS alone.

Missing Data Handling

Missing data in time-to-event analyses will be treated as censored observations. For secondary outcomes and exploratory endpoints with potentially missing data, methods such as multiple imputations or last observation carried forward (LOCF) will be considered, depending on the nature and extent of the missing data. Review and implementation of missing data handling strategies will follow guidelines in the detailed Statistical Analysis Plan, ensuring robustness and appropriateness for each specific endpoint.

# Safety

Safety

Safety Parameters

Safety parameters will include the assessment of adverse events (AEs), serious adverse events (SAEs), physical examination findings, vital signs (e.g., blood pressure), Eastern Cooperative Oncology Group (ECOG) performance status, and clinical laboratory test results. These evaluations will track the incidence and severity of treatment-emergent adverse events throughout the study period.

Adverse Event Definitions

Adverse events will be defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. This classification will be used to evaluate the severity of all AEs reported during the trial and will range from Grade 1 (mild) to Grade 5 (death related to AE).

Adverse Event Reporting

All AEs, irrespective of their perceived association with the study drug, will be collected from the signing of the informed consent until 30 days following the last administration of the study drug. Investigators are responsible for documenting all AEs in the electronic case report form (eCRF) and reporting SAEs to the sponsor within 24 hours of awareness. Follow-up on reported AEs will continue until resolution or stabilization.

Safety Monitoring

Safety monitoring will be conducted through regular assessments, including physical examinations, vital sign measurements, ECOG performance status evaluations, and clinical laboratory tests at specified intervals throughout the treatment and follow-up phases. Additionally, patient-reported outcomes related to pain and fatigue will be monitored using the Brief Pain Inventory-Short Form (BPI-SF) and the Brief Fatigue Inventory (BFI).

Risk Management

Risk management will focus on minimizing potential treatment-related toxicities. Dose modifications will follow the protocol-specified rules to manage toxicity, ensuring treatment continuation whenever feasible, without compromising safety. Subjects will be monitored closely for any signs or symptoms consistent with known risks, including those related to androgen blockade such as cardiovascular events and fractures.

Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will oversee the study, conducting interim analyses as outlined in the protocol at approximately 50% and 70% of total OS events. The IDMC will provide independent review and recommendations to the sponsor regarding safety data and, if necessary, early termination or modification of the trial procedures.

Stopping Rules

Stopping rules will be guided by the IDMC recommendations, based on interim efficacy and safety evaluations. The study may be stopped prematurely if significant safety concerns arise or if there is clear evidence of overwhelming efficacy or futility. Additionally, individual subject participation can be discontinued for reasons including unacceptable toxicity, significant protocol violation, or at the subject's request.

Reporting Requirements

The investigator must report all adverse events in a timely manner, adhering to regulatory requirements for prompt reporting of serious and unexpected AEs. All SAEs must be reported to the sponsor immediately and no later than 24 hours from the time of awareness. Furthermore, regular safety updates will be compiled and submitted to regulatory authorities as required by local regulations and study governance guidelines.

Safety Oversight Procedures

Comprehensive safety oversight will be maintained through structured procedures involving continuous monitoring, regular communication with investigators, and rigorous data review by the sponsor and IDMC. Updates on blinded safety data will be periodically reviewed to identify potential safety signals, ensuring that any required adjustments to the study protocol or informed consent process can be implemented promptly.