Clinical Trial Protocol

# Background

Background

Disease Background  
Prostate cancer is a significant health concern worldwide, ranking as one of the most frequently diagnosed cancers among men. Metastatic hormone-sensitive prostate cancer (mHSPC) represents a stage of prostate cancer characterized by the spread of cancer cells to distant parts of the body such as bones and lymph nodes, while still responding to hormone deprivation therapies. The disease burden in mHSPC is substantial, with progressive symptoms that significantly affect patients' quality of life. Despite initial responses to androgen deprivation therapy (ADT), resistance eventually develops, transitioning the disease to a castration-resistant state with limited therapeutic options and a poor prognosis.

Current Treatment Landscape  
The primary standard of care for patients with mHSPC is androgen deprivation therapy (ADT), which aims to reduce levels of male hormones that fuel prostate cancer growth. ADT can be achieved through surgical castration or the use of gonadotropin-releasing hormone analogs or antagonists. Recent advancements have introduced chemotherapy and newer androgen receptor-targeting agents into the treatment paradigm, showing improved outcomes over ADT alone in certain subpopulations. However, these treatments can be associated with considerable side effects and are not always suitable for all patients. Moreover, the optimal sequence of therapies remains an area of ongoing investigation. The need for treatments that improve survival while maintaining quality of life is paramount in the management of mHSPC.

Product Background  
Apalutamide is an orally administered, non-steroidal, selective antagonist of the androgen receptor. It has been designed to block the effects of androgens at their receptor level, preventing androgen-driven tumor growth. Apalutamide is already utilized in other prostate cancer settings and has demonstrated significant anti-tumor activity in clinical trials. Its mechanism of action involves inhibiting the transcriptional activity of androgen receptors, which can slow or reverse the growth of prostate cancer cells dependent on these signals. Given its properties, apalutamide represents a promising intervention for enhancing the effects of ADT in patients with mHSPC.

Study Rationale  
The rationale for this study is based on the hypothesis that the combination of apalutamide with ADT could result in superior clinical outcomes compared to ADT alone in patients with mHSPC. This hypothesis is supported by preliminary evidence suggesting that apalutamide may effectively extend radiographic progression-free survival and overall survival—key measures of treatment efficacy. Clinical improvement in parameters such as pain progression, opioid use, and the delay of skeletal-related events also supports the exploration of apalutamide's utility in this disease setting. An evaluation of safety, pharmacokinetics, and patient-relevant outcomes will contribute to understanding the full spectrum of effects of apalutamide when combined with ADT, ultimately informing its potential role in the mHSPC treatment landscape.

# Objectives

Objectives

Primary Objective(s)  
1. 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. Improvement in radiographic progression-free survival (rPFS) or overall survival (OS) in subjects with mHSPC receiving apalutamide plus ADT compared to those receiving placebo plus ADT.

Secondary Objectives  
1. 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. Characterize the safety profile of adding apalutamide to ADT in subjects with mHSPC.  
3. Characterize the population pharmacokinetics (PK) and pharmacodynamics (PD) of apalutamide.  
4. Evaluate the concentration of leuprolide and assess the PD effect of leuprolide on testosterone concentrations, when used alone or in combination with apalutamide.  
5. Evaluate treatment effectiveness with the addition of apalutamide to ADT for subpopulations of subjects with low-volume or high-volume mHSPC.

Secondary Endpoint(s)  
1. Time to pain progression, time to skeletal-related events (SREs), time to chronic opioid use, and time to initiation of cytotoxic chemotherapy in subjects receiving apalutamide plus ADT compared to placebo plus ADT.  
2. Incidence and intensity of treatment-emergent adverse events (AEs) and other safety parameters for subjects treated with apalutamide plus ADT compared to placebo plus ADT.  
3. PK parameters such as trough plasma concentration levels of apalutamide and its active metabolite.  
4. Testosterone concentrations and PD effects of leuprolide therapy in the presence versus absence of apalutamide.  
5. Treatment outcomes specific to subjects with low-volume versus high-volume mHSPC receiving apalutamide plus ADT.

# Study Design

Study Design

Overall Design  
This study is a Phase 3, randomized, double-blind, placebo-controlled, multinational, multicenter clinical trial. The purpose is 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). Approximately 1,000 eligible subjects will be enrolled and randomized in a 1:1 ratio to either the experimental arm (apalutamide plus ADT) or the control arm (placebo plus ADT). Stratification factors for randomization include Gleason score at diagnosis (≤7 versus >7), geographical region (North America and European Union versus Other Countries), and prior docetaxel use (yes versus no). The primary endpoints include radiographic progression-free survival (rPFS) and overall survival (OS).

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| **Study Schema** |
| Screening |
| Subject eligibility assessmentTreatment |
| Up to 28 daysRandomized 1:1 to apalutamide + ADT or placebo + ADTFollow-up |
| 28-day cycles until progression or unacceptable toxicityData collection on secondary endpoints and survival |

Study Duration  
The study duration is planned to be approximately 54 months, with an enrollment period of around 30 months. Subjects will undergo a Treatment Phase until disease progression, unacceptable toxicity, or study termination by the sponsor. Follow-up for survival and secondary endpoint data collection will occur every 4 months until the subject's death, withdrawal, lost to follow-up, or study termination. An Open-label Extension Phase will be available for subjects to receive apalutamide for approximately 3 years following a positive study result.

Treatment Groups  
1. \*\*Experimental Arm\*\*: Subjects will receive 240 mg of apalutamide (4 x 60 mg tablets) orally once daily, alongside standard of care ADT, defined as medical castration (using a GnRHa, either agonist or antagonist) or surgical castration (bilateral orchiectomy). This continues in 28-day cycles until disease progression or the occurrence of unacceptable treatment-related toxicity.  
   
2. \*\*Control Arm\*\*: Subjects will receive matching placebo (4 tablets) orally once daily, in addition to standard of care ADT, with similar dosing and progression criteria as the experimental arm.

All treatments should be documented in compliance with protocol specifications, and any changes or dose modifications will follow predefined modification rules detailed in the protocol.

Study Schema

# Population

Study Population

Overview of Study Population  
The study population consists of subjects with metastatic hormone-sensitive prostate cancer (mHSPC). Eligible subjects must have a diagnosis of prostate cancer and demonstrate an Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 or 1. This population is targeted to evaluate the efficacy and safety of combining apalutamide with androgen deprivation therapy (ADT) compared to ADT alone.

Inclusion Criteria  
1. \*\*Diagnosis and Disease Confirmation\*\*  
 - Subjects must have a confirmed diagnosis of prostate cancer with distant metastatic disease.  
 - Metastases must be documented by a positive bone scan showing one or more bone lesions. Subjects with a solitary bone lesion require confirmation by computed tomography (CT) or magnetic resonance imaging (MRI).

2. \*\*Performance Status\*\*  
 - ECOG PS must be grade 0 (fully active) or grade 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature).

3. \*\*Prior Treatment\*\*  
 - Subjects may have received up to 6 cycles of docetaxel chemotherapy for mHSPC, with the last dose administered no more than 2 months prior to randomization.  
 - Up to 6 months of prior ADT is permitted.  
 - Subjects may have undergone one course of radiation or surgical intervention for mHSPC.

4. \*\*Prostate Cancer History\*\*  
 - For previously localized prostate cancer, subjects may have received up to 3 years of prior ADT. Completion of any prior therapies (including radiation therapy, prostatectomy, lymph node dissection, and systemic therapies) must have occurred at least 1 year before randomization.

Exclusion Criteria  
1. \*\*Disease Criteria\*\*  
 - Subjects with only local recurrence or nodal disease without distant metastasis are excluded.

2. \*\*Comorbid Conditions\*\*  
 - Subjects with uncontrolled comorbid conditions or other malignancies that could interfere with study participation or affect compliance.

3. \*\*Treatment Limitations\*\*  
 - Concurrent treatment with another investigational agent or participation in a study testing another investigational drug is disallowed.

4. \*\*Health Status\*\*  
 - Subjects with a significant history of hypersensitivity to apalutamide or to any components of the formulation are ineligible.

Withdrawal Criteria  
- Subjects are required to be withdrawn from the study medication if they experience disease progression defined by clinical criteria or unacceptable treatment-related toxicity.   
- Withdrawal will also occur if informed consent is withdrawn, or if the subject is lost to follow-up.

Replacement Policy  
- If a subject is withdrawn from the study, replacement with another subject will not occur unless specific conditions outlined in the protocol necessitate maintaining the required sample size to ensure sufficient statistical power.

# Procedures

Study Procedures

Study Procedures Overview  
This section describes the specific procedures that will be followed throughout the study, including the Screening/Baseline, Treatment, and Follow-up phases. Each phase includes detailed assessments that will be conducted by designated study personnel.

Screening/Baseline Procedures  
- \*\*Informed Consent:\*\* Must be obtained from each subject by the study investigator before any other screening activities are conducted.   
- \*\*Demographics and Medical History:\*\* Include a thorough collection of the subject's medical history and demographic information.  
- \*\*Physical Examination:\*\* Conducted by the study investigator to assess the subject's overall health status.  
- \*\*Vital Signs:\*\* Measurements including blood pressure, heart rate, and temperature to be recorded by qualified medical personnel.  
- \*\*Laboratory Assessments:\*\* Blood samples will be collected to perform hematology and clinical chemistry evaluations.  
- \*\*Disease Assessment:\*\* Baseline imaging studies, such as CT/MRI and bone scans, will be performed to confirm metastatic disease.  
- \*\*Inclusion/Exclusion Criteria Review:\*\* Ensured by the study investigator to verify eligibility based on protocol specifics.

Treatment Phase Procedures  
- \*\*Drug Administration:\*\*   
 - Apalutamide 240-mg (4 x 60-mg tablets) or matching placebo to be taken orally, once daily. Administration should be documented by study staff.  
 - GnRHa will be administered as per standard of care, with dosing documented in the electronic case report form (eCRF).  
- \*\*Safety Monitoring:\*\* Continuous monitoring for adverse events (AEs) with regular follow-ups.  
- \*\*Efficacy Assessments:\*\* Include regular imaging and biomarker studies to assess radiographic progression, carried out by the study team.  
- \*\*Laboratory Tests:\*\* Regular PK and PD sampling and baseline evaluation repeated on Day 1 of specified cycles (2, 3, 4, 5, and 6).  
- \*\*Quality of Life Assessments:\*\* Conducted using tools such as the Brief Pain Inventory-Short Form, Brief Fatigue Inventory, and EQ-5D-5L as managed by study personnel.  
- \*\*Adverse Event Monitoring:\*\* Systematic recording and management of adverse events using the NCI-CTCAE criteria.  
- \*\*Concomitant Medication Review:\*\* Documented regularly to track any ongoing medications or new prescriptions.

Follow-up Procedures  
- \*\*Safety Follow-up:\*\* Conduct a final safety assessment within 30 days post last dose of the study drug.  
- \*\*Disease Assessment:\*\* Includes imaging and PSA evaluations at intervals specified in the protocol.  
- \*\*Survival Status:\*\* Collected every 4 months to assess overall survival.  
- \*\*Subsequent Therapy Documentation:\*\* Any new therapies for prostate cancer are to be recorded.

Safety Assessments  
- Conducted throughout the study, including:  
 - \*\*Physical Examinations:\*\* Routine checks by the study investigator.  
 - \*\*Vital Signs:\*\* Regular monitoring by medical staff.  
 - \*\*Laboratory Tests:\*\* Regular analysis for safety markers.  
 - \*\*Adverse Event Monitoring:\*\* Using standard grading scales, managed by the study investigator.

Efficacy Assessments  
- Efficacy will be measured by:  
 - \*\*Radiographic Progression Assessments:\*\* Evaluated according to RECIST 1.1 and bone scan protocols.  
 - \*\*Overall Survival Tracking:\*\* Monitored and documented.  
 - \*\*Patient-reported Outcomes:\*\* Analyzed using validated scales such as FACT-P.

Laboratory Assessments  
- Conducted at specified intervals:  
 - \*\*Hematology and Chemistry Panels:\*\* Regular blood work.  
 - \*\*Biomarker Sampling:\*\* Analyzing AR mutations and other relevant markers.  
 - \*\*PK/PD Assessments:\*\* Ensure proper collection and handling of samples for drug concentration analysis.

Other Assessments  
- \*\*Biomarker Evaluation:\*\* To predict response or resistance, requiring specific collection and storage of biological materials.  
- \*\*Medical Resource Utilization Collection:\*\* Handled meticulously by study coordinators to track healthcare encounters for future analysis.

Each listed procedure will adhere to protocol standards, ensuring consistency and compliance with regulatory requirements while safeguarding subject confidentiality and well-being.

# Statistical

Statistical Analysis

Statistical Hypotheses  
The primary hypotheses of this study are that the addition of apalutamide to androgen deprivation therapy (ADT) will result in statistically significant improvements in radiographic progression-free survival (rPFS) and overall survival (OS) compared to ADT alone. These hypotheses will be tested using the dual-primary endpoints of rPFS and OS.

Sample Size Determination  
The study will use an overall type I error rate of 5% with 0.005 allocated for the rPFS endpoint and 0.045 for OS. A total of approximately 368 events of rPFS are required to achieve at least 85% power to detect a hazard ratio (HR) of 0.67. For OS, approximately 410 death events are needed to detect a HR of 0.75 with 80% power. The study will enroll approximately 1,000 subjects over 30 months, with a total study duration of approximately 54 months to achieve these event numbers.

Analysis Populations  
The Intent-To-Treat (ITT) population will include all randomized subjects and will serve as the primary analysis set for efficacy endpoints. The Safety Population will comprise all subjects who received at least one dose of the study drug and will be used for analyzing safety data.

Statistical Methods  
For primary efficacy endpoints, the Kaplan-Meier method will be used to estimate survival functions, while the Cox proportional hazards model will provide hazard ratios and 95% confidence intervals. The dual-primary endpoint analysis will apply multiplicity adjustments to control the type I error rate. Secondary endpoints related to time-to-event outcomes will also utilize the Cox model.

For biomarker analysis, associations with clinical response or time-to-event endpoints will be evaluated using analysis of variance (ANOVA), survival models, or categorical approaches as appropriate.

Interim Analyses  
Two interim analyses for OS are planned after 50% (~205 events) and 70% (~287 events) of total death events. The first interim analysis will also include the final assessment of the rPFS dual-primary endpoint. A Lan-DeMets alpha-spending approach with an O’Brien-Fleming boundary will be used to guide interim decision-making.

Missing Data Handling  
Missing data for time-to-event endpoints will be handled using censoring, consistent with the last available assessment date. Sensitivity analyses may be performed to assess the impact of missing data on key results.

Overall, the statistical analysis plan will define the exact methods in greater detail, ensuring robust and reproducible analyses of the study outcomes.

# Safety

Safety

Safety Parameters  
The safety profile of the study drug, apalutamide, combined with androgen deprivation therapy (ADT), will be characterized by evaluating the incidence and intensity of adverse events (AEs), results from clinical laboratory tests, physical examination findings, and changes in vital signs. Safety assessments will be conducted from the time of informed consent until 30 days after the last dose of the study drug.

Adverse Event Definitions  
Adverse events (AEs) are defined as any untoward medical occurrences that appear in a subject receiving study treatment, regardless of whether these are related to the study drug. Treatment-emergent adverse events (TEAEs) are those that arise after the initiation of the study drug that were not present prior to starting the treatment or that worsen after the baseline assessment. The severity of AEs will be graded per the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, as follows:  
- Grade 1: Mild  
- Grade 2: Moderate  
- Grade 3: Severe  
- Grade 4: Life-threatening  
- Grade 5: Death

Adverse Event Reporting  
All AEs and serious adverse events (SAEs) must be reported promptly by the investigator in accordance with protocol requirements and regulatory guidelines. This includes any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or any event judged by the investigator as serious and requiring intervention.

Safety Monitoring  
Continuous safety monitoring will be implemented throughout the study. Regular safety evaluations will include detailed reviews of AEs, physical examinations, laboratory test results, and vital signs. Data on concomitant medications, dose modifications, and study drug discontinuations due to safety concerns will also be collected and analyzed.

Risk Management  
Risk management strategies include predefined dose modification rules to manage AE severity. Dose interruptions, reductions, or discontinuations will be implemented as per protocol-specific criteria for managing AEs. Investigative staff will receive training on the identification and management of potential risks associated with the study drug.

Data Monitoring Committee  
An Independent Data Monitoring Committee (IDMC) will oversee the safety of study participants and review accumulating study data at regular intervals. The IDMC is tasked with making recommendations regarding the safety of the participants, ongoing study conduct, and any modifications needed to ensure participant welfare.

Stopping Rules  
The study may be paused or terminated if significant safety concerns are identified, such as unforeseen SAEs that indicate a greater risk than potential benefit to study participants. The IDMC has the authority to recommend study discontinuation based on interim safety data analyses.

Safety oversight measures are in place to ensure rapid response to any emerging safety issues, ensuring both the integrity of the study and the well-being of its participants.