Clinical Trial Protocol

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# 1.2 Background

Background

Disease Background  
Prostate cancer is one of the most prevalent cancers affecting men and remains a significant health concern worldwide. It is characterized by the uncontrolled growth of cells in the prostate gland, which can potentially spread to other parts of the body, resulting in metastatic prostate cancer. A subset of prostate cancer is classified as metastatic hormone-sensitive prostate cancer (mHSPC), where the cancer has spread beyond the prostate and lymph nodes but still responds to hormonal therapies that lower androgen levels in the body. The management of mHSPC aims to control disease progression, alleviate symptoms, and improve survival.

Current Treatment Landscape  
The current standard of care for mHSPC involves androgen deprivation therapy (ADT), which reduces androgen levels and, in turn, slows the growth of prostate cancer cells. ADT can be achieved either surgically through bilateral orchiectomy or medically with gonadotropin-releasing hormone (GnRH) analogs. In recent years, the addition of docetaxel to ADT has been associated with improved overall survival in certain high-risk groups. However, despite these treatment options, there remains a significant unmet need for therapies that can further delay disease progression and enhance survival rates while maintaining quality of life for patients.

Product Background  
Apalutamide, a non-steroidal anti-androgen, is an oral medication designed to inhibit the action of androgens by selectively targeting the androgen receptor (AR). By binding to the AR, apalutamide prevents androgens from stimulating the growth of prostate cancer cells. It is currently under development to address various stages of prostate cancer, including mHSPC. Apalutamide is distinguished by its ability to provide potent and selective AR antagonism, which could offer therapeutic benefits in prolonging progression-free survival and overall survival in men with mHSPC when used in combination with ADT.

Study Rationale  
The rationale for this study is grounded in the hypothesis that apalutamide, in conjunction with ADT, will provide superior efficacy in extending radiographic progression-free survival (rPFS) and overall survival (OS) compared to ADT alone in individuals with mHSPC. The study is designed to assess not only the dual primary endpoints of rPFS and OS but also secondary endpoints such as pain progression, opioid use, and the occurrence of skeletal-related events. By exploring the safety, pharmacokinetics, and additional biomarkers, the study aims to comprehensively determine the potential benefits and risks of adding apalutamide to current treatment protocols. This research could significantly impact treatment guidelines by providing evidence for a new combination therapy that effectively delays disease advancement and improves survival outcomes in this patient population.

# 6.1 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) as assessed by the investigator, defined as the time from the date of randomization to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurs first.
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 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 evaluations including incidence and intensity of treatment-emergent adverse events, clinically significant changes in physical examination findings, vital signs measurements, and clinical laboratory results.
6. • Population pharmacokinetic and pharmacodynamic parameters of apalutamide.
7. • Plasma concentration of leuprolide and its effect on testosterone levels.
8. • Treatment efficacy in subpopulations with low- or high-volume mHSPC.

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 of apalutamide plus ADT compared with ADT alone.
4. • To collect medical resource utilization data that may be used in future economic modeling.

Other Endpoints

1. • Presence of biomarkers associated with response and resistance.
2. • Patient-reported outcomes such as pain, fatigue, urination, functioning, and quality of life measures.
3. • Improvements in additional clinically relevant endpoints not specified in the dual-primary or secondary endpoints.
4. • Data on medical resource utilization for potential economic analyses.

# 13.1 Study Design

Study Design

Overall Design

This study is a Phase 3, randomized, double-blind, placebo-controlled, multinational, and multicenter clinical trial designed 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 subjects meeting the inclusion criteria and none of the exclusion criteria will be enrolled. These subjects will be stratified based on Gleason score at diagnosis, geographical region, and prior docetaxel use before being randomly assigned in a 1:1 ratio to receive either apalutamide plus ADT or matching placebo plus ADT.

Study Schema

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Schedule | Screening | Treatment Phase (28-day cycles) | Follow-up | Open-label Extension/Long-Term Extension |
| -------------- | ------------- | ------------------------------------ | ------------- | ------------------------------------------ |
| Duration | Up to 28 days | Until disease progression, unacceptable toxicity, or study termination | Every 4 months up to 12 months post-treatment | Approximately 3 years for open-label and continued benefit for LTE |

Study Duration

The total study duration is estimated to be approximately 54 months, including an enrollment period of about 30 months. The study will continue until approximately 410 death events have been observed, allowing the collection of sufficient data to assess overall survival (OS) as a primary endpoint. The follow-up period will consist of regular survival data and secondary endpoints assessments every four months, continuing until subjects die, withdraw consent, or the study is terminated by the sponsor.

Treatment Groups

Subjects will be assigned to one of two treatment groups:

1. • Apalutamide plus ADT Group\*\*: Subjects in this group will receive apalutamide in combination with standard of care ADT. Apalutamide will be administered as 240 mg orally once daily (4 x 60-mg tablets) with or without food. ADT will be maintained either by medical castration (use of GnRH analogs) or surgical castration, as determined by the investigator.

2. \*\*Placebo plus ADT Group\*\*: Subjects in this group will receive a matching placebo administered in the same manner as apalutamide (4 tablets orally once daily) in combination with ADT. The ADT regimen will mirror that of the apalutamide group, based on medical or surgical castration.

For both groups, dose modifications will follow protocol-specified rules, and safety will be closely monitored in accordance with National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

Study Schema

```mermaid  
graph TD  
 A[Screening] --> B[Randomization]  
 B --> C[Treatment Group 1]  
 C --> F[Follow-up]  
 B --> D[Treatment Group 2]  
 D --> F[Follow-up]  
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# 19.1 Population

STUDY POPULATION

Overview of Study Population

The study population will consist of male subjects diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). All participants must have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of grade 0 or 1, indicating that they are fully active or have some restrictions but can perform work of a light or sedentary nature. Subjects must present with distant metastatic disease, confirmed by a positive bone scan with at least one bone lesion visible via Technetium 99m (99mTc) scanning. In cases where only a single bone lesion is identified, confirmation of the metastasis via computed tomography (CT) or magnetic resonance imaging (MRI) is required.

Inclusion Criteria

1. • Male subjects aged 18 years or older with a confirmed diagnosis of mHSPC.
2. • ECOG performance status of 0 or 1.
3. • Evidence of metastatic disease as confirmed by a positive bone scan (≥1 bone lesion on 99mTc scan) or confirmation of solitary bone lesions using CT/MRI.
4. • Subjects may have received up to 6 cycles of docetaxel for mHSPC, with the final dose administered ≤2 months prior to randomization.
5. • Prior androgen deprivation therapy (ADT) for mHSPC should not exceed 6 months in duration prior to randomization.
6. • Subjects may have received a single course of radiation or surgical intervention for mHSPC.
7. • For localized prostate cancer, ADT duration must not exceed 3 years in total, with all treatments, including radiation therapy, prostatectomy, and systemic therapies, completed at least 1 year prior to randomization.

Exclusion Criteria

1. • Subjects with prior exposure to anti-androgens, other than ≤6 months of ADT for mHSPC or ≤3 years of ADT for localized prostate cancer (completed ≥1 year prior to randomization).
2. • Presence of brain metastases identified through imaging.
3. • Previous treatment with apalutamide or any investigational AR-targeting agents.
4. • Unresolved toxicities from prior therapies except for alopecia or Grade 1 peripheral neuropathy.
5. • History of seizures or conditions that may predispose to seizures.

Withdrawal Criteria

1. • Subjects who experience unacceptable treatment-related toxicity, clinical progression based on protocol-specified criteria, or request withdrawal from the study.
2. • Subjects may be withdrawn from the study by the investigator, in consultation with the study sponsor, if they fail to adhere to the study protocol requirements.

Replacement Policy

Subjects who withdraw prior to randomization or become ineligible during the screening phase may be replaced to meet the target enrollment of approximately 1,000 participants. However, once randomized, subjects who withdraw or are lost to follow-up will not be replaced to maintain the integrity of the randomization schema.

# 19.2 Procedures

Study Procedures

Overview  
This section outlines the procedures to be conducted during the study, comprising the screening, treatment, and follow-up phases. It details the specific activities required at each phase, the timing and frequency of these activities, and the responsible personnel for conducting them.

Screening/Baseline Procedures  
The screening phase will establish eligibility for study participation and will include the following procedures, conducted within 28 days prior to randomization:

1. • Informed Consent\*\*
2. • Obtain signed informed consent from the subject.
3. • Conducted by study coordinator or principal investigator.

2. \*\*Demographics and Medical History\*\*  
 - Collect subject's age, sex, ethnicity, medical history, and prior treatment details.  
 - Conducted by study coordinator or medical personnel.

3. \*\*Physical Examination\*\*  
 - Perform a complete physical examination.  
 - Conducted by a qualified healthcare professional.

4. \*\*Vital Signs\*\*  
 - Record blood pressure, heart rate, temperature, and respiratory rate.  
 - Conducted by nursing staff.

5. \*\*Laboratory Assessments\*\*  
 - Collect blood samples for hematology and clinical chemistry profiles.  
 - Conducted by phlebotomist or laboratory technician.

6. \*\*Disease Assessment\*\*  
 - Conduct imaging studies such as bone scans and CT/MRI to confirm metastatic disease.  
 - Conducted by a radiologist or qualified medical professional.

7. \*\*Inclusion/Exclusion Criteria Review\*\*  
 - Ensure the subject meets all inclusion and none of the exclusion criteria.  
 - Conducted by the principal investigator or designated study team member.

Treatment Phase Procedures  
Subjects will be administered the assigned treatment and monitored regularly. Activities during the treatment phase include:

1. • Drug Administration\*\*
2. • Apalutamide or matching placebo will be administered orally once daily.
3. • Conducted by study pharmacists or nursing staff.

2. \*\*Safety Monitoring\*\*  
 - Monitor for adverse events and record any new symptoms.  
 - Conducted by study nurses or investigators during clinic visits.

3. \*\*Efficacy Assessments\*\*  
 - Perform imaging studies for radiographic progression-free survival (rPFS) and collect survival data.  
 - Conducted by radiologists or designated medical personnel every assessment cycle.

4. \*\*Laboratory Tests\*\*  
 - Collect periodic blood samples for routine laboratory assessments and PK/PD analysis.  
 - Conducted by a phlebotomist or laboratory technician.

5. \*\*Quality of Life Assessments\*\*  
 - Utilize patient-reported outcome measures such as BPI-SF, BFI, and EQ-5D-5L.  
 - Conducted by study coordinators via structured interviews.

6. \*\*Adverse Event Monitoring\*\*  
 - Document and grade adverse events using NCI-CTCAE Version 4.03 criteria.  
 - Conducted by clinical staff throughout the treatment phase.

7. \*\*Concomitant Medication Review\*\*  
 - Record any medications taken by the subject during the study.  
 - Conducted by the study coordinator or pharmacy staff.

Follow-up Procedures  
Follow-up activities post-treatment discontinuation include:

1. • Safety Follow-up\*\*
2. • Conduct safety evaluations 30 days after the last dose.
3. • Conducted by study nurses or investigators.

2. \*\*Disease Assessment\*\*  
 - Continue monitoring disease progression every 4 months.  
 - Conducted by the clinical team.

3. \*\*Survival Status\*\*  
 - Collect data on survival and any subsequent therapies initiated.  
 - Conducted by study coordinators.

4. \*\*Subsequent Therapy Documentation\*\*  
 - Record the date and type of any new therapy for prostate cancer.  
 - Conducted by study coordinators or medical staff.

Safety Assessments  
Comprehensive safety evaluations will be conducted regularly, including:

1. • Physical Examinations\*\*
2. • Conducted at each clinic visit by healthcare professionals.
3. •
4. • Vital Signs\*\*
5. • Checked and recorded at each visit by nursing staff.
6. •
7. • Laboratory Tests\*\*
8. • Includes hematology, clinical chemistry, and other relevant tests as per schedule.
9. •
10. • Adverse Event Monitoring\*\*
11. • Ongoing throughout the study by clinical investigators.
12. • ECG Monitoring\*\*
13. • Performed when indicated, conducted by trained medical staff.

Efficacy Assessments  
The efficacy of the intervention will be evaluated through:

1. • Disease-specific Assessments\*\*
2. • Radiographic progression and survival metrics.
3. •
4. • Response Evaluation\*\*
5. • Based on RECIST 1.1 criteria and other relevant markers.
6. •
7. • Patient-Reported Outcomes\*\*
8. • Utilize standardized questionnaires to evaluate quality of life and symptoms.
9. • Quality of Life Measures\*\*
10. • Conducted through validated PRO instruments.

Laboratory Assessments  
Laboratory assessments will include:

1. • Hematology and Clinical Chemistry\*\*
2. • Routine analysis as per protocol schedule.
3. • Biomarker Sampling\*\*
4. • Collect samples for exploratory biomarker analysis.
5. • PK/PD Assessments\*\*
6. • Pre-dose samples collected on specified cycles.

Other Assessments  
Additional assessments include:

1. • Medical Resource Utilization\*\*
2. • Data collection on healthcare usage during treatment for potential future modeling.
3. • Biomarker and Genetic Analysis\*\*
4. • Exploratory studies to identify predictive markers of response and resistance.

All procedures must adhere to the study protocol and any amendments, and deviations must be documented and justified as per regulatory requirements.

# 28.1 Statistical

Statistical Analysis

Statistical Hypotheses

The primary hypotheses for this study are centered on evaluating the efficacy of apalutamide plus androgen deprivation therapy (ADT) compared to ADT alone in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). The null hypotheses for the dual-primary endpoints are:   
- H0 for radiographic progression-free survival (rPFS): There is no difference in rPFS between the treatment arm (apalutamide plus ADT) and the control arm (ADT plus placebo).  
- H0 for overall survival (OS): There is no difference in OS between the treatment arm and the control arm.

The study will utilize a type I error rate of 5%, with significance levels of 0.005 allocated for the rPFS endpoint and 0.045 for the OS endpoint. The study is considered successful if at least one of the dual-primary endpoints is statistically significant.

Sample Size Determination

The sample size determination is designed to ensure adequate power to detect clinically meaningful differences in the primary endpoints. The study anticipates requiring approximately 368 rPFS events to achieve at least 85% power for detecting a hazard ratio (HR) of 0.67, assuming a median rPFS of 20 months for the control group compared to 30 months for the treatment group, at a two-tailed significance level of 0.005. Additionally, around 410 death events will be necessary to detect a HR of 0.75 for OS, assuming a median OS of 44 months for the control group, providing approximately 80% power at a two-tailed significance level of 0.045. The expected enrollment is approximately 1,000 subjects, with the total study duration estimated at 54 months.

Analysis Populations

1. • Intent-to-Treat (ITT) Population\*\*: This includes all randomized subjects and will be used for the primary analysis of efficacy endpoints (rPFS and OS).
2. • Safety Population\*\*: Consists of all subjects who receive at least one dose of the study drug and will be employed for safety evaluations.

Statistical Methods

Efficacy analyses for time-to-event endpoints such as rPFS and OS will employ the Kaplan-Meier product limit method to estimate survival functions. Cox proportional hazards models will be used to estimate hazard ratios and their 95% confidence intervals. For secondary endpoints, appropriate statistical tests (such as log-rank tests or Wilcoxon rank-sum tests) will be used. Multiplicity adjustments will ensure control over type I error across the dual-primary endpoints. Secondary endpoints and exploratory analyses will be conducted in a hypothesis-generating framework without formal adjustment for multiplicity unless otherwise stated.

Interim Analyses

Two interim analyses are pre-planned for the OS dual-primary endpoint, occurring after approximately 50% (around 205 events) and 70% (around 287 events) of the required 410 death events have been observed. The final analysis of the rPFS endpoint will be conducted at the time of the first interim OS analysis. These analyses will utilize a group-sequential testing approach with appropriate significance level adjustments to maintain the study-wide alpha level.

Missing Data Handling

Missing data will be addressed using multiple imputation techniques and sensitivity analyses to assess the robustness of the primary findings. Survival analyses will treat subjects lost to follow-up without documented endpoints as censored data at the time of last contact unless death is confirmed post last contact.

This statistical analysis section defines the framework for evaluating the efficacy and safety of apalutamide plus ADT in mHSPC. Detailed methodologies and adjustments will be further specified in the Statistical Analysis Plan (SAP), developed before unblinding the study results.

# 35.1 Safety

Safety

Safety Parameters  
Safety evaluations in this study will include the assessment of adverse events (AEs), clinical laboratory tests, vital signs measurements (such as blood pressure), and physical examinations, as well as the Eastern Cooperative Oncology Group (ECOG) performance status. These assessments are crucial for determining the safety profile of apalutamide when combined with androgen deprivation therapy (ADT) in subjects with metastatic hormone-sensitive prostate cancer (mHSPC).

Adverse Event Definitions  
Adverse events are defined as any untoward medical occurrence in a subject who is administered the study drug, which does not necessarily have a causal relationship with the treatment. AEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, and their severity will be classified as follows:  
- 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 indicated.  
- Grade 5: Death related to AE.

1. • Activities of Daily Living (ADL)
2. • Self-Care Activities of Daily Living

Adverse Event Reporting  
All treatment-emergent AEs will be reported from the time that informed consent is signed until 30 days after the last dose of the study drug. Serious adverse events (SAEs) must be reported within 24 hours to ensure prompt regulatory notification and subject safety. The occurrence, intensity, relationship to study drug, and outcome of each AE will be documented and submitted according to regulatory requirements.

Safety Monitoring  
Safety will be closely monitored throughout the study. Investigators will perform regular assessments, including laboratory tests and reviews of ECOG performance status. Any significant findings will be evaluated to determine if they warrant dose adjustments or discontinuation of the study drug as outlined in the dose modification guidelines. The safety data will be reviewed in aggregate by the sponsor and an Independent Data Monitoring Committee (IDMC) to identify any emerging safety concerns.

Risk Management  
Potential risks associated with apalutamide therapy will be managed through pre-defined dose modification rules and continuous safety surveillance. Subjects who experience unacceptable toxicity may receive dose adjustments or discontinue treatment based on the severity and clinical significance of the toxicity, as per protocol specifications.

Data Monitoring Committee  
An Independent Data Monitoring Committee (IDMC) will oversee the safety data throughout the clinical trial. The IDMC will perform regular safety reviews at planned intervals and provide recommendations to the sponsor regarding the continuation, modification, or termination of the study based on interim safety and efficacy data.

Stopping Rules  
Stopping rules for the study are in place and will be implemented if there is compelling evidence of significant harm or lack of efficacy. The IDMC will have the authority to recommend halting the study in case of an unacceptable risk-to-benefit ratio or based on pre-specified interim analysis criteria that indicate a lack of efficacy.

The safety section will provide comprehensive oversight and management procedures to ensure subject safety and the integrity of the study are maintained throughout its duration. The adherence to these standardized procedures will help mitigate potential risks and facilitate prompt action in response to any safety concerns observed during the trial.