SYNOPSIS

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of JNJ-56021927 in Subjects with High-risk, Localized or Locally Advanced Prostate Cancer Receiving Treatment with Primary Radiation Therapy

Apalutamide (JNJ-56021927, also referred to as ARN-509) is an orally available, non-steroidal selective antagonist of the androgen receptor (AR). It is currently being developed for the treatment of both hormone-sensitive and castration-resistant prostate cancer (CRPC).

OBJECTIVES AND HYPOTHESIS

Primary Objective

- To determine if apalutamide plus gonadotropin releasing hormone (GnRH) agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary radiation therapy (RT) results in an improvement of metastasis-free survival (MFS) evaluated by blinded independent central review (BICR)

Secondary Objectives

- To characterize the safety profile of apalutamide plus GnRH agonist in subjects with high-risk localized or locally advanced prostate cancer receiving primary RT
- To determine if apalutamide plus GnRH agonist in subjects with high-risk localized or locally advanced prostate cancer receiving primary RT results in an improvement of:
    - Time to local-regional recurrence
    - Time to castration-resistant prostate cancer (CRPC)
    - Time to distant metastasis
    - Overall survival (OS)

Other Objectives

- To determine if apalutamide plus GnRH agonist in subjects with high-risk localized or locally advanced prostate cancer receiving primary RT delays the development of:
    - Skeletal-related events (SREs)
    - Disease progression-related pain
    - Biochemical failure (BCF)
    - Progression/relapse on or after the next line of treatment
- To evaluate the effect of apalutamide plus GnRH agonist in subjects with high-risk localized or locally advanced prostate cancer receiving primary RT on the normalization of testosterone
- To evaluate the effect of apalutamide plus GnRH agonist in subjects with high-risk localized or locally advanced prostate cancer receiving primary RT on patient relevant outcomes including symptoms, function, and health-related quality of life
- To characterize the population pharmacokinetics (PK) of apalutamide
- To demonstrate the cost benefit of apalutamide plus GnRH agonist compared with GnRH agonist in subjects with high-risk localized or locally advanced prostate cancer receiving primary RT
- To evaluate the effect on PSA response of apalutamide plus GnRH agonist compared with GnRH agonist in subjects with high-risk localized or locally advanced prostate cancer receiving primary RT
- To evaluate potential biomarkers predictive of response and resistance to apalutamide treatment.

Hypothesis

Metastasis-free survival (MFS) evaluated by BICR is improved with apalutamide plus GnRH agonist compared with GnRH agonist in subjects with high-risk localized or locally advanced prostate cancer receiving primary RT.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter study of apalutamide plus GnRH agonist compared with GnRH agonist in subjects with high-risk localized or locally advanced prostate cancer receiving primary RT. All subjects will receive active treatment with a GnRH agonist and primary RT as standard of care. Approximately 1,500 subjects will be randomly assigned in a 1:1 ratio to receive apalutamide or control. Randomization will be stratified by Gleason score (7 or ≥8), N0 or N1, brachytherapy boost (yes or no), and region (NA, EU, or Other Countries).

The study will include a Screening Phase, Treatment Phase, a Posttreatment Phase and a Long-term Follow-up Phase.

The Screening Phase will allow for assessment of subject eligibility, demographics, PSA, and testosterone up to 35 days prior to randomization.

The Treatment Phase will include 30 cycles of therapy (each cycle is 28 days +/-2 days through C4 and +/-6 days from C5 onward).

All subjects will receive GnRH agonist therapy throughout the Treatment Phase (GnRH agonist may be started up to 3 months prior to C1D1, but must be started by C1D1):

- Neoadjuvant to primary RT (2, 28-day cycles [Cycle 1, Day 1; C1D1 to C2D28])
  - Investigational group will receive apalutamide plus bicalutamide placebo daily
  - Control group will receive bicalutamide plus apalutamide placebo daily
- Concurrent with primary RT (2, 28-day cycles [C3D1 to C4D28])
  - Investigational group will receive apalutamide plus bicalutamide placebo daily
  - Control group will receive bicalutamide plus apalutamide placebo daily

  NOTE: Bicalutamide/placebo will stop on C4D28, even if RT continues after that day.
- Adjuvant to primary RT (26, 28-day cycles [C5D1 to C30D28])
  - Investigational group will receive apalutamide daily
  - Control group will receive apalutamide placebo daily

The Posttreatment Phase will begin after a subject completes the Treatment Phase and the End-of-Treatment Visit. The Posttreatment Phase will continue until documented distant metastasis by BICR, death, lost to follow-up, withdrawal of consent or termination of the study by the sponsor, whichever occurs first.

The Long-term Follow-up Phase will begin after a subject completes the Posttreatment Phase and End-of-Posttreatment Phase Visit. The Long-term Follow-up Phase will continue until death, lost to follow-up, withdrawal of consent or termination of the study by the sponsor, whichever occurs first.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. The IDMC will review the safety and efficacy data during the study and make recommendations as to the further conduct of the study.

SUBJECT POPULATION

The study population will be composed of men ≥18 years of age with high-risk localized or locally advanced prostate cancer (with or without N1 disease) defined by 1 of the following at diagnosis: 1) Gleason score of ≥8 and ≥cT2c or 2) Gleason score of 7 and PSA ≥20 ng/mL and ≥cT2c. Subjects must not have undergone prior systemic (eg, chemotherapy) or procedural (eg, radical prostatectomy, cryotherapy) treatment for prostate cancer and be indicated and planned for primary RT. Key inclusion criteria also include an Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 or 1, and Charlson comorbidity index (CCI) of ≤3. Key exclusion criteria include distant metastasis, a history of bilateral orchiectomy, pelvic radiation, or seizure.

DOSAGE AND ADMINISTRATION

Subjects will receive 30 cycles (each cycle is 28 days +/-2 days through C4 and +/-6 days from C5 onward) of study drug during the Treatment Phase as described below. Cycle 1 Day 1 of treatment must start within 3 days after randomization. An End-of-Treatment visit will take place within 30 days after the last dose of study drug. The table below summarizes the treatment groups and timing of therapies:

Timing		Investigational Group[a,b]	Control Group[a,b]
Investigational Group	Control Group	apalutamide (240 mg) and bicalutamide placebo	Bicalutamide (50 mg) and apalutamide placebo
Cycles 3-4	Concurrent with RT		
Cycles 5-30	Adjuvant to RT	apalutamide (240 mg)	apalutamide placebo

GnRH=gonadotropin releasing hormone; RT=radiation therapy
a. All subjects will receive GnRH agonist therapy throughout the Treatment Phase (GnRH agonist may be started up to 3 months prior to C1D1, but must be started by C1D1)
b. All study drug is taken orally and daily (QD)
NOTE: Bicalutamide/placebo will stop on C4D28, even if RT continues after that day

Apalutamide, bicalutamide, and their corresponding placebos may be taken with or without food.

EFFICACY EVALUATIONS/ENDPOINTS

To assess for distant metastasis, bone scan and chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) are required at the time of BCF (Phoenix definition: 2 ng/mL increase in PSA over the nadir achieved after completion of RT treatment) and will continue as outlined in the Time and Events Schedule until documented distant metastasis by BICR or death. All clinically indicated unscheduled imaging must be reviewed by BICR. The primary endpoint of the study is MFS. The secondary endpoints are the time to local-regional recurrence, time to CRPC, time to distant metastasis, and OS.

Where possible, a PET scan must also be performed utilizing a prostate cancer-specific tracer such as, for example, PSMA-targeting tracer, ^{18}F-fluciclovine, or ^{11}C-choline. Conventional imaging must continue every 6 months (±4 weeks) until documented distant metastasis by BICR or death. PET will be performed at the same interval as conventional imaging until either the PET scan reveals distant metastases per local review, or BICR of conventional imaging indicates distant metastasis, whichever occurs first. In the event that the PET scan reveals distant metastases and the BICR of conventional imaging does not, conventional imaging must be continued every 6 months until distant metastasis are seen by BICR.

The PROs included in this study are the FACT-P and the EQ-5D-5L. These questionnaires will be completed at the time points specified in the Time and Events Schedule.

PHARMACOKINETIC EVALUATIONS

Population PK assessments will be performed on approximately 750 subjects. Pre-dose blood samples for population PK will be collected as described in the Laboratory Manual.

BIOMARKER EVALUATIONS

Archival formalin-fixed paraffin-embedded (FFPE) tumor blocks or slides will be collected from all subjects consenting to genomic research to evaluate expression of high-risk markers and molecular classifiers such as OncotypeDx. Androgen-receptor splice variant 7 (AR-V7) expression and AR_{F876L} levels will be evaluated.

MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Duration of medical care encounters, duration of hospitalization, the number and type of diagnostic and therapeutic tests and procedures, and outpatient medical encounters and treatments will be collected and may be used to conduct exploratory economic analyses.

SAFETY EVALUATIONS

Safety evaluations will include adverse events (AEs) (incidence, intensity, and type), vital sign measurements, clinical laboratory test results, and limited physical examinations.

STATISTICAL METHODS

Sample Size Determination

Assuming a median MFS of 5.0 years in the control group, approximately 445 MFS events will be required to provide approximately 85% power to detect a 1.7-year improvement in median MFS (hazard ratio [HR] 0.75) at the 2-sided significance level of 0.05 and with a 1:1 randomization ratio. The study is also designed to evaluate the secondary endpoint of OS. Assuming a median OS of 13.9 years in the control group, approximately 446 death events will be required to provide approximately 80% power to detect a 4.5-year improvement in median OS (HR 0.76) at the 2-sided significance level of 0.05 and with a 1:1 randomization ratio. With an enrollment rate of 375 subjects per year, a sample size of 1,500 subjects will allow 446 death events to be observed in approximately 10 years from the randomization of the first subject.

Efficacy Analysis

For the primary endpoint, MFS, the final analysis of MFS will be performed after approximately 445 MFS events are observed or at the time of the first OS IA, whichever occurs later, but no later than approximately 7 years from the randomization of the first subject. For the secondary endpoint of OS, 2 interim analyses (IAs) are planned and will occur when approximately 223 and 335 death events are observed.

The distribution of time to event endpoints will be estimated using the Kaplan-Meier method. The comparison of time to event endpoints will be based on log-rank test, and the hazard ratio and corresponding confidence intervals will be estimated using a Cox proportional hazards model. The efficacy analyses will be performed on the Intent-to-Treat (ITT) Analysis Set, which includes all randomized subjects irrespective of whether or not treatment was administered.

Pharmacokinetic Analysis

Descriptive statistics will be provided for the study drug pre-dose plasma concentrations. Population PK analysis of plasma concentration-time data of apalutamide will be performed.

Safety Analysis

The safety parameters to be analyzed are the incidence, intensity, and type of AEs, vital signs, clinical laboratory results, and limited physical examinations (abnormalities will be recorded as AEs). The safety analyses will be performed in the Safety Analysis Set, which includes all randomized subjects who received at least 1 dose of study drug, with treatment assignments designated according to actual study treatment received.