Janssen Research & Development *

Statistical Analysis Plan

The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men with Biochemically Relapsed Hormone Sensitive Prostate Cancer

Protocol ARN-509-002; Phase 2

JNJ-56021927 (apalutamide)

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AMENDMENT HISTORY

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ABBREVIATIONS

ADT	androgen deprivation therapy
AlkP	alkaline phosphatase
ALT	alanine aminotransferase
AR	androgen receptor
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASTRO	American Society for Therapeutic Radiology and Oncology
BCR	biochemical relapse
BMD	bone mineral density
BMI	body mass index
CAB	combined androgen blockade
CBC	complete blood count
CI	confidence interval
eCRF	electronic case report form
CRPC	castrate-resistant prostate cancer
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAO	data as observed
DEXA	dual energy x-ray absorptiometry
DHT	dihydrotestosterone
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
HDL	high-density lipoprotein
HR	hazard ratio
IADT	intermittent androgen deprivation therapy
ITT	intent-to-treat
mITT	modified intent-to-treat
LDL	low-density lipoprotein
LHRH	luteinizing hormone-releasing hormone
LHRHa	LHRH agonist
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
OS	overall survival
PAB	peripheral androgen blockade
PBMC	peripheral blood mononuclear cells
PQC	product quality complaint
PSA	prostate-specific antigen

PSADT	PSA doubling time
QOL	quality of life
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
TSH	thyroid stimulating hormone
SHIM	Sexual Health Inventory for Men

1. INTRODUCTION

This document describes the planned statistical analyses for study protocol ARN-509-002 **(**The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men with Biochemically Relapsed (BCR) Hormone Sensitive Prostate Cancer). This statistical analysis plan (SAP) is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the clinical study report.

1.1 Trial objectives

1.1.1 Primary Objective(s)

- To test for superiority of apalutamide monotherapy vs. LHRHa monotherapy in prostate cancer patients with BCR by comparing the mean change from baseline in quality of life (QOL) as measured by total FACT-P score over a period of 12 months of therapy.
- To test for non-inferiority of the combination apalutamide + LHRHa vs. LHRHa monotherapy in prostate cancer patients with BCR by comparing the mean change from baseline in QOL as measured by total FACT-P score over a period of 12 months of therapy.

1.1.2 Secondary Objectives

- To compare (a) apalutamide monotherapy vs. LHRHa monotherapy and (b) combination apalutamide + LHRHa vs. LHRHa monotherapy with regards to change over time in QOL as measured by EORTC QLQ-C30 and SHIM.
- To compare (a) apalutamide monotherapy vs. LHRHa monotherapy and (b) combination apalutamide + LHRHa vs. LHRHa monotherapy with regards to PSA modulation.
- To compare (a) APALUTAMIDE monotherapy vs. LHRHa monotherapy and (b) combination apalutamide + LHRHa vs. LHRHa monotherapy with regards to metabolic and hormonal effects.

1.1.3 Other Objectives

- To characterize the safety profile of apalutamide monotherapy and in combination with LHRHa.
- To conduct biomarker analyses from all 3 treatment groups.

1.2 Trial Design

This is a randomized, multicenter, open-label, 3-arm phase 2 clinical trial evaluating 12 months of treatment with luteinizing hormone releasing hormone agonist (LHRHa) monotherapy, apalutamide monotherapy, or the combination of apalutamide and LHRHa, in men with non-metastatic BCR prostate cancer with rapidly rising PSA levels after prior definitive therapy for localized prostate cancer. Enrollment of approximately 90 subjects (30 per arm) is planned for this study. Patients will be followed for safety and efficacy as per the schedule of assessments and will remain on study treatment until the time of PSA or radiographic progression or initiation of non-protocol therapy or subject/physician withdrawal from the study, whichever occurs first. Subjects will be stratified by PSADT (< 6 months vs. 6-12 months) and age (≤ 70 vs. > 70). There will be 2 periods of 12 months each in the 24-month-long treatment period: 1) an on-

therapy period lasting 12 months, during which time subjects receive randomly assigned protocol therapy, and 2) an off-therapy observation period also lasting 12 months. If there is no evidence of PSA or radiographic progression after 24 months from Day 1 of the on-treatment period, subjects will enter a follow-up period. Subjects will remain on study until the time of PSA or radiographic progression or initiation of non-protocol therapy or subject/physician withdrawal from the study, whichever occurs first. Patients who discontinue before completion of the on-therapy period in the absence of progressive disease will enter the off-therapy observation period of the study.

1.3 Statistical Hypotheses for Trial Objectives

1.3.1 Hypothesis 1

For men with non-metastatic, non-castrate prostate cancer who have rapidly rising PSA levels after definitive local therapy, treatment with 12 months of apalutamide monotherapy compared with 12 months of ADT in the form of LHRHa monotherapy will result in better preservation of QOL as measured by the FACT-P scale. Parallel and exploratory findings demonstrating comparable PSA suppression, and less negative impact on the metabolic profile (including measurements of fasting lipid profiles, insulin resistance, and bone mineral density) of subjects who receive apalutamide monotherapy as opposed to therapy with an LHRHa would form the preliminary basis for further definitive study of apalutamide monotherapy in biochemically relapsed prostate cancer.

1.3.2 Hypothesis 2

For men with non-metastatic, non-castrate prostate cancer who have rapidly rising PSA levels after definitive local therapy, treatment with 12 months of therapy with the combination of apalutamide + LHRHa, compared with 12 months of therapy with LHRHa alone, will not be associated with a clinically significant worsening of QOL as measured by the FACT-P scale. Parallel, exploratory findings suggesting more durable PSA suppression coupled with adequate serum testosterone recovery, favorable PSA modulation with respect to PSA nadir and time to PSA progression, along with acceptable safety data, would form the preliminary basis for larger clinical trials testing the combination of apalutamide plus LHRHa vs. LHRHa alone in the hormone sensitive prostate cancer disease setting.

1.4 Sample Size Justification

The expected mean decline in FACT-P score and within group standard deviation for the control arm treated with 12 months of LHRHa monotherapy are 4-8 and 8-12 points, respectively, based on prior studies of measuring QOL using FACT-P among men treated with ADT [1, 2, 3]. A change in total FACT-P score that is clinically meaningful and impacts treatment in prior studies ranges from 5-8 points depending on cancer subtype [4]. Approximately 30 subjects will be randomized to each of the 3 treatment arms for this comparison. Accounting for a dropout/questionnaire non-completion rate of 10%, this will allow for 27 evaluable subjects per study arm. For the comparison of the mean change in FACT-P score between apalutamide monotherapy and LHRHa monotherapy, this sample size has 80% power to detect an effect size of at least 0.86, corresponding to a difference of 7.5 points in mean 12 month change in FACT-P

score between treatment groups with a common standard deviation for the change in each arm of 8.7 which is similar to the reported standard deviation for LHRHa monotherapy. This is based upon a 2-group t test, using a bi-directional level of significance of 0.025 (adjusted for 2 comparisons). To test for non-inferiority in QOL with apalutamide + LHRHa compared with LHRHa monotherapy, inferior QOL is defined as a greater than 7-point difference in mean change in FACT-P score between the treatment groups and the common standard deviation is again assumed to be 8.7. This sample size has 82% power to reject the null hypothesis of a difference in mean score and accept the alternative hypothesis of non-inferiority with an effect size of at least 0.81, using a 2-group t-test with 2-sided α of 0.025.

1.5 Randomization and Blinding

1.5.1 Randomization

Upon verification of inclusion and exclusion criteria, eligible patients will be centrally randomized in a 1:1:1 ratio to apalutamide monotherapy, apalutamide + LHRHa, or LHRHa monotherapy. The randomization will be stratified as follows:

- PSADT (< 6 months vs. 6-12 months)
- Age at study entry (≤ 70 years vs. > 70 years)

Balance in treatment assignment will be achieved using a randomized block design. Randomization will be carried out via computer generated random assignment. All subjects must commence treatment within (5 calendar days) of randomization. Study sites will email the Eligibility Checklist to the sponsor to obtain the subject's treatment assignment. Once subject eligibility is confirmed by the sponsor, an email with the treatment assignment number will be provided to the study site.

1.5.2 Blinding

This is an open-label study.

2. GENERAL ANALYSIS DEFINITIONS

Study Day: For safety, study day will be calculated in reference to the date of first dose. Study Day 1 corresponds to the date the subject receives first dose of study drug. For efficacy analysis, Study Day will be calculated in reference to the date of randomization.

Cycle: For the purpose of the study, a treatment cycle is defined as 28 days. Subjects will begin taking study drug on Day 1 of Cycle 1. All subjects should be following a 28-day, 28-day, 35-day schedule for their monthly visit (i.e., the 1st post-Day 1 visit is scheduled for 28 days later, the 2nd post-Day 1 visit is scheduled for 28+28 days later, the 3rd post-Day 1 visit is scheduled for 28+28+35 days later, the 4th post-Day 1 visit is scheduled for 28+28+35+28 days later, etc).

Baseline Value: Unless otherwise specified, the baseline value will be defined as the closest measurement prior to or on the day of the first dose of study drug. Change from baseline will be defined as (post-baseline value – baseline value).

Treatment Duration: Treatment duration will be defined as the duration of time from the date of the first dose of study drug to the date of last dose of study drug.

Time to event: Time to event calculations will be defined as the time from randomization to the date of the event of interest. Time to event or duration of event endpoints will be based on the actual date of the event, not visit number or visit label.

2.1 Analysis Sets

The following analysis sets will be used for this study:

Intent-to-Treat (ITT) Population: The ITT population includes all randomized subjects and will be classified according to their assigned treatment group, regardless of the actual treatment received. Subject disposition and efficacy analyses will be performed on data from the ITT population.

Safety Population: The safety population includes all subjects who received at least 1 dose of study drug as actually treated.

Modified Intent-to-Treat Population (mITT): For outcomes related to testosterone recovery, subjects who withdrew from the study prior to 24 months after day 1 will be excluded from the analysis.

2.2 Study Period I: On-therapy Period (Months 1-12)

The 24-month study treatment period will be divided into two 12-month periods: the on-therapy period during which subjects receive protocol therapy (apalutamide monotherapy, apalutamide + LHRHa, or LHRHa monotherapy). Subjects will commence protocol therapy on Day 1 of the on-therapy period. The study timeline is defined as Day 1 = first dose of study treatment. Subsequent study time points will be defined based on study calendar, irrespective of subsequent dose delays/interruptions.

Subjects will be treated with protocol therapy for 12 months, or until disease progression (either by PSA or radiographic), unacceptable toxicity, subject/physician withdrawal, or initiation of non-protocol therapy. PSA progression is defined as an increase in PSA to > 50% of the baseline value or an increase of > 2 ng/mL above the nadir, whichever is higher confirmed by repeat measurement at least 2 weeks later. Radiographic progression is defined as the detection of new metastasis on either bone scan or cross-sectional imaging (CT or MRI) [5]. If subjects develop progressive disease (either by PSA or radiographic) while receiving protocol therapy, they will discontinue protocol therapy, have a Progression Visit, and be treated as per individual investigator discretion.

If there is no evidence of disease progression (by serum PSA or radiographically) after 12 months of protocol therapy or if subject discontinues treatment before 12 months of protocol therapy for reasons other than disease progression, subjects will enter the 12-month Off-therapy Observation Period. Continuation of hormone therapy or initiation of any form of anti-cancer

therapy in the absence of PSA or radiographic progression will be considered non-protocol therapy and will result in study removal.

Efforts will be made to ensure that subjects who develop progressive disease before 12 months of therapy still complete QOL scales at 3 and 12 months.

2.2.1 Day 1 of Study Treatment

Patients will return to study site for a history and physical exam including weight, measurement of serum PSA, and dispensing of study drug(s), including the first injection of LHRHa and 1-month supply of apalutamide for subjects randomized to those arms. Collection of optional samples (samples for banking, archival FFPE blocks or slides for transcriptome profiling (RNAseq), whole blood for RNA testing, and plasma for biomarker testing) should occur before pre-dose.

2.2.2 LHRH Agonist

For subjects randomized to either the LHRHa monotherapy or the LHRHa + apalutamide combination treatment arms, the choice and schedule of LHRHa will be up to individual investigator's discretion and will be administered for a total of 12 months of therapy in the absence of disease progression or unacceptable toxicity. No change in dosing schedule of LHRHa will be permitted once the subject has commenced protocol therapy. For example, the use of every 3 month subcutaneously injected LHRHa would be administered on Day 1 and on Months 3, 6, and 9. The use of LHRH antagonists (ie, degarelix) will not be permitted. No dose reductions or interruptions of LHRHa will be permitted. If a subject does not receive a scheduled LHRHa injection within ±7 days of the scheduled due date for injection, he will be removed from study. Subjects on the LHRHa monotherapy arm will not be allowed to crossover to receive apalutamide.

2.2.3 Apalutamide

Subjects randomized to either of the two apalutamide-containing arms will receive apalutamide dosed orally on a daily basis with or without food. The starting dose of apalutamide is 240 mg/day. With Amendment 7 (Version 8.0), subjects who are receiving the soft gel capsules will switch to the tablet formulation. Ongoing subjects on a reduced dose of capsules should continue with that dose with lowest allowed dose being 120 mg. Dose delays and dose reductions will be permitted as per guidelines outlined in the study protocol/

2.2.4 Safety Assessment

Subjects will be assessed for adverse events at each monthly clinic visit during the On-therapy Period. Adverse event collection starts with the signing of the ICF. Adverse events will be graded according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (available at http://ctep.cancer.gov). See the study protocol for attribution of adverse events. Dose modifications (interruptions, reductions or both) for apalutamide, will be allowed as per guidelines outlined in the study protocol.

2.2.5 Quality of Life

The FACT-P, EORTC QLQ-C30/QLQ-PR25, and SHIM questionnaires will be completed at the end of Month 3 and Month 12 or at the time of PSA or radiographic progression (if occurs before Month 12, every effort will be made to obtain the 12-month questionnaires for those who discontinue before 12 months).

2.2.6 Laboratory Assessments

Subjects who experience disease progression (PSA or radiographically) before the end of 12 months should complete laboratory assessments at the Progression Visit as outlined in the Study Schedule. During treatment, laboratory assessments include the following:

- Serum PSA level measured by ultrasensitive assay at the end of each month
- Complete blood count including differential and platelet count at the end of Months 3, 6, 9, and 12 of protocol therapy.
- Total bilirubin, alkaline phosphatase, AST, ALT at the end of Months 3, 6, 9, and 12.
- TSH at the end of Months 3, 6, 9, and 12.
- Fasting glucose, fasting lipid panel (total cholesterol, LDL, HDL, triglyceride), and hemoglobin A1C at the end of Months 3, 6, 9, and 12.
- Peripheral blood collection for measurement of serum testosterone, DHT, estradiol, and fasting serum insulin levels at the end of Months 3, 6, 9, and 12.
- Peripheral blood and urine collection for banking of, serum, plasma, and urine at the end of Months 3, 6, 9, and 12 of protocol therapy (optional).
- Whole blood collected for PAXgene analysis (optional) on Day 1 and end of Month 12

2.2.7 Radiographic Assessments

A whole-body nuclear bone scan, along with cross-sectional imaging of the abdomen/pelvis (CT or MRI) will be obtained as prompted by signs and symptoms of metastatic disease and at the time of PSA progression. DEXA scan measuring BMD at the femoral neck, and lumbar spine will be obtained after 12 months of protocol therapy or at the time of PSA or radiographic progression (if occurs before Month 12, see Progression Visit in Study Schedule).

Subjects who are intolerant of IV CT contrast agents may have CT scans performed with oral contrast or without, if method is identical each time new scans are done. There will be no central reading of the scans and radiographic progression will be based upon investigator assessment.

2.3 Study Period II: Off-therapy Observation Period (Months 13-24)

Subjects without progressive disease (by PSA or radiographic) after 12 months of protocol therapy will stop protocol therapy and enter the Off-therapy Observation Period from Month 13 to Month 24. Continuation of hormonal therapy or initiation of any other of anti-cancer therapy in the absence of PSA or radiographic progression will be considered non-protocol therapy and

will result in study removal. Use of concomitant medications, which may affect serum PSA will not be permitted.

Subjects who develop either PSA or radiographic progression during the Off-therapy Observation Period will have a Progression Visit and be treated as per individual investigator discretion. Efforts will be made to ensure that subjects who develop progressive disease (PSA or radiographic) or discontinue in the absence of progressive disease before 24 months still complete QOL scales after 24 months as prespecified in the study protocol.

2.3.1 Safety Assessment

Subjects will be assessed for adverse events at clinic visits at the end of every 2 months during the Off-therapy Observation Period.

2.3.2 Quality of Life

The FACT-P, EORTC QLQ-C30/QLQ-PR25, and SHIM questionnaires will be completed at the time of progression (PSA or radiographic) or after 24 months.

2.3.3 Laboratory Assessments

Subjects who experience disease progression (PSA or radiographic) before the end of 24 months should complete laboratory assessments at the Progression Visit as outlined in the Study Schedule. During the Off-therapy Follow up Period laboratory assessments include the following:

- Serum PSA level at the end of every 2 months.
- Peripheral blood collection for measurement of serum testosterone levels at the end of every 2 months.
- Fasting glucose, fasting lipid panel (total cholesterol, LDL, HDL, triglyceride), and hemoglobin A1C at the end of Months 18 and 24.
- Peripheral blood collection for measurement of fasting serum insulin at the end of Months 18 and 24.

2.3.4 Radiographic Assessment

A whole-body nuclear bone scan, along with cross-sectional imaging of the abdomen/pelvis (CT or MRI; with IV contrast per individual investigator discretion), will be obtained as prompted by signs and symptoms of metastatic disease and at the time of PSA progression. Subjects who are intolerant of IV CT contrast agents may have CT scans performed with oral contrast or without, as long as method is identical each time new scans are done There will be no central reading of the scans and radiographic progression will be based upon investigator assessment.

2.4 Follow Up Period (Month 25+)

Subjects without progressive disease (PSA or radiographic) at end of 24 months will enter a Follow-up Period. During this period, subjects will be followed by history and physical exam, serum PSA, and testosterone levels every 3 months. Subjects who develop PSA or radiographic

progression or initiate non-protocol therapy will be removed from study and treated as per individual investigator discretion. If no progressive disease occurred during Months 1 to 24 and it occurs during the Follow-up Period, whole blood RNA and plasma sample collections for biomarker testing should be collected from subjects who consented to this optional sample collection.

3. INTERIM ANALYSIS

No interim analysis will be planned for efficacy due to the expected rate of accrual, the primary endpoint being analyzed, and total sample size. An interim safety review will be performed after 20 subjects have completed at least 1 month of therapy with either apalutamide monotherapy or apalutamide + LHRHa. If there are more than 5 subjects with Grade 3 or higher toxicities not related to ADT (anemia, fatigue, gynecomastia, hot flushes, decreased libido, erectile dysfunction, mood changes, and weight gain), that the study investigator deems as possibly, probably, or definitely treatment-related, the study will be terminated. This indicates that at least 30% of the subjects had unacceptable toxicities. If accrual is completed and all 60 subjects were treated with apalutamide (with or without LHRHa) and if unacceptable toxicity is > 30%, then the exact 95% lower bound for unacceptable toxicity of 30% would be 20.4%. Study enrollment will continue during the interim safety review.

4. SUBJECT INFORMATION

4.1 Demographics and Baseline Characteristics

The following will be summarized by treatment group and overall using the ITT population:

- Age, race, ethnicity, height, and weight.
- Baseline ECOG performance status
- Baseline PSA value
- Number of years since diagnosis of prostate cancer
- Gleason grade/clinical stage/pathologic stage (if prior prostatectomy)/PSA at the time of diagnosis
- Fasting glucose, fasting lipid panel (total cholesterol, LDL, HDL, triglyceride), and hemoglobin A1C
- Use of (neo) adjuvant ADT and time interval since prior ADT (if applicable)
- Type and date(s) of definitive local therapy (radical prostatectomy and/or radiation therapy)
- Time interval from definitive therapy to biochemical relapse to study entry
- PSA doubling time at the time of study entry
- QOL as measured by FACT-P, EORTC QLQ-C30/QLQ-PR25, and SHIM scores at study entry

4.2 Disposition Information

Subject enrollment and disposition will be summarized by treatment group. The summary of subject disposition will display the number of subjects randomized, and the numbers of subjects

in ITT, safety. The summary will also include the number and percent of subjects who completed the study and who discontinued from the study and study treatment, respectively, and reason for discontinuation as documented in the subject status case report form.

4.3 Treatment Compliance and Extent of Exposure

The safety population will be used to summarize drug exposure, treatment compliance, and dose modifications by treatment group.

Treatment duration will be defined as the duration from the date of the first dose of study drug to the date of last dose of study drug. The number of tablets taken will be calculated based on the number of tablets dispensed at the study visits minus the number of returned tablets.

For apalutamide, the overall percent treatment compliance will be defined as the number of tablets taken during the study divided by the expected number of tablets, multiplied by 100. Each subject should be taking a maximum of 4 x 60-mg tablets of study drug per day while on the study. A subject's expected number of tablets will be calculated as the number of assigned tablets per day multiplied by treatment duration.

Choice of specific LHRHa to be used in this study will be per investigator discretion/site practice guidelines. Options include Eligard®, Lupron Depot®, Zoladex®, or Trelstar®. Dosing schedule will be per individual investigator discretion. The use of LHRH antagonists (e.g. degarelix) will not be permitted. The LHRHa injections will be delivered either subcutaneously (Eligard®, Zoladex®) or intramuscularly (Lupron Depot®, Trelstar®) by a trained health care provider while on protocol therapy. Subjects with at least one dose modification and the reason for the dose modification will be summarized by treatment group.

4.4 Protocol Deviations

Protocol deviations and eligibility deviations will also be summarized by treatment group. Protocol deviations will be reviewed on a case-by-case basis and assessed if they are considered major deviations for this study. The final list will be compiled before database lock. Examples of major protocol deviations may include, but are not limited to, the following:

- Deviation from inclusion/exclusion criteria that may affect efficacy endpoints
- Major study drug dosing errors or dose modifications that are not within the protocol specifications that may compromise subject safety or efficacy assessments.
- Administration of prohibited concomitant medication during the course of the study treatment period
- Any other deviation that impacts subject safety

4.5 Pre-study and Concomitant Therapy

Concomitant medications, other than study treatment, and medications taken prior to starting study treatment will be summarized for all subjects using the Safety population analysis set by treatment group. Concomitant medications will be recorded at each monthly clinic visit. Subjects are recommended to take calcium 1000 mg/day and vitamin D (cholecalciferol) 800 IU/day in

divided doses. Phosphodiesterase inhibitors such as sildenafil used to treat erectile dysfunction may be initiated or continued as per individual investigator discretion. Breast irradiation and/or tamoxifen to prevent and/or treat painful gynecomastia will also be permitted per individual investigator discretion. Subjects who require the initiation of bisphosphonate or other bone-targeted therapy (eg, those sustaining an osteoporotic fracture) while on study will be permitted to do so and remain on study, but subjects who have used a bone-modifying agent within 3 months prior to randomization will be excluded.

4.6 Prohibited Medications

No concomitant use of any anti-cancer therapy will be permitted. This will include surgery, radiation therapy, and other secondary hormonal therapies including first generation antiandrogens, 5-alpha reductase inhibitors (i.e. finasteride, dutasteride), megestrol acetate, immunotherapy, chemotherapy, or other investigational agents while on study. Start of any of these therapies will result in discontinuation from the study. Nutritional supplements containing saw palmetto or pomegranate are also specifically prohibited.

As a class effect, androgen receptor antagonists have been associated with seizures due to an off-target mechanism of action ($GABA_A$ inhibition). To date, no subjects receiving apalutamide have experienced seizures, however, in preclinical experiments, at very high doses, dogs treated with apalutamide had tremors and generalized seizures. Subjects will be closely monitored for seizures, but as a precautionary measure, the following drugs known to decrease the seizure threshold or cause seizure will be prohibited.

- Aminophylline, theophylline
- Atypical anti-psychotic drugs: clozapine, olanzapine, ziprasidone, bupropion
- Phenothiazine anti-psychotic drugs: chlorpromazine, mesoridazine, thioridazine
- Tricyclic and tetracyclic anti-depressants: amitriptyline, desipramine, doxipine, imipramine, maprotiline, mirtazapine (Remeron)
- Lithium
- Meperidine (Demerol) and pethidine

4.7 Reasons for Study Discontinuation

Subjects will discontinue study protocol treatment for the following reasons, whichever comes soonest:

- PSA progression
- Radiographic progression, defined as the detection of new metastasis on either bone scan or cross-sectional imaging (CT or MRI).
- Subject or treating physician decision
- Unacceptable toxicity
- Non-protocol therapy

5. EFFICACY

This section outlines the planned analyses of the primary, secondary, and other efficacy endpoints of the study.

Efficacy analyses will be performed in the ITT population, incorporating the randomization stratification factors. All continuous variables will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized with count and percentage.

Time-to-event endpoints will be summarized using the Kaplan-Meier method [6] and displayed graphically where appropriate. Median event times and two-sided 95% confidence interval (CI) for each treatment group will be provided. Stratified Cox proportional-hazard models will be used to estimate the hazard ratio (HR) and its 95% CI. The stratification factors to be used in the analysis are PSADT (< 6 months vs. 6-12 months), and age at study entry (≤ 70 years vs. > 70 years).

The testing for the time-to-event endpoints will be based on the stratified log rank test; non-stratified log rank test will be performed as a sensitivity analysis, as appropriate. Multivariate Cox regression analysis, adjusting for important selected prognostic factors.

The proportional hazard assumption will be assessed graphically by plotting log (-log [estimated survival distribution function]) against log (survival time). The resulting graphs should have approximately parallel lines when the assumption holds. If the proportional hazards assumption is reasonably met, then the HR will be used as an estimate of treatment effect. If the proportional hazards assumption is violated, then the inference remains statistically valid for testing equality in survival distributions, but treatment effect will only be estimated using the median time to event in each treatment group.

Endpoints with binary outcome will be summarized by descriptive statistics (count and percentage) by the treatment group. The risk ratio or risk difference (treatment: control) will be reported along with the corresponding two-sided 95% CI. The two treatment groups will be compared by using the chi-square test; Fisher's exact test may be used if the expected counts in some of the cells are less than 5.

5.1 Analysis Specification

5.1.1 Level of Significance

In general, a two-sided significance level of $\alpha = 0.05$ will be used for all hypothesis testing and all CIs will be calculated on the two-sided 95% confidence level, unless otherwise specified. Since this is a three-arm study testing two simultaneous hypotheses, $\alpha/2 = 0.025$ level of significance will be used to test each.

5.1.2 Data Handling Rules

In general, no imputation method is planned for handling missing or incomplete data. Sensitivity analyses with censoring rules may be conducted if warranted and will be documented in the clinical study report.

5.2 Primary Endpoint

The primary efficacy endpoint is the mean change from baseline in total FACT-P score at 12 months. The FACT-P scale is described in section 5.4.1.

5.2.1 Analytic Plan for the Primary Endpoint

Change from baseline in FACT-P total scale will be analyzed using a mixed-model for repeated measures. The model will include baseline scale, treatment, month (categorical), and treatment-by-month interaction as covariates. An unstructured variance-covariance matrix will be used to model within-subject errors, but simpler structures (eg, compound symmetry) may be used to ensure estimation convergence. Change from baseline will be estimated using least-squares means with factor levels weighted according to overall baseline sample means. Data up to 12 months will be included in the analysis and the primary time point of interest will be at 12 months. Contrasts will be set up to compare apalutamide monotherapy vs. LHRHa monotherapy and apalutamide + LHRHa vs. LHRHa monotherapy. To test for non-inferiority with respect to apalutamide + LHRHa compared with LHRHa monotherapy, inferior boundary is defined as a greater than 7-point difference in mean change in FACT-P total score. The estimated least-squares mean (+/- SE) over time will be presented using a line plot. A sensitivity analysis will be conducted by including data up to 24 months.

5.3 Secondary Endpoints

The following secondary endpoints will be analyzed:

A) Quality of Life:

- Mean change from baseline in total FACT-P score over time
- Mean change from baseline in EORTC QLQ-C30/PR25 score over time
- Mean change from baseline in SHIM score over time

B) PSA Modulation:

- Time to PSA progression, which is defined as a rise to greater than 50% of the baseline serum PSA or rise of 2 ng/mL or more above the nadir, whichever is higher, confirmed by repeat measurement at least 2 weeks later (see Table 1 for the censoring rules).
- Proportion of subjects without evidence of PSA or radiographic progression during the 24-month treatment period and with recovery of serum testosterone at 24 months. Testosterone recovery will be defined as a serum testosterone greater than 150 ng/dL.
- Proportion of subjects with a PSA less than 0.2 ng/mL after 7 months of protocol therapy

C) Metabolic and Hormonal

- Mean change from baseline in markers of insulin resistance (including body mass index, fasting glucose/insulin, and hemoglobin A1C), fasting lipid profile, and bone mineral density as measured at the femoral neck, and lumbar spine by DEXA scan over time
- Time to testosterone recovery to greater than 50 ng/dL (non-castrate) and greater than 150 ng/dL during the off-therapy observation period for subjects randomized to the LHRHa-based treatment arms (see Table 1 for the censoring rules)
- The mean change from baseline in serum DHT and estradiol levels over time

5.3.1 Analytic Plan for the Secondary Endpoints

5.3.1.1 Quality of Life

The secondary QOL endpoints will be analyzed using a mixed-model for repeated measures like the primary endpoint. The model will include baseline scale, treatment, month (categorical), and treatment-by-month interaction as covariates. FACT-P, EORTC QLQ-C30/PR25, and SHIM scales are described in sections 5.4.1, 5.4.2, and 5.4.3, respectively.

5.3.1.2 PSA Modulation

The proportion of subjects without PSA or radiographic progression and who have recovered serum testosterone to greater than 150 ng/dL at 24 months from Day 1 will be compared for subjects treated apalutamide monotherapy vs. LHRHa monotherapy and for apalutamide + LHRHa vs. LHRHa monotherapy. The proportions by treatment will be compared using the chi-square test or Fisher's exact test as appropriate and summarized using either risk ratio or risk difference and corresponding 95% confidence interval. Results will be summarized at 24 months from Day 1 with 95% confidence intervals for each treatment arm. Subjects who withdraw from the study prior to 24 months after Day 1 will not be included and this analysis will be conducted as modified intent-to-treat (mITT).

The proportion of subjects with a PSA less than 0.2 ng/mL after 7 months of protocol therapy will be analyzed using similar approaches for proportion of subjects without evidence of PSA or radiographic progression during the 24-month treatment period and with recovery of serum testosterone at 24 months.

The probability distributions by treatment group of the time to PSA progression will be estimated using the Kaplan-Meier method. Durations will be measured from Day 1 of study treatment to the first date of PSA progression. The log-rank test will be used to compare the distribution of time to PSA progression.

5.3.1.3 Metabolic and Hormonal Parameters

The mean change from baseline for markers of insulin resistance (including fasting glucose, insulin, body mass index, and hemoglobin A1C), fasting lipid panel (including total cholesterol, LDL, HDL, and serum triglycerides), and hormone levels (including DHT and estradiol) analyzed using a similar approach as for the primary endpoint.

The mean change in bone mineral density at the femoral neck, and lumbar spine as measured by DEXA scan will be compared for apalutamide monotherapy vs. LHRHa monotherapy and apalutamide + LHRHa vs. LHRHa monotherapy using an analysis of covariance that controls for baseline values of the corresponding measurement.

The time to serum testosterone recovery to > 50 ng/dL and > 150 ng/dL after the cessation of protocol therapy at 12 months will be compared for apalutamide + LHRHa vs. LHRHa monotherapy. The probability distributions by treatment group of the time to testosterone recovery will be estimated using the Kaplan-Meier method. The log-rank test will be used to compare the distribution of time to testosterone recovery. Subjects who discontinue study drug prior to 12 months for disease progression, unacceptable toxicity, or study withdrawal, as well as subjects who continue hormonal therapy after 12 months or receive non-protocol therapy, will not be included in the analysis of this exploratory endpoint.

No adjustment for multiple comparisons will be made for the analysis of the secondary and correlative endpoints.

Table 1: Key censoring rules

Scenario	Censoring rule
Time to PSA Progression	• Any increase in PSA to > 50% of the baseline value or an increase of ≥ 2 ng/mL above the nadir, whichever is higher, and confirmed by repeat measurement at least 2 weeks later is considered an event. • Subjects who have no PSA progression at the time of analysis will be censored at the last known date of PSA assessment. • Subjects without a baseline PSA or without any post baseline values will be censored at randomization date.
Time to Serum Testosterone Recovery	• Any testosterone value between 12 months to 24 months that is greater than 150 ng/dL (or 50 ng/dL as the case may be) is considered an event. • If a subject had testosterone recovery (between 12 and 24 months) that happened after hormonal or subsequent therapy started, then the subject is censored at the hormonal or subsequent therapy start date. • If a subject had testosterone recovery (between 12 and 24 months) that happened before hormonal or subsequent therapy started, then the recovery is considered as an event. • Subjects who were not treated will be censored at randomization date. • Subjects who do not fall under any of the above-mentioned category will be censored at the end of on-therapy period or off-therapy period (if the subject is in the off-therapy period).

5.3.2 Other Evaluations

A) Safety:

- Incidence and severity of adverse events.
- Abnormal findings in physical exams and laboratory tests

B) Correlative Studies

- Frequency of subjects emerging with AR^{F876L} mutation at the end of treatment and progression.
- Frequency of subjects expressing various RNA markers previously demonstrated to confer resistance apalutamide at baseline, end of treatment, and progression

5.4 QOL Scales

5.4.1 FACT-P

The FACT-P scale [version 4.0] is a well validated metric [7] developed by Cella and colleagues, which includes a 27-item "core" quality of life measure (FACT-G) grouped into 4 subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. There are an additional 12 items specific to prostate cancer; 10 of which are prostate cancer specific physical problems. Items are rated on a 5-item Likert scale, from 0, "not at all", to 4, "very much" (see Section 11.1). The total range of scores is from 0 – 156. Higher scores indicate higher degree of functioning and better quality of life. Concurrent validity was confirmed by the ability to discriminate subjects by disease stage, performance status, and baseline prostate-specific antigen (PSA) level. Prior clinical trials have established that minimally important differences that are clinically significant and may impact treatment decisions range from 5 to 8 points depending on tumor subtype [8].

5.4.2 EORTC QLQ-C30

The EORTC QLQ-C30 [Version 3] is a well validated [9], and widely used measure of health-related quality of life among cancer patients. The EORTC QLQ-C30 consists of 30 items, which list the functioning and symptoms of cancer patients. Five multi-item function scales are scored: physical function (PF), role function (RF), emotional function (EF), social function (SF), and global health status/quality of life. Furthermore, nine single-item scales (symptoms) are scored, including fatigue, pain, dyspnea, and gastrointestinal problems. The scales are, according to the EORTC guidelines, linearly transformed: all scales range from 0 to 100, in which a higher scale score represents a higher level of functioning. With respect to the single-item scale, a higher score indicates more symptoms or problems; scores of these items will be inverted for the purposes of statistical analysis. In addition, a subscale related to prostate cancer (EORTC QLQ-PR25) will also be administered, consisting of 25 items, with the same linear transformation to a scale ranging from 0 to 100 (see Section 11.2).

5.4.3 Sexual Health Inventory for Men (SHIM)

The Sexual Health Inventory for Men (SHIM) is a well validated [10] abridged 5-item of the 15-item International Index of Erectile Function, which has been extensively studied in men with erectile dysfunction due to various etiologies, including prostate cancer-related therapies. It consists of 5 items pertaining to sexual functioning, with scores ranging from 0-5 for most items. Higher scores indicate higher level of sexual function and less erectile dysfunction (see Section 11.3).

6. SAFETY

6.1 Adverse Events

The verbatim terms used in the electronic case report form (eCRF) by investigators to identify adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Toxicities will be graded for severity according to NCI-CTCAE Version 4.03. All reported adverse events with onset during the On-therapy Period up to 30 days after the last dose of study medication will be included in the analysis.

Specifically, the following adverse events will be summarized:

- All adverse events
- Grade 3 or higher adverse events
- Serious adverse events
- Adverse events leading to discontinuation of treatment
- Adverse events leading to death

Summaries, listings, or subject narratives may be provided, as appropriate, for those subjects who died, who discontinue treatment due to an adverse event, or who experience a ≥Grade 3 or higher or a serious adverse event.

In addition, abnormal findings in physical exams and laboratory tests will be summarized.

All AEs reported during the AE reporting period (inclusive of the 30-day post last dose of study drug period) will be considered as treatment-emergent adverse events and will be summarized by treatment group as treated using all subjects in the safety population.

For each treatment group, AE incidence rates will be summarized with frequency and percentage by SOC and preferred term, with all subjects treated in that treatment group as the denominator, unless otherwise specified. In addition, AE incidence rates will also be summarized by severity and relationship to study drug. Treatment-related AEs are those judged by the Investigator to be at least possibly related to the blinded study drug. Subjects with multiple occurrences of events will only be counted once at the maximum severity to study drug for each preferred team, SOC, and overall. Deaths that occur within 30 days after the last dose of study drug are defined as on-study deaths.

AE onset date will not be imputed if it's completely missing. Partial AE onset date will be imputed as follows:

- If the AE onset date is missing day only, it will be set to:
  - the first day of the month that the AE occurred, if the month/year of the onset of AE is different from the month/year of the study treatment start.

  - the day of the study treatment start, if the month/year of the onset of AE is the same as month/year of the study treatment start but different from the month/year of the AE resolution date.
  - the day of the study treatment start or the day of AE resolution date, whichever is earlier if the month/year of the onset of AE and month/year of the study treatment start and month/year of the AE resolution date are same.
- If the AE onset date is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is after the study treatment start
  - the day and month of the study treatment start, if this date is the same year as that the AE occurred.
  - the AE resolution date.

Summary tables of the following AEs will be provided:

- Overall summary of AEs: the number and percentage of subjects who experienced any AE, any serious adverse event (SAE), any treatment-related AE, any treatment-related SAE, any discontinuations due to an AE, and any deaths
- All AEs by SOC and preferred term All AEs by SOC, preferred term, and toxicity grade
- Grades 3 or 4 AEs by SOC and preferred term
- Treatment-related AEs by SOC and preferred term
- Treatment-related AEs by SOC, preferred term, and toxicity grade
- Treatment-related Grades 3 or 4 AEs by SOC and preferred term
- AEs that led to study drug discontinuation by SOC and preferred term. Study drug discontinuation will be determined from the treatment disposition CRF (where reason for discontinuation is "Adverse Event") and the specific AE will be determined from the AE CRF page (where action taken is "Drug withdrawn")
- AEs that led to study drug discontinuation by SOC, preferred term, and toxicity grade
- AEs that led to dose modification by SOC, preferred term, and toxicity grade
- All SAEs by SOC and preferred term
- All SAEs by SOC, preferred term, and toxicity grade
- Deaths will be summarized by time period (on-study vs. during follow-up) and cause of death.

Subject listings of all AEs by toxicity grade, Grades 3 or 4 AEs, all SAEs, AEs that led to study drug discontinuation, dose modification, and all deaths will be provided as well.

Narratives will be written for the following subjects in the final clinical study report:

- Subjects who die ≤ 30 days after the last dose of study drug
- Subjects who discontinue study drug due to treatment-emergent AE

- Subjects who experience a treatment-emergent SAE
- Subjects who experience seizure,
- Subjects who experience other Grade 3 or higher treatment-emergent adverse events of special interest

6.1.1 Clinical Laboratory Tests

Lab data collected centrally by UCSF and by local labs will be summarized. Normal ranges will be used to identify values that are outside the normal ranges and abnormal laboratory results will be graded according to the NCI-CTCAE Version 4.03.

Descriptive statistics will be provided for each test result and for the change from baseline by visit. A shift summary of baseline grade by maximum post baseline NCI-CTCAE toxicity grade will be presented, as appropriate for selected parameters. For each laboratory parameter, the baseline laboratory value will be defined as the last laboratory value collected on or prior to the date of the first dose of study drug. A listing of subjects who develop toxicities of Grade ≥ 3 will be provided for each lab type. Liver function test data will be summarized based on eDISH and Hy's Law criteria [11]. Listings will be provided for subjects who meet the eDISH criteria and Hy's Law criteria, respectively.

6.1.2 Vital Signs

Each vital sign (temperature, blood pressure (systolic and diastolic), respiration rate, and heart rate) and change from baseline for blood pressure will be summarized and presented by treatment group and study visit. Subjects with clinically significant abnormalities in vital signs as compared to baseline will be listed.

Data will be summarized and presented according to the following categories:

Parameter		Criteria for Clinically Significant Abnormality
Systolic Pressure	Blood	Absolute result > 160 mmHg and increase from baseline > 20 mmHg
		Absolute result < 90 mmHg and decrease from baseline > 20 mmHg
Diastolic Pressure	Blood	Absolute result > 100 mmHg and increase from baseline > 10 mmHg
		Absolute result < 50 mmHg and decrease from baseline > 10 mmHg
Weight		5 - < 10% weight loss from baseline
		10 - < 20% weight loss from baseline
		>= 20% weight loss from baseline

6.1.3 Electrocardiogram

Electrocardiograms (ECGs) (12-lead) will be recorded at Screening. Abnormalities noted at screening will be included in the medical history.

ARN

7. PHARMACOKINETICS

Pharmacokinetic assessment (trough PK samples) will be performed per protocol.

8. BIOMARKERS

Biomarker analyses will be conducted on archival FFPE blocks or slides, plasma and whole blood samples collected from subjects who consented to participate in biomarker analysis to assess AR^{F876L} mutation and other resistance markers from all 3 treatment groups.

Further association may be made with clinical endpoints with:

- Markers identified from RNAseq analysis of archival tumor samples
- Plasma DNA at progression or end of treatment will be used to assess the frequency of AR^{F876L} mutation
- Whole blood samples collected at baseline and end of treatment or progression will be used to identify the type and frequency of AR anomalies or other RNA based markers associated with apalutamide treatment resistance or response

The association of the rest of the biomarkers with clinical response or relevant survival endpoints may be assessed using appropriate statistical methods (eg, analysis of variance [ANOVA], categorical or survival models), depending on the endpoints. Analyses may be performed within and between each treatment group. Other clinical covariates (such as baseline tumor characteristics and subject demographics) may also be included in the model. Correlation of baseline biomarker expression levels with clinical response or relevant time-to-event endpoints may be performed to identify responsive (or resistant) subgroups.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and adequate subject material. Therefore, some analyses may be deferred or not done if, for any reason, the analysis will have no scientific value. Biomarker data from this study may be compared with or combined with data obtained from prior studies.

9. MEDICAL RESOURCE UTILIZATION

Medical resource utilization will be descriptively summarized by treatment group. This report will be prepared separately and will not be a part of the clinical study report.

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