DF/HCC Protocol #: 18-530

TITLE: A randomized Phase III study – Conventional Androgen Deprivation Therapy with or without Abiraterone acetate + prednisone and Apalutamide following a detectable PSA After Radiation and Androgen Deprivation Therapy: A randomized Clinical Trial in Men with High Risk Prostate Cancer.

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NCI-supplied agents: N/A

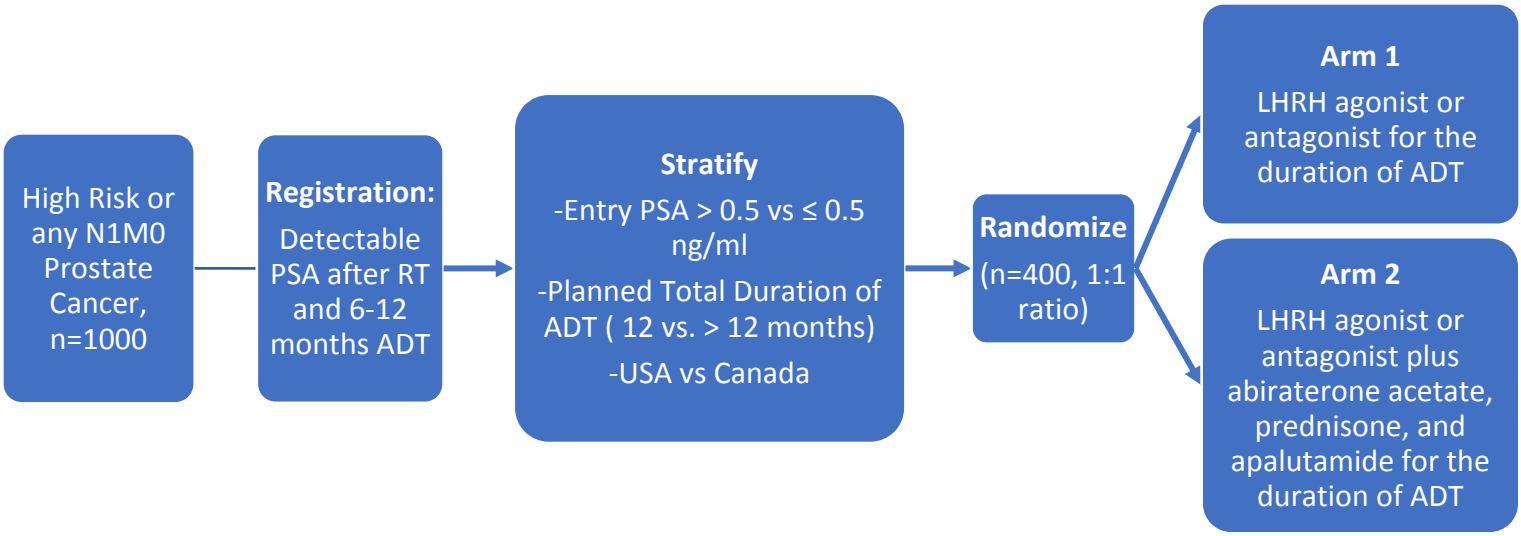
Janssen Scientific Affairs, LLC to supply:
Apalutamide
Abiraterone acetate

Commercial:
LHRH Agonist or Antagonist
Prednisone

Janssen Scientific Affairs, LLC is supplying funding for this study.

IND #: 141406
IND Sponsor: Anthony V. D'Amico, M.D. Ph.D.
Protocol Type = amended / Version # = 10.0 / Version Date = September 7, 2022

SCHEMA



Arm 1
LHRH agonist or antagonist for the duration of hormonal therapy

Arm 2
LHRH agonist or antagonist for the duration of hormonal therapy
Abiraterone acetate by mouth once/day for the duration of ADT
Prednisone by mouth twice per day for the duration of ADT
Apalutamide by mouth once/day for the duration of ADT

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1. OBJECTIVES

1.1 Study Design

The goal of this study is to assess whether metastasis free survival is prolonged after completing novel androgen deprivation therapy (ADT) in men with high risk prostate cancer whose PSA remains detectable (defined as, at or above the minimum level defined as measurable by the assay. For example, 0.02 would be eligible on an assay which defines undetectable PSA as <0.02) following radiation and 6-12 months of conventional ADT. This is a randomized phase III study involving the use of 2 novel hormonal therapy agents (apalutamide and abiraterone acetate with prednisone) in addition to conventional ADT with a LHRH agonist or antagonist as compared to conventional ADT alone for the duration of treatment with ADT.

1.2 Primary Objective

The primary objective is to evaluate whether metastasis free survival is prolonged in men undergoing novel ADT (LHRH agonist or antagonist, apalutamide, and abiraterone acetate with prednisone) as compared to conventional ADT with a LHRH agonist or antagonist alone in men whose PSA remains detectable after radiation therapy and 6-12 months of ADT for high risk prostate cancer.

1.3 Secondary Objectives

- To evaluate the PSA nadir following randomization
- To evaluate castrate resistant PSA failure
- To evaluate prostate cancer -specific survival
- To evaluate overall survival
- To evaluate disease free survival

2. BACKGROUND

2.1 Study Disease and Rationale

Prostate cancer is the most commonly diagnosed non-cutaneous cancer in the U.S. male population and the second leading cause of cancer death. While many men who present with high risk prostate cancer are curable, some will die from castrate resistant disease. Accumulating evidence suggests that a PSA that remains detectable following radiation therapy and at least 6 months of ADT is associated with an increased risk of prostate cancer-specific and all-cause mortality (PCSM, ACM).[9,10] Following initiation of this treatment, the median level and time to PSAn has been observed to be 0.1 ng/mL and 6 months, respectively.[9,10] Moreover, a PSAn > 0.5 ng/ml has been shown to be a surrogate for all-cause mortality (ACM)[6] and the median time to death from PC shortens as the PSAn increases.[9,10] The clinical implication of these observations is that men whose PSA level is detectable at the end of RT and 6-12 months of ADT, which

comprises 40% of men with high risk PC[10], harbor residual prostate cancer that is likely castrate resistant with a concomitant increase in the biological aggressiveness of the residual disease with increasing PSA level.

With the advent of agents[11,12,13] that have been shown to prolong survival in men with castrate resistant metastatic PC and prolong the time to metastasis and any cause of death in men with non-metastatic PC,[7] the opportunity exists to evaluate in the setting of prospective randomized controlled trial (RCT) whether the time to metastasis and any cause of death can be prolonged with the addition of these agents to the standard of care (ADT using an LHRH agonist or antagonist) in men with high-risk PC whose PSA level remains detectable following RT and 6-12 months of ADT.

We propose a randomized Phase III study in order to assess the impact on metastasis free survival and overall survival that novel ADT vs LHRH agonist or antagonist alone provides in men with high risk prostate cancer whose PSA level remains detectable following RT and 6-12 months of conventional ADT.

This study is open to patients who underwent radiation and hormone therapy after presenting with localized, high risk, and pelvic node positive or negative prostate cancer, and now have a detectable PSA 6-12 months after ADT initiation, and a planned total ADT duration of at least 12 months based on the results of the ASCENDE RT trial.[1] Pelvic node positive disease is defined as disease including pelvic lymph nodes that are clinically suspicious on CT, MRI or PET imaging up to and including the bifurcation of the common iliac vessels. Radiation therapy will be completed prior to the patient being randomized. It will be treatment to the prostate and seminal vesicles that could include dose escalated conventionally fractionated (75.6 to 79.2 Gray (Gy) in 1.8 to 2.0 Gy fractions) or hypofractionated (60.0 Gy in 3 .0 Gy fractions) treatment, or 45 to 50.4 Gy RT and a brachytherapy boost as that these are all accepted standards of care.[1,4-5] Pelvic radiation would be permitted.

Abiraterone acetate is a CYP17 inhibitor blocks mineralocorticoid synthesis in the adrenal gland (see section 2.2.2). Given that apalutamide (section 2.2.1) may be effective in a subset of prostate cancer patients with acquired resistance to abiraterone acetate[3] we propose combining these two drugs in addition to conventional ADT (defined in this protocol as LHRH agonist or antagonist) in the experimental arm. The control arm of this study is the current standard of care, a 12- to 36-month course of conventional ADT. Eighteen months of ADT will be commonly used based on recent results showing that 18 months of ADT appears to provide similar cancer control compared to 36 months of ADT with respect to all-cause mortality (ACM) given the upper limit of the 95% confidence interval on the point estimate (1.02) for the hazard ratio for ACM of 1.29 ($p = 0.84$) after a median follow up of 9.4 years and absolute survival rates at 10 years differing by 0.4%.[2] Twelve months of ADT with brachy boost following EBRT is also considered standard of care based on the ASCENDE RT trial.[1] Men will be stratified by the planned total duration of ADT (12 vs. > 12 months).

A stratification by the PSAn level following RT and 6-12 months of ADT, which has been shown to be a potential surrogate for ACM (> vs ≤ 0.5 ng/ml) during an era before agents

capable of treating castrate resistant disease were discovered, would be prudent in order to ensure that this potential surrogate endpoint for ACM[6] is balanced between the two randomized treatment arms.

In addition, in order to adjust for the potential uptake in the use of PET at the time of castrate resistant PSA failure (defined as PSA nadir + 2 ng/ml and serum testosterone < 50) and at the q6 months following documentation of castrate resistant PSA failure, we are including a pre-randomization stratification by country (USA vs Canada) since PET usage will track with country given national guidelines for its use and reimbursement by insurers. In men scanned for recurrence following PSA failure in the castrate sensitive post-operative setting, a > 90% positive predictive value for PET has been observed when the PSA level is > 2 ng/ml and the testosterone level is normal (NCT # 03515577). Therefore, it is expected that the positive predictive value of PET in men who have castrate resistant PSA failure (defined as PSA nadir + 2 ng/ml and serum testosterone < 50) will be at least > 90%.

2.2 IND Agents

2.2.1 Apalutamide

Apalutamide is FDA approved for the treatment of non-metastatic castration resistant prostate cancer and for metastatic castration sensitive prostate cancer, however apalutamide is still considered investigational in this trial setting. Apalutamide is a novel androgen receptor (AR) antagonist that lacks partial agonist activity. Apalutamide impairs nuclear translocation and DNA binding of AR, preventing transcriptional activation of AR target genes.[8] Anticipated AEs from apalutamide clinical trials include fatigue, diarrhea, weight loss, taste alterations, joint pain or muscle spasms, increased blood pressure, rash, itching, hot flashes, falls, fractures, seizures, reduced or blocked blood flow to the heart and brain including heart attack and stroke, changes in thyroid function, increase in triglycerides, increase in blood cholesterol, and decreased appetite. Subjects will be closely monitored for seizures in human clinical trials of apalutamide and medications that potentially lower the seizure threshold will be prohibited (see section 5.4.4). Further details about the ongoing and completed clinical studies with apalutamide may be found in the Investigator's Brochure.

2.2.2 Abiraterone Acetate

Abiraterone acetate inhibits CYP17 (17a-hydrolase / 17,20-lyase), an adrenal enzyme important in the synthesis of testosterone (T) and dihydrotestosterone (DHT). In pre-clinical and early-phase clinical studies, abiraterone acetate was found to impair synthesis of adrenal androgens and corticosteroids. Consequently, abiraterone acetate is administered in combination with low-dose steroid supplementation (e.g., prednisone). Abiraterone acetate given with a low dose of prednisone is FDA approved for the treatment of patients with metastatic CRPC who experienced disease progression after docetaxel chemotherapy, and also for metastatic high risk castration sensitive prostate cancer patients. The approved dose of abiraterone acetate is 1000 mg/day in combination with prednisone 5 mg twice daily. A randomized Phase III study of patients with docetaxel-refractory metastatic CRPC demonstrated a statistically significant increase in overall survival (14.8 vs. 10.9 months; HR 0.65; P < 0.0001) and time to tumor

progression, as well as increased radiographic progression-free survival and rate of PSA response in patients treated with the combination of abiraterone acetate + prednisone compared to placebo + prednisone. The combination of abiraterone acetate and prednisone was well-tolerated. The most frequent adverse events were hypertension, hypokalemia, and fluid retention. Abiraterone acetate is currently approved and marketed for the treatment of patients with metastatic CRPC and metastatic high-risk castration sensitive prostate cancer in combination with prednisone.

2.3 Other Agents

2.3.1 Prednisone

Prednisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Prednisone is used with abiraterone to reduce the mineralocorticoid-related adverse events that arise because of CYP17A1 inhibition with abiraterone. Coadministration with the recommended dose of glucocorticoid compensates for abiraterone-induced reductions in serum cortisol and blocks the compensatory increase in adrenocorticotropic hormone seen with abiraterone.

2.3.2 LHRH Agonists or Antagonists

Gonadotropin-releasing hormone agonists or antagonists when chronically administered, result in marked reductions in blood levels of testosterone and estrogen. The most frequent side effects are loss of muscle mass, hot flashes, loss of libido and erectile dysfunction.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

A bone scan and/or PET (of any kind) will be used to ensure M0 high risk prostate cancer. A bone scan and/or PET is to be done up to 6 months prior to the start of initial ADT therapy or up to one month after initiation of ADT to rule out bony metastatic disease. Subjects must meet all of the following applicable inclusion criteria to participate in this study:

3.1.1 Histologically confirmed prostate cancer

3.1.2 PSA> undetectable (any value at or above the lower limit of detection for the assay used) after radiation and at least 6, but not more than 12 months of conventional ADT (LHRH agonist or antagonist with or without oral anti-androgens, excluding abiraterone acetate and apalutamide) in patients with non-metastatic high risk or N1 prostate cancer[8]

- High risk is defined per the NCCN guidelines – clinical, radiographic, or pathological (biopsy proven) T3 or higher, Gleason 8-10, PSA > 20 ng/mL, the presence of intraductal, ductal, or cribriform features with any Gleason score, and can be N0 or N1
- A month is defined as 28 days

3.1.3 Written informed consent and HIPAA authorization for release of personal health information prior to registration. NOTE: HIPAA authorization may be included in the informed consent or obtained separately. Subject must have the ability to understand and willingness to sign the written informed consent document.

3.1.4 Age ≥18 at the time of consent

3.1.5 ECOG Performance Status ≤ 2 (Appendix A)

3.1.6 Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 3 months of registration.

System	Laboratory Value
Hematological:	
Platelet count (plt)[1]	≥ 100,000/ µL
Hemoglobin (Hgb)[1]	≥ 9 g/dL
Absolute neutrophil count (ANC)	≥ 1000 cells/µL
Renal:	
CrCl[2]	≥ 45 mL/min
Hepatic and Other:	
Bilirubin[3]	≤ 1.5 × upper limit of normal (ULN)
Aspartate aminotransferase (AST)	< 2.5 × ULN
Alanine aminotransferase (ALT)	< 2.5 × ULN
Serum Albumin	> 3.0 g/dL
Serum potassium	≥ 3.5 mmol/L
Coagulation:	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 × ULN (unless on prophylactic or therapeutic dosing with low molecular weight heparin)

[1] Independent of transfusion and/or growth factors within 3 months prior to randomization

[2] Cockcroft-Gault formula will be used to calculate creatinine clearance

[3] In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin; if direct bilirubin is ≤1.5 × ULN, subject may be eligible

3.1.7 Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential OR agrees to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.

3.1.8 Ability to understand and comply with study procedures for the entire length of the study as determined by the site investigator or protocol designee

3.1.9 Medications known to lower the seizure threshold (section 5.4.4) must be discontinued or substituted prior to C1D1 of study treatment for patients on Arm 2

3.1.10 Able to swallow pills.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

3.2.1 Prior radical prostatectomy (excluding TURP and simple prostatectomy)

3.2.2 History of any of the following:

- Seizure or known condition that may predispose to seizure (e.g., prior stroke within 1 year of randomization, brain arteriovenous malformation, Schwannoma, meningioma, or other benign CNS or meningeal disease which may require treatment with surgery or radiation therapy)
- Severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias within 6 months prior to randomization

3.2.3 Known current evidence of any of the following:

- Uncontrolled hypertension. Participants with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive therapy
- Gastrointestinal disorder affecting absorption
- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.
- Known active or chronic hepatitis B infection (defined as having a positive hepatitis B surface antigen (HBsAg) test at screening). Subject with past or resolved hepatitis B infection (defined as having a negative HBsAg test and positive antibody to hepatitis B core antigen test) are eligible. Hepatitis B viral DNA must be obtained in subjects with positive hepatitis B core antibody prior to first treatment start.

- Active hepatitis C infection. Subjects positive hepatitis C antibody test are eligible if PCR is negative for hepatitis C viral DNA.
- Pre-existing condition that warrants long-term corticosteroid use greater than the equivalent of 10 mg prednisone daily. Physiologic replacement is permitted. Topical, intra-articular steroids or inhaled corticosteroids are permitted.
- Any condition that, in the opinion of the site investigator, would preclude participation in this study
- Baseline moderate or severe hepatic impairment (ChildPugh Class B or C)

3.2.4 Patients who are currently receiving treatment with a prohibited medication according to Section 5.4 (Tables 2 and 3), must discontinue that medication prior to starting treatment and must not restart for the duration of the study if randomized to ARM 2.

3.2.5 Avoid co-administration of abiraterone acetate with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to study drugs

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, psychiatric illness or social situations that would limit compliance with study requirements

3.2.8 Individuals with a history of another malignancy are not eligible if the cancer is under active treatment or the cancer can be seen on radiology scans or if they are off cancer treatment but in the opinion of their oncologist have a high risk of relapse within 5 years.

3.3 Inclusion of Women and Minorities

Every effort will be made to include men from minority populations. The enrollment of minority men will reflect the proportion of minority subjects at the sites participating in the trial. Women by birth are not affected by prostate cancer and therefore are not eligible.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the DF/HCC Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered

ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

The eligibility checklist(s) and all pages of the consent form(s) will be faxed to the ODQ at 617-632-2295. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

Following DF/HCC registration, participants may begin protocol therapy. Following registration, participants should begin protocol therapy within 21 days. Start of protocol therapy for patients on Arm 2 is defined as the start of the experimental drugs (apalutamide and abiraterone acetate). Since Arm 1 is a continuation of the treatment they are currently receiving, they will be considered on protocol therapy once they are randomized. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101A) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at DF/HCC. The required forms will be provided to sites by the study coordinator. Following registration, participants should begin protocol therapy within 21 days. Start of protocol therapy for patients on Arm 2 is defined as the start of the experimental drugs (apalutamide and abiraterone acetate). Since Arm 1 is a continuation of the treatment they are currently receiving, they will be considered on protocol therapy once they are randomized. Issues that would cause treatment delays should be discussed with the Overall PI.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and e-mailed to the Coordinating Center:

- Copy of screening test results, including imaging and pathology results
- Signed participant consent form

- HIPAA authorization form
- Eligibility checklist
- Clinic note, covering screening requirements and baseline AEs
- Additional screening assessments

The research nurse or data manager at the participating site will send the registration packet via email to the project manager at DFCI CTO. To complete the registration process, the coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101A) and register the participant on the protocol. The coordinator will e-mail the participant study number and treatment assignment to the participating site.

4.5 Randomization

Subjects will be randomized by DF/HCC Office of Data Quality (ODQ) in a 1:1 ratio to either ARM 1 or ARM 2. Cycle 1 Day 1 is considered the first day of treatment. Following registration and randomization, subjects may begin protocol treatment. Issues that would cause treatment delays should be discussed with the sponsor-investigator.

4.6 Stratification Factors

Stratification will be done prior to the randomization process and will include the following factors to ensure they are balanced between the treatment arms:

- PSAn level following RT and 6-12 months of ADT (> vs ≤ 0.5 ng/ml)
- Planned total duration of ADT (12 vs. > 12 months)
- USA vs. Canada

5. TREATMENT PLAN

5.1 Treatment Regimen

Subjects randomized to Arm 1 (control group) will continue to receive an LHRH agonist or antagonist for the duration of planned ADT. Treatment with an anti-androgen (bicalutamide) as well is at the discretion of the physician.

Subjects randomized to Arm 2 (investigational treatment arm) will continue to receive an LHRH agonist or antagonist and apalutamide, abiraterone acetate (Zytiga), and prednisone for the duration of planned ADT. If patient is taking an anti-androgen at the time of randomization (i.e. bicalutamide), the patient is to discontinue use at least 24 hours prior to start of study drugs.

Table 1:

Arm	Treatment	Dose	Frequency of administration	Route of administration
1	LHRH Agonist or Antagonist	As prescribed		

2	Abiraterone Acetate	1000 mg	Daily	Orally
	Prednisone	5 mg	Twice Daily	Orally
	Apalutamide	240 mg	Daily	Orally
	LHRH Agonist or Antagonist	As prescribed		

5.2 Pre-Treatment criteria

See eligibility criteria (Section 3.1).

5.3 Agent Administration

5.3.1 Arm 1

Guidelines for each medication are provided below and site investigator's discretion may be used. Subjects on ARM 1 will not be asked to record actual dosing of all medications in a drug diary.

5.3.1.1 LHRH Agonist or Antagonist

In both Arms, LHRH agonist or antagonist should be prescribed per standard of care and according to the product information. Permitted LHRH agonists or antagonists include but are not limited to leuprolide, goserelin, triptorelin, histrelin, and degarelix.

5.3.2 Arm 2

Guidelines for each medication are provided below and site investigator's discretion may be used. There is no specified order of administration of the study drugs (abiraterone acetate and apalutamide) prescribed in this protocol. Subjects on ARM 2 will be asked to record actual dosing of all medications in a drug diary (Appendix C). This diary should be brought to each clinic visit and reviewed by research staff. At the start of each cycle, patients should start new 30 day bottle. Once a new cycle starts, patients are to review drug accountability of previous cycle with study team member (MD/NP/PA/RN) and leave any unused drug from that cycle in the respected bottles. At their next in person visit, patient will return all drug bottles, any unused drug, and drug diaries.

5.3.2.1 Abiraterone Acetate (AA)

Abiraterone acetate 1000 mg orally (four 250-mg tablets) will be taken daily. Each bottle contains a 30-day supply (120 tablets). Abiraterone acetate should be taken at the same time every day on an empty stomach. No food should be consumed for at least two hours before the dose and for at least one hour after the dose. The tablets should be swallowed whole with water. Do not crush or chew tablets. If a dose is skipped or missed, it should only be taken if within 12

hours of schedule dosing time. If vomited, do not retake. Subjects will be asked to return unused drug and empty drug containers at each clinic visit. Women who are pregnant or who may be pregnant should wear gloves if they need to touch AA tablets. Study staff and caregivers should be notified of this information, to ensure that appropriate precautions are taken.

5.3.2.2 Prednisone

Prednisone 5 mg orally will be taken twice daily. Prednisone will be provided as a prescription (30, 60, or 90-day supply with refills) at the subject's local pharmacy. It is recommended that prednisone is taken with food. If a dose is skipped or missed, it should only be taken if within 12 hours of scheduled dosing time. Prednisone is given in conjunction with abiraterone acetate to decrease the risk of mineralocorticoid excess caused by abiraterone acetate.

5.3.2.3 Apalutamide

Apalutamide 240 mg orally (four 60-mg tablets) will be taken daily. Each bottle contains a 30-day supply (120 tablets). Apalutamide can be taken with or without food at the same time every day. If a dose is skipped or missed, it should only be taken if within 12 hours of scheduled dosing time. If vomited, do not retake. Subjects will be asked to return unused drug and empty drug containers at each clinic visit.

5.3.2.4 LHRH Agonist or Antagonist

LHRH agonist or antagonist should be prescribed per standard of care and according to the product information. Permitted LHRH agonists or antagonists include but are not limited to leuprolide, goserelin, triptorelin, histrelin, and degarelix. LHRH agonist or antagonist will be administered in clinic. Receipt of LHRH agonist or antagonist does not need to be documented in the drug diary.

5.4 Concomitant Medications

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject. All concomitant medications administered within 14 days prior to Cycle 1 Day 1 and throughout the study until the treatment termination visit will be collected on study-specific electronic Case-Report Forms (eCRFs). The reason(s) for treatment and dates of treatment should be reported to the site investigator and recorded as instructed on the study-specific eCRFs.

5.4.1 Allowed Concomitant Medications

It is recommended that subjects take calcium carbonate (e.g., Caltrate, Tums) at a dose of at least 500 mg orally per day every evening and Vitamin D orally at least 400 IU daily. Calcium is best absorbed when taken with meals.
Treatment or prevention of osteoporosis:

- Zoledronic acid
- Denosumab (e.g., Prolia)
- Other approved agents

5.4.2 Prohibited Concomitant Medications

Traditional herbal medicines should not be administered because the ingredients of many herbal

medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.

If it is necessary for the well-being of the subject and alternative therapies are not available, these drugs should be used with caution and after discussion with the sponsor-investigator.

If a site investigator suspects a drug-drug interaction, the sponsor-investigator should be contacted.

5.4.3 Potential Drug Interactions with Abiraterone Acetate and CYP3A4 Inducers and Inhibitors

Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. During the treatment phase of this trial, strong CYP3A4 inducers are prohibited. If a strong CYP3A4 inducer must be co-administered, the patient will be ineligible for this trial. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone. Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate. In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index, if used.

Concomitant use of medications that may alter pharmacokinetics of abiraterone acetate or apalutamide will not be allowed on this study. Specifically, strong CYP3A4 inhibitors or inducers that decrease the exposure of abiraterone acetate will not be allowed. Apalutamide is metabolized primarily by human CYP3A4, thus co-administration with strong inhibitors or inducers of CYP3A4 is not allowed. The CYP3A4 inhibitors and inducers listed in Table 2 are prohibited concomitant medications.

Table 2 Strong CYP3A4 Inducers and Inhibitors

Strong CYP3A4 Inducers	Strong CYP3A4 Inhibitors
Aminoglutethimide	Atazanavir
Bexarotene	Clarithromycin
Bosentan	Delavirdine
Carbamazepine	Diltiazem
Dexamethasone	Erythromycin
Efavirenz	Indinavir
Fosphenytoin	Itraconazole
Griseofulvin	Nefazodone

Modafinil	Nelfinavir
Nafcillin	Ritonavir
Nevirapine	Saquinavir
Oxcarbazepine	Telithromycin
Phenobarbital	Verapamil
Phenytoin	Voriconazole
Primidone	Grapefruit juice (or grapefruits)
Rifabutin	
Rifampin	
Rifapentine	
Tipranivir	
St. John's wort	

5.4.4 Potential Drug Interactions with Apalutamide and Anti-Seizure Medications

As a class effect, AR antagonists have been associated with seizures due to an off-target mechanism of action (gamma amino butyric acid chloride channel [$GABA_A$] inhibition). Drugs known to lower the seizure threshold or cause seizures are prohibited and a representative list is included below:

- Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperidine and pethidine
- Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
- Tricyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine

Table 3 Medications prohibited while on active treatment with Apalutamide

Generic Name	Brand Name*
aminophylline	Aminocont; Aminomal; Diaphyllin; Filotempo; Neophyllin; Norphyl; Phyllocontin; Syntophyllin; Tefamin; Truphylline; Xing You Shan;
aminophylline in combination	Asmeton; Cha Xin Na Min; Emergent-Ez; Fufang Dan An Pian; Ke Zhi
amitriptyline	Amirol; Amitrip; Amixide; Deprelio; Diapatol; Elatrol; cElatrolet; Elavil; Endep; Enovil; Emitrip; Klotriptyl; Laroxyl; Levate; Limbitrol; Limbitryl; Mutabase; Mutabon; Nobritol; Novo-Triptyn; Pertriptyl; Redomex; Saroten; Sarotex; Sedans; Syneudon; Teperin; Triptizol; Triptyl; Tryptizol
amitriptyline in combination	PMS-Levazine
bupropion	Aplenzin; Buproban; Contrave; Elontril; Forfivo; Fortivo XL; Le Fu Ting; Prexaton; Quomem; Voxra; Wellbutrin; Wellbutrin XL; Wellbutrin SR; Yue Ting; Zyban
chlorpromazine	Aminazin; Chlorazin; Hibernal; Klorproman; Largactil; Megaphen;

	Ormazine; Plegomazin; Solidon; Taroctyl;Thorazine; Vegetamin; Wintermin; Zuledin *NOTE: in Ireland also called "Clonazine" – very easy to confuse with clozapine.*
clozapine	Azaleptin; Clopine; Closastene; Clozaril; CloZAPine; Denzapine; Elcrit; Fazacio ODT; Klozapol; Lanolept; Leponex; Lozapine; Nemea; Ozapim; Synthon, Versacloz; Zaponex
desipramine	Deprexan; Norpramin; Nortimil; Pertofrane
doxepin	Adapin; Anten; Aponal; Deptran; Gilex; Li Ke Ning; Quitaxon; Silenor; Sinepin; Sinequan; Zonalon
imipramine	Impril; Melipramin; Mipralin; Norfranil; Novo-Pramine; Persamine; Pertofram; Pryleugan; Talendep; Tofranil; Tolerade
lithium	Arthriselect; Camcolit; Carbolith; Carbolithium; Eskolith; Hypnorex; Li-Liquid; Licarbium; Limas; Liskonum; Litarex; Lithane; Lithicarb; Lithioderm; Lithionit; Lithobid; Liticarb; Litiomal; Lito; Maniprex; Neurolepsin; Plenur; Priadel; Quilonorm; Quilonum; Saniquiet; Sedalit; Teralithe
lithium in combination	Boripharm No 23; Emser Salz; Girheulit HOM; Helidonium-Plus; Heweurat N; rheuma-loges; Rhus Toxicodendron Compose; Rhus-Plus; Ricinus Compose
maprotiline	Cronmolin; Deprilept; Ludiomil; Mapromil; Melodil; Neuomil; Psymion
meperidine/pethidine	Alodan; Atropine and Demerol; Centralgine; Demerol; Dolantin; Dolantina; Dolantine; Dolargan, Dolcontral; Dolestine; Dolosal; Dolsin; Fada; Hospira; Liba; Mepergan; Meprozine, Mialgin; Opystan; Pethidine; Petigan Miro; Psyquil compositum
meperidine/pethidine in combination	Pamergan P100
mesoridazine	Serentil; Mesorin

mirtazapine	Arintapin; Avanza; Axit; Combar; Esprital; Mi Er Ning; Miro; Mirta TAD; Mirtabene; Mirtachem; Mirtadepi; Mirtagamma; Mirtalan; MirtaLich; Mirtamylan; Mirtaron; Mirtaz; Mirtazelon; Mirtazon; Mirtazonal; Mirtel; Mirtin; Mirtor; Mirzaten; Norset; Noxibel; Paidisheng; Psidep; Remergil; Remergon; Remeron; Remirta; Rexer; Yarocen; Zispin
olanzapine	Anzorin, Arenbil; Arkolamyl; Atyzyo; Bloonis; Clingozan; Egolanza; Lansyn; Lanzek; Lazapix; Nolian; Nykob; Olafid; Olanzaran; Olanzep; Olanzin; Olanzine; Olapin; Olasyn; Olazax; Olpinat; Olzapin; Olzin; Ou Lan Ning; Ozilormar; Parnassan; Ranofren; Sanza; Stygapon; Synza; Ximin; Zalasta; Zamil; Zappa; Zapris; Zerpi; Zolafren; Zolaxa; Zonapir; Zopridoxin; Zylap; Zypadhera; Zypine; Zyprexa; Zyprexa Relprew; Zydis
olanzapine in combination	Symbyax
risperidone	Aleptan; Apo-Risperid; Arketin; Calmapride; Diaforin; Doresol;

	Hunperdal; Jing Ping; Ke Tong; Leptinorm; Lergitec; Orizon; Ozidal; Perdox; Ranperidon; Resdone; Ridal; Ridonex; Rileptid; Ripedon; Risepro; Rispa; Rispaksole; Rispefar; Rispemylan; Rispen; Rispera; Risperanne; Risperdal; Risperdalconsta; Risperdaloro; Risperigamma; Risperon; Rispolept; Rispolux; Rispond; Rispons; Risset; Rixadone; Rorendo; Ryspolit; Si Li Shu; Sizodon; Speridan; Suo Le; Torendo; Zhuo Fei; Zhuo Fu; Ziperid; Zoridal
theophylline	Aerolate; Afonilum; Aminomal; An Fei Lin; Apnecut; Apo-Theo; Asmalix; Asmalon; Bi Chuan; Bronchoparat; Bronchoretard; Cylmin; Diffumal; Elixifilin; Elixophyllin; Etipramid; Euphyllin; Euphyllina; Euphylline; Euphylong; Frivent; Gan Fei Lin; Nuelin; Protheo; Pulmophylline; Quelesu; ratio-Theo-Bronc; Respicur; Retafyllin; Shi Er Ping; Slo-Bid; Slo-Phyllin; Telbans; Teotard; Terdan; Teromol; Theo-24; Theo-Dur; Theo; Theochron; Theodur; Theofol; Theolair; Theoplus; Theospirex; Theostat ; Theotard; Theotrim; Theovent; Tromphyllin; Unicon; Unicontin; Unifyl; Uniphyl; Uniphyllin Continus; Uniphyllin; UniXan; Xanthium; Xi Fu Li; Yan Er
theophylline in combination	Antong; Baladex; Bi Chuan; Binfolipase; Broncho-Euphyllin; Broncomar; Do-Do ChestEze; Elixophyllin-GG; Elixophyllin-KI; Insanovin; Marax ; Neoasma; Theofol Comp; Theophedrinum-N; Xu Hong; Yi Xi Qing
thioridazine	Detril; Elperil; Melleril; Ridazin; Ridazine; Thiodazine; Thioril; Sonapa
ziprasidone	Geodon; Li Fu Jun An; Pramaxima; Si Bei Ge; Ypsila; Zeldox; Zipwell; Zypsila; Zypsilan

** NOTE: this document is intended as an aid in identifying prohibited meds, but due to the global scope of the apalutamide studies it may not be all inclusive.

5.4.5 Potential Drug Interactions with Apalutamide and Anti-Coagulation Medications

The potential for drug-drug interaction between apalutamide and warfarin (eg, Coumadin), as well as other anti-coagulation medications, is unknown at present. If a subject is taking warfarin, re-assess PT (prothrombin time)/international normalized ratio (INR) as clinically indicated and adjust the dose of warfarin accordingly.

5.4.6 Effect of apalutamide on abiraterone acetate and prednisone

The potential for drug-drug interactions between abiraterone acetate and prednisone with apalutamide to assess whether combined intake of abiraterone acetate and prednisone with apalutamide may lead to reduced abiraterone and prednisone exposure levels because of induction caused by apalutamide was assessed in a Phase 1b open label study conducted in subjects with mCRPC. Exposure to abiraterone decreased by 24% and 14% for C_{max} and AUC_{0-24}, respectively, and exposure to prednisone decreased by 51% and 61% for C_{max} and AUC_{0-24}, respectively when co-administered with apalutamide. Based on these data, the recommended dose of prednisone is 5 mg two times per day when abiraterone is co-administered with apalutamide. No change to the usual clinical dose of abiraterone acetate is recommended

5.5 Supportive Care

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, anti-emetics, etc., when appropriate.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on subject response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for the duration of hormonal therapy or until one of the following criteria applies, whichever comes first:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Subject decides to withdraw from the protocol therapy
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the site investigator
- Protocol therapy is interrupted for ≥ 21 days
- Requirement of 2 dose reductions

Subjects will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the subject was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the subject.

When a participant is removed from protocol therapy and/or is off the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

5.7 Duration of Follow Up

Patients will be on treatment for the duration of their originally planned ADT, which would be anywhere between at least 6 months to 30 months. After completion of study drug, active follow up will be every 6 months until study completion, being when we reach the required number of observed metastasis to do the final study analysis. At baseline and at each follow up, a PSA and total serum testosterone level will be obtained in addition to physician assessed toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events. CT or MRI of the chest, abdomen and pelvis, and bone scan **or** any type of PET CT are to be done once; at the time of initial **PSA failure**, defined as PSA at nadir + 2 ng/ml and testosterone level above 50 ng/dl. After results of protocol required scans at sign of PSA failure, investigator should initiate salvage therapy at their discretion. Then, if the PSA is still + 2 ng/ml above nadir and the testosterone is lower than 50 ng/dl while still on salvage ADT, also known as **castrate resistant PSA failure**, imaging is to be done every 6 months or sooner if the investigator chooses, until distant metastasis defined as bone, lymph node or visceral metastasis is documented. Survival status can be assessed using public records.

Note: If the treating physician decides to initiate salvage therapy prior to the patient's PSA reaching nadir +2 ng/ml, and the testosterone level is < 50 ng/ml, then this would also be considered castrate resistant PSA failure and the imaging should be done then and every 6 months thereafter.

5.8 Criteria for Taking a Participant Off Study

Subjects will be removed from the study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a subject off study, and the date the subject was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

5.9 Replacement

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been assigned to treatment or administered at least one dose of the study drug. Subjects who have dropped out will not be replaced.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following tables. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 should be utilized for dose delays and dose modifications. A copy of the CTCAE version 5 can be downloaded from the CTEP website: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm .

All adverse events experienced by subjects will be collected from the time of the first dose of study treatment, throughout the study, until the end-of-treatment visit. Subjects continuing to experience toxicities at the end-of-treatment visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

If study medications are held for more than a total of 21 days, the subject should be discontinued from protocol treatment. Treatment interruption and re-initiation not covered in the following guidelines should be discussed with the sponsor-investigator.

6.1 Dose Modifications for Toxicity Attributed to Apalutamide

Dose modifications are provided as guidance and should not replace the site investigator's

clinical judgment.

Toxicity	Dose of Abiraterone Acetate	Dose of Prednisone	Dose of Apalutamide
Grade 1 or 2	No change	No change	No change
Grade ≥ 3	No change	No change	Hold until Grade 1 or baseline, resume at full dose
First Recurrence Grade ≥ 3	No change	No change	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)
Second Recurrence Grade ≥ 3	No change	No change	Hold until Grade 1 or baseline, resume at 120 mg (2 tablets)
Third Recurrence Grade ≥ 3	No change	No change	Discontinue
First occurrence of seizure (any grade) or Grade 4 neurotoxicity	No change	No change	Discontinue

Rash

Dose modifications for rash are allowed only for apalutamide and are summarized in below table. If the skin rash has any component of desquamation, mucosal involvement, or pustules, stop dosing with apalutamide, refer to dermatologist for evaluation, and a skin biopsy is recommended (in addition to the interventions listed in below Table) If the skin rash is Grade 3 or higher, asking the subject to consent to documentation by a photograph and further evaluation by a dermatologist should also be considered.

Severity	Intervention

Grade 1	• Continue apalutamide at current dose
	• Initiate dermatological treatment[a]
	  o Topical steroid cream AND
	  o Oral Antihistamines
	• Monitor for change in severity[a]

Grade 2 (or symptomatic Grade 1)[b]	• Hold apalutamide for up to 21 days
	• Initiate dermatological treatment[a]
	  o Topical steroid cream AND
	  o Oral Antihistamines
	• Monitor for change in severity[a]

	○ If rash or related symptoms improve, reinitiate apalutamide when rash is Grade ≤ 1. Consider dose reduction at a 1 dose level reduction[c].
Grade ≥3[d]	• Hold apalutamide for up to 21 days • Initiate dermatological treatment[a] ○ Topical steroid cream AND ○ Oral Antihistamines AND ○ Consider short course of oral steroids • Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the subject to a dermatologist ○ Reinitiate apalutamide at a 1 dose level reduction[e] when rash is Grade ≤ 1. ○ If the dose reduction will lead to a dose less than 120mg, the study drug must be stopped (discontinued) • If after 21 days, rash has not resolved to Grade ≤ 1, contact PI who will contact Janssen to discuss further management and possible discontinuation of study drug.

Note: Rash may be graded differently according to the type of rash and associated symptoms. For example, maculo-papular rash is graded by body surface area covered and not severity of the rash. Please consult NCI-CTCAE Version 5 for specific grading criteria for other types of rash.

a Obtain bacterial/viral cultures if infection is suspected

b Subject presents with other rash related symptoms such as pruritus, stinging, or burning

c 1 dose level reduction = 60mg (1 apalutamide tablet)

d If there is blistering or mucosal involvement, stop apalutamide dosing immediately and contact PI who will contact Janssen

e If a subject previously started oral corticosteroids, continue for at least 1 week after resumption of reduced dose of apalutamide. If the proposed total oral steroid use will exceed 28 days, contact PI who will contact Janssen.

6.2 Dose Modifications for LFT Abnormalities Attributed to Abiraterone Acetate

Dose modifications are provided as guidance and should not replace the site investigator's clinical judgment.

Toxicity	Dose of Abiraterone Acetate	Dose of Apalutamide	Dose of Prednisone
Grade 1 or 2	No change	No change	No change

Grade 3	Hold until return to baseline or until AST or ALT ≤ 2.5 x ULN and total bilirubin ≤ 1.5 x ULN, RESUME at 750 mg (3 tablets) only after discussion and agreement with sponsor-investigator	Hold until return to baseline	No change
Recurrence Grade 3	Hold until return to baseline or to AST or ALT ≤ 2.5 x ULN and total bilirubin ≤1.5 x ULN, RESUME at 500 mg (2 tablets) only after discussion and agreement with sponsor-investigator	Hold until return to baseline	No change
Grade 4	Discontinue abiraterone acetate treatment	Hold until return to baseline	No change or consider tapering if abiraterone acetate discontinued
Concurrent elevation of AST/ALT > 3x ULN with bilirubin >2x ULN (unless the concurrent elevation is related to biliary obstruction or other causes unrelated to study treatment)	Discontinue abiraterone acetate treatment		No change or consider tapering if abiraterone acetate discontinued

ALT=alanine aminotransferase; AST=aspartate aminotransferase; LFT=liver function tests; ULN=upper limit of normal

Permanently discontinue abiraterone acetate for subjects who develop a concurrent elevation of ALT greater than 3 X ULN and total bilirubin greater than 2 X ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

6.3 Dose Modifications for Hypokalemia Attributed to Abiraterone Acetate

Dose modifications are provided as guidance and should not replace the site investigator's clinical judgment.

Toxicity	Dose of Abiraterone Acetate	Dose of Apalutamide	Dose of Prednisone

Grade 1 or 2	Initiate oral potassium supplementation, titrate to ≥ 3.5 to ≤ 5.0 mmol/L, maintenance at ≥ 4.0 mmol/L recommended	No change	No change
Grade ≥ 3	Hold abiraterone acetate and initiate IV potassium and cardiac monitoring, resume only after discussion and approval by the sponsor-investigator	No change	No change or consider tapering if abiraterone acetate is discontinued

6.4 Dose Modifications for Hypertension and Edema/Fluid Retention Attributed to Abiraterone Acetate

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

Toxicity	Dose of Abiraterone Acetate	Dose of Apalutamide	Dose of Prednisone
Grade 1 or 2	No change	No change	No change
Grade ≥ 3	Hold until Grade 1 or baseline, resume at full dose	No change	No change
First Recurrence Grade ≥ 3	Hold until Grade 1 or baseline, resume at 750 mg (3 tablets)	No change	No change
Second Recurrence Grade ≥ 3	Hold until Grade 1 or baseline, resume at 500 mg (2 tablets)	No change	No change
Third Recurrence Grade ≥ 3	Discontinue	No change	No change or consider tapering if abiraterone acetate is discontinued

6.5 Dose Modifications for Toxicity Attributed to LHRH agonist

There are no dose modifications for LHRH agonist or antagonist.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Adverse Events

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. A list of anticipated adverse events can be found in Section 8 of this protocol. The following list of reported and/or potential AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting **in addition** to routine reporting.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 should be utilized for dose delays and dose modifications. All appropriate treatment areas should have access to a copy of the CTCAE version 5. A copy of the CTCAE version 5 can be downloaded from the CTEP website: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

7.2 Overview

As the Sponsor of the study, Anthony V. D'Amico, M.D. Ph.D. shall be solely responsible for complying, within the required timelines, with any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co- or sub-) investigators, as defined in applicable laws and regulations. Safety data includes adverse events, product quality complaints (PQCs), and special situations including partner pregnancies.

Anthony D'Amico, M.D. Ph.D. will provide safety information to Janssen on adverse events, special situations including partner pregnancies and product quality complaints (PQC).

7.3 Management of Safety Data

This study has been designated as an interventional study. As such, all adverse events regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and PQCs with or without an adverse event will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal products are:

Abiraterone acetate
Apalutamide (JNJ-56021927)

7.4 Definitions

7.4.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

7.4.2 Adverse Events of Special Interest (AESI)

Adverse events of special interest are events that Janssen is actively monitoring as a result of a previously identified signal (even if non-serious).

- There are currently no adverse of special interest identified for apalutamide or abiraterone acetate.

7.4.3 Individual Case Safety Report (ICSR)

ICSRs are documentation required by Janssen for AE reporting. A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

7.4.4 Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential

quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

7.4.5 Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

7.4.5.1 Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious

adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

7.4.5.2 Life Threatening Conditions

The cause of death of a subject in a study within 30-days of the last dose of apalutamide or abiraterone acetate, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

7.4.6 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. Please refer to section 8 for a partial list of expected AEs for each drug.

7.4.7 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is not related to the study drug(s)
Unlikely	Adverse Event is doubtfully related to the study drug(s)
Possible	Adverse Event may be related to the study drug(s)
Probable	Adverse Event is likely related to the study drug(s)
Definite	Adverse Event is clearly related to the study drug(s)

7.5 Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

For apalutamide, the link to the package insert is:

http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ERLEADA-pi.pdf

For abiraterone acetate, the link to the package insert is:

http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ZYTIGA-pi.pdf

7.6 Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product, such as lack of any decline in PSA after 3 months.
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen **within 24 hours of becoming aware of the event.**

7.7 Pregnancy

Because the Janssen medicinal product may have an effect on sperm, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by Anthony V. D'Amico, M.D **within 24 hours of his knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7.8 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. DF/HCC and Anthony V. D'Amico, MD shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within

a reasonable timeframe at Janssen's request.

7.9 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen

All adverse events and special situations whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

7.9.1 SAEs and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

DF/HCC and Dr. Anthony D'Amico will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by Janssen in accordance with Section 7.11, Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

Participating investigators must report each SAE to the Sponsor Investigator (Dr. Anthony D'Amico) within 24 hours of learning of the occurrence. In the event a participating investigator is not made aware of the SAE immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

Non-DF/HCC sites participating in this research are also expected to submit each SAE to its local Ethics Committee according to FDA and local IRB guidelines.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by Dr. Anthony D'Amico, **within 24 hours becoming aware**, to the Janssen using the Janssen's Serious Adverse Event Report.

All available clinical information relevant to the evaluation of a related SAE or special situation is required.

- DF/HCC and/or the PI are responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen using a transmission method in Section 11 within **24 hours of such report or correspondence being sent to applicable health authorities.**

7.9.2 Non-Serious AEs

All non-serious adverse events should be reported to Janssen according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

7.9.3 PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen, and are mandated by regulatory agencies worldwide. Janssen has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen by the PI **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PI must report the PQC to Janssen according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen.

7.10 Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the PI should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

7.11 Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen.

7.12 Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen will provide to the institution and/or PI, a listing of all SAEs reported to Janssen. The PI will review this listing and provide any discrepancies to Janssen.

Upon request, the PI shall provide Janssen with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

7.13 Dissemination of Safety Information from Janssen to Principal Investigators

The PI will be responsible for submitting IND safety reports for the Study Product to the institution's IRB in accordance with Federal regulations 21 CFR 312.66. The PI will provide a copy of each IND safety report to sub-investigators where the study design is either a multi-center or cooperative study.

Janssen agrees to provide to the PI IND safety reports for the Janssen Medicinal Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

7.14 Contacting Janssen Regarding Safety

The names (and corresponding contact information) of the individuals who should be contacted regarding safety issues will be provided separately by Janssen.

7.15 Final Study Report

The PI will prepare a final report including a complete and full summary of all adverse events, special situations and pregnancy reports according to the timeframe outlined in the Research Funding Agreement.

7.16 Reporting

7.16.1 Adverse Events

- AEs will be recorded from time of signed informed consent until completion of the last study-related procedure.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).

- **All AEs** will be reported to the sponsor-investigator, recorded in the subject's medical record, and reported to Janssen and the DF/HCC IRB according to its requirements.
- Subjects who have an ongoing study treatment-related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the site investigator as stable, new anticancer treatment is initiated, the subject is lost to follow-up, the subject withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

7.17 IND Safety Reports Unrelated to this Trial

Janssen will provide IND safety reports from external studies that involve the study drug(s) to the sponsor-investigator. The sponsor-investigator will determine if revisions are needed to the protocol or consent. DF/HCC study coordinator or project manager will forward these reports to participating sites within 1 business day of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required).

Site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

7.18 Expedited Adverse Event Reporting

7.18.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.18.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.18.3 <u>DF/HCC Expedited Reporting Guidelines</u>

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

	DF/HCC Reportable AEs				
Attribution	**Gr. 2 & 3 AE Expected**	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**

Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.19 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.20 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.21 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

8.1 Abiraterone Acetate (AA)

Refer to the package insert for detailed pharmacologic and safety information.

8.1.1 Description

The chemical nomenclature of AA is 3β-acetoxy-17-(3-pyridyl) and rosta-5,16-diene. Its empirical formula is C26H33NO2 and it has a molecular weight of 391.55. Once absorbed after oral administration, AA is rapidly deacetylated and converted to the active form abiraterone. Abiraterone is metabolized by CYP3A4 and is an inhibitor of CYP2D6.

8.1.2 Form

AA 250-mg tablets are oval, white to off-white and contain abiraterone acetate and compendial (USP/NF/EP) grade lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and purified

water, in descending order of concentration (the water is removed during tableting).

8.1.3 Storage and Stability

Pharmacy Storage Requirements: The study treatment must be stored in a secure area and administered only to subjects entered into the clinical study in accordance with the conditions specified in this protocol. Bottles of study treatment should be stored at a room temperature between 20-25º C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Bottles should be stored with the cap kept on tightly and should not be refrigerated.

8.1.4 Storage Requirements for the Subject

Bottles of study treatment should be stored at room temperature with the cap kept on tightly and should not be refrigerated. Subjects should be advised to keep all medications out of the reach and out of sight of children.

8.1.5 Compatibility

We do not anticipate any excess toxicity combining ARN-509 (apalutamide), AA, prednisone and LHRH agonists or antagonists.

8.1.6 Handling

Study treatment must only be dispensed by a Pharmacist or medically qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once the study treatment is prepared for a subject, it can only be administered to that subject. Based on its mechanism of action, abiraterone acetate may harm a developing fetus. Women who are pregnant or who may be pregnant should wear gloves if they need to touch AA tablets. Study staff and caregivers should be notified of this information, to ensure the appropriate precautions are taken.

8.1.7 Availability

Drug will be supplied by Janssen Scientific Affairs. Subjects will be provided with either a 30, 60, or 90 day supply. Information presented on the labels for the investigative product will comply with applicable local regulations. Site pharmacist will dispense the study treatment to each subject in accordance with this protocol under the guidelines of the site's dispensation standard operating procedure. The agent will be provided free of charge to study subjects.

8.1.8 Ordering

Janssen does not ship product directly to individual participating study sites. It will ship to a designated drug vendor who will handle the further distribution to sites.

8.1.9 Accountability

Accountability for study treatment is the responsibility of the site investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment (abiraterone acetate) received, to whom dispensed (subject), and accounts of any study treatment accidentally or deliberately destroyed. Subjects will be asked to return unused drug and empty drug containers at each clinic visit. At the end of the study, reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed. At the time of delivery of study treatment to the site, the site investigator, designee, or Pharmacist (where

appropriate) will confirm that the supplies for the study have been received. This following information will be confirmed: lot numbers, quantities shipped/delivered, and date of receipt.

8.1.10 Destruction and Return

Drug should be destroyed at the site, after the sponsor– investigator approves the drug destruction policy at the site. Destruction will be documented in the Drug Accountability Record Form.

8.1.11 Adverse Events

Consult the package insert for the comprehensive list of adverse events. The most frequently reported AEs for abiraterone acetate include fatigue due to reduced cortisol level, resulting from CYP17 inhibition; hypertension; peripheral edema; and hypokalemia. Co-administration of prednisone 5 mg by mouth twice daily is anticipated to mitigate these anticipated AEs. Other less common side effects associated with Abiraterone acetate include adrenocortical insufficiency (AI), hepatotoxicity, fatigue, joint swelling/discomfort, edema, hot flashes, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. The most common laboratory abnormalities are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia. Consult the investigator's brochure for the comprehensive list of adverse events.

8.2 Apalutamide (ARN-509, JNJ-56021927)

Refer to the package insert for detailed pharmacologic and safety information.

8.2.1 Description

Apalutamide is a potent and specific antagonist of the AR that is being developed for the treatment of men with prostate cancer. The mechanism of action of ARN-509 is through antagonism of the androgen receptor and inhibition of AR nuclear translocation and DNA binding to ARs.

8.2.2 Form - Tablets

The ARN-509 drug substance is an almost white to slightly brown powder that is formulated in tablets at a strength of 60 mg.

8.2.3 Storage and Stability

Tablets: ARN-509 tablets (60 mg) are packaged in 120-count, 160 cc HDPE bottles with CRC and include desiccant, and should at all times be kept in the original packaging.

8.2.4 Compatibility

We do not anticipate any excess toxicity combining ARN-509, AA, prednisone and LHRH agonist or antagonist.

8.2.5 Handling

There are no specific instructions for handling ARN-509. Study treatment must only be dispensed by a Pharmacist or medically qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once the study treatment is prepared for a subject, it can only be

administered to that subject.

8.2.6 Availability

Drug will be supplied by Janssen Scientific Affairs. Subjects will be provided with either a 30, 60, or 90 day supply. Information presented on the labels for investigative product will comply with applicable local regulations. Site pharmacist will dispense the study treatment to each subject in accordance with this protocol under the guidelines of the site's dispensation standard operating procedure. The agent will be provided free of charge to study subjects.

8.2.7 Ordering

Janssen does not ship product directly to individual participating study sites. It will ship to a designated drug vendor who will handle the further distribution to sites.

8.2.8 Accountability

Accountability for study treatment is the responsibility of the site investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment (apalutamide) received, to whom dispensed (subject), and accounts of any study treatment accidentally or deliberately destroyed. Subjects will be asked to return unused drug and empty drug containers at each clinic visit.

At the end of the study, reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed. At the time of delivery of study treatment to the site, the site investigator, designee, or Pharmacist (where appropriate) will confirm that the supplies for the study have been received. This following information will be confirmed: lot numbers, quantities shipped/delivered, and date of receipt.

8.2.9 Destruction and Return

Drug should be destroyed at the site, after the sponsor– investigator approves the drug destruction policy at the site. Destruction will be documented in the Drug Accountability Record Form.

8.2.10 Adverse Events

Anticipated AEs from apalutamide clinical trials include fatigue, nausea, vomiting, diarrhea, constipation, anorexia, abdominal pain, taste alterations, rash, itching, insomnia, hot flashes, dizziness, falls, seizures, changes in thyroid function, increase in blood cholesterol, and decreased appetite. Consult the package insert for the comprehensive list of adverse events.

8.3 Prednisone

Refer to the package insert for detailed pharmacologic and safety information.

8.3.1 Description

Prednisone is a corticosteroid.

8.3.2 Form

Prednisone 5-mg tablets are small, white tablets.

8.3.3 Storage and Stability

Prednisone will be prescribed by prescription and prescriptions may be filled at a pharmacy chosen by the subject.

8.3.4 Compatibility

We do not anticipate any excess toxicity combining apalutamide, abiraterone acetate, prednisone and LHRH agonist or antagonist.

8.3.5 Handling

There are no specific instructions for handling prednisone.

8.3.6 Availability

Prednisone will not be provided by the study and will be prescribed by standard prescriptions.

8.3.7 Adverse Events

Prednisone may be associated with fatigue, increased appetite, insomnia, weakness, hyperglycemia, ecchymosis, and symptoms related to gastroesophageal reflux. Consult the package insert for the comprehensive list of adverse events.

8.4 LHRH Agonist or Antagonist

Refer to the package inserts for detailed pharmacologic and safety information.

8.4.1 Description

Leuprolide and goserelin are LHRH agonists. Degarelix is an LHRH antagonist.

8.4.2 Form

Leuprolide is a sterile solution administered as an intramuscular injection. Goserelin implant is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer impregnated with goserelin acetate in a disposable syringe device. Degarelix is supplied as a powder to be reconstituted with Sterile Water for Injection, USP (WFI).

8.4.3 Storage and Stability

Leuprolide, goserelin, and degarelix will be stored at the site pharmacy.

8.4.4 Compatibility

We do not anticipate any excess toxicity combining apalutamide, AA, prednisone and LHRH agonist or antagonist, or with combining LHRH agonist or antagonist with Bicalutamide.

8.4.5 Handling

There are no specific instructions for handling leuprolide, goserelin, or degarelix.

8.4.6 Availability

Leuprolide, goserelin, and degarelix will not be provided by the study and will be prescribed by standard prescriptions.

8.4.7 Adverse Events

Class-related toxicity is generally a manifestation of the mechanism of action and due to low testosterone levels. The most common reported side effects of LHRH agonists and antagonists include hot flashes, edema, gynecomastia, bone pain, thrombosis, and gastrointestinal disturbances. Other side effects include impotence and loss of libido, weight gain, depression, dizziness, loss of bone density, anemia, increased thirst and urination, unusual taste in the mouth, skin redness or hives, pain at injection site, strength loss, hair changes, penile length and testicular volume loss, increased cholesterol, hypertension, diabetes exacerbation, emotional lability, nausea, vomiting, QT prolongation, and rarely allergic generalized rash and difficulty breathing. Consult the package insert for comprehensive toxicity information.

9. STUDY CALENDAR

9.1 Arm 1 Calendar & Evaluations

Study Evaluation	Screening	Screening	Study Visits q3 months during protocol treatment	End of Treatment	PSA Failure	Long Term Follow Up[4]
	Within 90 days prior to registration	Within 42 days prior to registration	± 14 days	± 7 days	± 28 days	± 28 days
REQUIRED ASSESSMENTS						
Informed Consent		X				
Medical History		X				
Diagnosis and Staging Information		X				
Physical Exam		X	X			
Vital signs and ECOG Performance Status[1]		X	X			
AEs & Concomitant medications		Conmeds only	X[8]	AEs only		
LABORATORY ASSESSMENTS						
Complete Blood Cell Count with diff (CBC)[2]	X		X			
Chemistry Profile[2]	X		X			
Liver Function Testing[3]	X		X			
PSA	X		X			X
Testosterone	X		X			X
Thyroid function (TSH) [7]	X					
Coagulation Testing (INR, PT, PTT)	X					
TREATMENT EXPOSURE						
LHRH Agonist or Antagonist			X[6]			
FOLLOW-UP						
Metastatic Status						X
Survival Status						X
CT or MRI of the Chest, Abdomen, and Pelvis					X[5]	
Bone Scan or any type of PET CT					X[5]	

Key to Footnotes

1: Vital signs to include upright blood pressure, heart rate, respiratory rate, temperature, body weight (kg) and height (cm). Height at SCREENING ONLY. If patients are unable to come into clinic and get vitals or a physical exam during treatment, as long as it is not a danger to the patient, it will not be considered a violation or deviation. However, patients should have a blood pressure recording done within window of study visit or it will be considered a violation or deviation. The blood pressure recording can be done at home or in clinic. If done at home, the measurements should be relayed to the provider or research team member so it can be recorded in the patient's medical record.

2: Hematology testing to include full CBC with WBC, ANC, hemoglobin, and platelet count and differential. Chemistry to include Na, K+, Chloride, CO2, BUN creatinine, calcium, glucose.

3: Liver functions testing to include Albumin, ALT, AST, Total protein, Alk Phos, Total Bilirubin. LFTs will be monitored at every 3 months follow up during protocol treatment or more often at the discretion of the treating physician for the entire course of study treatment.
4: Long term follow-up for metastasis and survival will occur every 6 months until we reach the required amount of metastasis for a total planned study duration of about 5 years, assuming 200 patients accrued per year.
5: CT or MRI of the chest, abdomen and pelvis, and bone scan **or** any type of PET CT to be done once, at the time of initial PSA failure, defined as PSA at nadir + 2 ng/ml and testosterone level above 50 ng/dl. After results of protocol required scans at sign of PSA failure, investigator should initiate salvage therapy at their discretion. Then, if the PSA is still + 2 ng/ml above nadir and the testosterone is lower than 50 ng/dl while still on salvage ADT, also known as castrate resistant PSA failure, imaging is to be done every 6 months or sooner if the investigator chooses, until distant metastasis defined as bone, lymph node or visceral metastasis is documented. Survival status can be assessed using public records. **Note:** If the treating physician decides to initiate salvage therapy prior to the patient's PSA reaching nadir +2 ng/ml, and the testosterone level is < 50 ng/ml, then this would also be considered castrate resistant PSA failure and the imaging should be done then and every 6 months thereafter.
6: **Arm 1 patients:** Telemedicine/virtual visits will be allowed during study treatment and follow up, per institutional policies. Only locally/institutionally approved systems may be used. C1D1 does not need to be done in person and can be done virtually since Arm 1 is a continuation of their current standard of care treatment/ADT regimen. Study visits will start when the patient's next LHRHA injection is due. LHRHA schedules can vary but in most cases, the patient's LHRHA injection will be every 3 months, therefore the first study visit will be when the next one is due. Should the patient be on monthly injections, the first study visit will be when the next monthly injection is due. In the instance where the patient is receiving 6-month injections, the patient's first study visit will be within 3 months (a month is defined as 28 days) after registration or when the next LHRHA injection is due, whenever is sooner. Regardless of patient's LHRHA injection schedule, study visits will be every 3 months after the first study visit.
7: Only patients who are participating in this trial in Canada should have TSH evaluated at screening. Patients randomized to Arm 1 do not need subsequent TSH tests. Free T3 and Free T4 should be done only if TSH is abnormal. Fasting not required.
8: If a patient is being seen virtually and not in person, AEs will still need to be followed, assessed, and documented throughout the course of the study treatment or until resolved.

9.2 Arm 2 Calendar and Evaluations (cycle = 28 days)

Number of months left of ADT at time of registration = number of cycles on study (i.e. if patient has 12 more months of ADT left, he will have 12 cycles on study)

Study Evaluation	Screening	Screening	Treatment Cycle Day 1	Treatment Cycle 1-3 Day 15	End of Treatment	PSA Failure	Long Term Follow Up[4]
	Within 90 days prior to registration	Within 42 days prior to registration	Every 28 days ± 3	± 3 days	± 7 days	± 28 days	± 28 days
REQUIRED ASSESSMENTS							
Informed Consent		X					
Medical History		X					
Diagnosis and Staging Information		X					
Physical Exam		X	X				
Vital signs and ECOG Performance Status[1]		X	X				
AEs & concomitant medications		Conmeds only	X[8]		AEs only		
LABORATORY ASSESSMENTS							
Complete Blood Cell Count with diff (CBC)[2]	X		X				
Chemistry Profile[2]	X		X				
Liver Function Testing[3]	X		X	X			
PSA	X		Q3rd Cycle				X
Testosterone	X		Q3rd Cycle				X
Thyroid function (TSH) [7]	X		C3D1				
Coagulation Testing (INR, PT, PTT)	X						
TREATMENT EXPOSURE							
LHRH Agonist or Antagonist			X[6]				
Abiraterone acetate			X				
Prednisone			X				
Apalutamide			X				
FOLLOW-UP							
Metastatic Status							X
Survival Status							X
CT or MRI of the Chest, Abdomen, and Pelvis						X[5]	
Bone Scan or any type of PET CT						X[5]	

Key to Footnotes

1: Vital signs to include upright blood pressure, heart rate, respiratory rate, temperature, body weight (kg) and height (cm). Height at SCREENING ONLY. AE review should include any cardiac events that may have happened since the last clinic visit. If patients are unable to come into clinic and get vitals or a physical exam during treatment, as long as it is not a danger to the patient, it will not be considered a violation or deviation. However, for C1D1 visits, patients should be seen in person by the sub-investigator to establish a baseline foundation. Study visits after C1D1 that are done virtually, those patients should still have a blood pressure recording done within window of study visit or it will be considered a violation or deviation. The blood pressure recording can be done at home or in clinic. If done at home, the measurements should be relayed to the provider or research team member so it can be recorded in the patient's medical record.

2: Hematology testing to include full CBC with WBC, ANC, hemoglobin, and platelet count and differential. Chemistry to include Na, K+, Chloride, CO2, BUN creatinine, calcium, glucose.

3: Liver functions testing to include Albumin, ALT, AST, Total protein, Alk Phos, Total Bilirubin. LFTs will be monitored every 15 days for the first 3 months and then monthly during protocol treatment or more often at the discretion of the treating physician for the entire course of study treatment.

4: Long term follow-up for metastasis and survival will occur every 6 months until we reach the required amount of metastasis for a total planned study duration of about 5 years, assuming 200 patients accrued per year.

5: CT or MRI of the chest, abdomen and pelvis, and bone scan **or** any type of PET CT to be done once, at the time of initial PSA failure, defined as PSA at nadir + 2 ng/ml and testosterone level above 50 ng/dl. After results of protocol required scans at sign of PSA failure, investigator should initiate salvage therapy at their discretion. Then, if the PSA is still + 2 ng/ml above nadir and the testosterone is lower than 50 ng/dl while still on salvage ADT, also known as castrate resistant PSA failure, imaging is to be done every 6 months or sooner if the investigator chooses, until distant metastasis defined as bone, lymph node or visceral metastasis is documented. Survival status can be assessed using public records. **Note:** If the treating physician decides to initiate salvage therapy prior to the patient's PSA reaching nadir +2 ng/ml, and the testosterone level is < 50 ng/ml, then this would also be considered castrate resistant PSA failure and the imaging should be done then and every 6 months thereafter.

6: **Arm 2 patients:** Telemedicine/virtual visits will be allowed during study treatment and follow up. Only locally/institutionally approved systems may be used. Patients must still get protocol-required bloodwork done and can be done at a local certified lab. C1D1 must be done in person, and then can be done virtually after the first cycle. Study visits will be monthly no matter what the LHRHA originally planned schedule is. Patients will receive their LHRHA when it is due or when instructed by their treating physician.

7: Only patients who are participating in this trial in Canada should have TSH evaluated at screening and at Cycle 3 Day 1. Free T3 and Free T4 should be done only if TSH is abnormal. Fasting not required.

8: If a patient is being seen virtually and not in person, AEs will still need to be followed, assessed, and documented throughout the course of the study or until resolved.

10. MEASUREMENT OF EFFECT

10.1 Progression Free Survival

10.1.1 **Metastasis or Any Cause Death:** Metastasis or any cause death, defined as the time from randomization to documentation of metastasis or death due to any cause, whichever occurs first, or censored at the date of last disease assessment for those alive and metastasis free. Metastasis is defined as radiographic evidence of lymph node, bone or visceral involvement and can be evaluated using a CT or MRI chest, abdomen, and pelvis, and bone scan, or any type of PET

10.1.2 **Castrate Resistant PSA Failure Free Survival**: Castrate resistant PSA failure is defined as the first PSA increase that is 2 ng/mL above the nadir, which is confirmed by a second value 3 or more weeks later, while the serum total testosterone level is < 50 ng/dl (per the PCWG2 criteria). Castrate resistant PSA failure free survival is the time from randomization to castrate resistant PSA failure or death from any cause, whichever comes first; or censored at the date of last disease assessment for those alive and PSA failure free.

10.1.3 **Prostate Cancer Specific Survival**: Prostate cancer specific survival is defined as the time from randomization to death from prostate cancer where death due to other causes are considered as competing risk, or censored at the last date of follow up in living patients.

10.1.4 **Overall Survival:** Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

10.1.5 **Disease Free Survival:** A composite disease free survival endpoint consisting of castrate resistant PSA failure and/or local, regional or distant failure and death from any cause. Disease free survival is measured from the date of randomization to the first recorded disease recurrence, or censored at the date of last disease assessment for those alive and disease recurrence free.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

The DF/HCC ODQ will collect, manage, and perform quality checks on the data for this study.

11.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

11.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

11.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from the third-party drug supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

11.4 Collaborative Agreements Language

N/A

12. STATISTICAL CONSIDERATIONS

12.1 Study Design and Primary Endpoint

This is a randomized phase III study to assess whether combination of LHRH agonist or antagonist with apalutamide, abiraterone acetate and prednisone (AAP) can prolong metastasis free survival (MFS) compared to LHRH agonist or antagonist alone in men whose PSA remains detectable after the completion of Radiation Therapy (RT) and 6-12 months of conventional ADT. Participants will be randomized with 1:1 allocation to receive LHRH agonist or antagonist alone (Arm1) versus LHRH + AAP (Arm2) using permuted blocks methods. Randomization will be stratified by the stratification factors described in section 4.6: (1) entry PSA level (> 0.5 vs ≤ 0.5 ng/ml), (2) planned total duration of ADT (12 vs. > 12 months), and (3) USA vs. Canada.

The primary endpoint is MFS, measured from the date of randomization to the date of documented metastatic disease or death from any cause, censored at the date of last disease assessment for those alive and metastasis free.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

The primary endpoint MFS is the composite of metastasis or any cause death, defined as the time from randomization to documentation of metastasis or death due to any cause, whichever occurs first, or censored at the date of last disease assessment for those alive and metastasis free. Metastasis is defined as radiographic evidence of lymph node, bone or visceral involvement and should be evaluated using a CT or MRI chest, abdomen, and pelvis, and bone scan or any type of PET.

12.2.2 Definition of Secondary Endpoints

12.2.2.1 **PSA Nadir:** PSA nadir is defined as the lowest PSA during the entire RT and ADT treatment. A nadir could occur prior to randomization or after randomization because patients will receive additional hormone therapy after randomization.

12.2.2.2 **Castrate Resistant PSA Failure Free Survival**: Castrate resistant PSA failure is defined as the first PSA increase that is 2 ng/mL above the nadir, which is confirmed by a second value 3 or more weeks later, while the serum total testosterone level is < 50 ng/dl (per the PCWG2 criteria). Castrate resistant PSA failure free survival is the time from randomization to castrate resistant PSA failure or death from any cause, whichever comes first; or censored at the date of last disease assessment for those alive and PSA failure free.

12.2.2.3 **Prostate Cancer Specific Survival**: Prostate cancer specific survival is defined the time from randomization to death from prostate cancer where death due to other causes are considered as competing risk, or censored at the last date of follow up in living patients.

12.2.2.4 **Overall Survival**: Overall survival is defined as the time from randomization to death from any cause with men censored at time of last follow up if alive.

12.2.2.5 **Disease Free Survival:** Disease free survival is measured from the date of randomization to the first recorded disease recurrence consisting of castrate resistant PSA failure and/or local, regional or distant failure and death from any cause, whichever comes first, or censored at the date of last disease assessment for those alive and disease recurrence free.

12.2.2.6 **Toxicity as measured by CTCAE v.5:** We will measure Grade 1-5 toxicities at study visits and follow-up using the CTCAE v.5 forms and determine attribution. All subjects will be evaluable for toxicity from the time of their first treatment.

12.3 Sample Size, Accrual Rate and Study Duration

The recent findings from Intermediate Clinical Endpoints of Cancer of the Prostate (ICECaP) Working Group suggested MFS is a strong surrogate of OS in localized prostate cancer; the estimated 5-year MFS rate was 76% (95%CI: 75-77%) and 8-year OS was 66% (65-67%) from diagnosis in men who received RT plus ADT for high risk localized disease defined by NCCN or D'Amico criteria.[15] For this study, we will enroll men with high-risk prostate cancer and whose PSA remains detectable after completing radiation and 6-12 months of ADT. Therefore, we assumed the 4-year MFS rate of 65% in this population.

Recent phase III studies suggested apaplutamide[8] (HR=0.28 from SPARTAN study), enzalutamide[17] (HR=0.29), and darolutamide[16] (HR=0.41 from ARAMIS study) improves MFS in men with M0 CRPC who continued to receive ADT. The Stampede trial had shown that adding abiraterone acetate improved OS for men with high risk N0M0 or N1M0 prostate cancer treated with RT and ADT (HR=0.75). MFS was not analyzed by the Stampede study, but we would expect a greater treatment effect on MFS than OS. Given our high-risk prostate cancer population of N0M0 or N1M0 patients but who are showing signs of castrate resistance (i.e. detectable PSA) despite RT and 6-12 months of ADT, MFS HR of 0.52 was assumed for this population

This study is designed to have adequate power to detect a 48% reduction in the MFS hazard rate (from 0.1077 to 0.0558, hazard ratio=0.52) on the LHRH plus AAP arm. This difference corresponds to an improvement in 4-year MFS rate from 65% to 80% under the exponential distribution assumption. There will be 90% power to detect this MFS difference assuming that 400 men are enrolled over 2 years (200 patients per year) with 3 years of additional follow-up (a

total of study duration of 5 years) at one-sided alpha of 0.025 assuming 10% drop out rate. Full information under the alternative hypothesis will occur at 105MFS events. One interim analysis of MFS will be conducted at 65% information time. Given that 40% of men with high risk prostate cancer would be expected to have a detectable PSA after 6-12 months of ADT, we expect at least 1000 men will be screened to identify 400 eligible men for study.[10]

12.4 Interim Monitoring Plan

One interim analysis of MFS is planned at 65% of information (68 events, approximately at 3.3-3.4 years after the first participant randomized). The final analysis will be conducted when 105MFS events have been observed.

Early stopping for efficacy will be monitored using O'Brien Fleming use function boundaries. The O'Brien Fleming boundary at 65% and 100% information is 2.55 and 1.99 with corresponding one-sided normal significance levels of 0.005 and 0.023. Monitoring for early stopping in favor of the null hypothesis (lack of difference in MFS) will be done using repeated confidence interval methodology similar to that described by Jennison and Turnbull (1989). At each interim analysis a nominal (1-2*alpha) % confidence interval on the hazard ratio will be computed, where alpha is the nominal significance level of the O'Brien Fleming use function boundary at that analysis time. If the confidence interval excludes the target HR of 0.52, the study will be stopped early for lack of effect.

This study will be monitored by the DF/HCC Data and Safety Monitoring Board (DSMB). The DSMB meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMB will also review interim analyses of outcome data. Reports regarding outcome will remain blinded to the investigators until full information is achieved or as directed by the DSMB.

12.5 Analysis of Primary Endpoints

Final analysis of MFS will be performed after the full information (105 events) is achieved. MFS distribution will be estimated using the method of Kaplan-Meier; 4-year MFS rate and 95% two-sided confidence interval (CI) will be provided by treatment arm. The primary analysis is a superiority test of MFS, performed using a stratified log-rank test, which includes the stratification factors defined at randomization. A one-sided p-value from the stratified log-rank test less than 0.023 or two-sided p-value less than 0.046 (accounting for one interim analysis conducted at 65% information) will indicate that the experimental arm is superior to the control arm. A stratified Cox proportional hazards regression model will estimate the MFS treatment hazard ratio with 95% 2-sided CI.

12.6 Analysis of Secondary Endpoints

Analysis of other efficacy endpoints, including OS, disease free survival and castrate resistant PSA failure free survival, will be similar to those described for the MFS analysis. Prostate cancer-specific survival will be analyzed using a competing risk model, where cumulative

incidence of prostate cancer mortality, cardiovascular (CV) mortality and deaths from other causes will be estimated and compared between treatment arms using Gray's test with adjustment of stratification factors of randomization. A nominal p-value ≤ 0.05 (two-sided) is considered as statistically significant.

To compare MFS and OS by randomized treatment groups, we will conduct subgroup analysis defined by: (1) biopsy Gleason score (≤7 vs. >7), (2) baseline comorbidity groups ("none or minimal" vs. "moderate or severe" comorbidity using the established Adult Comorbidity Metric), (3) baseline serum testosterone levels (< 50 vs. ≥ 50 ng/mL), (4) planned total duration of ADT (12 vs. > 12 months), (5) baseline PSA(<0.5 vs. ≥0.5 ng/mL) and (6) N0 vs. N1 at diagnosis. Subgroup analyses would be considered exploratory with limited statistical power unless large difference exists between groups regarding treatment effect on these outcomes.

For toxicity reporting, all adverse events will be graded and analyzed using CTCAE version 5. The worst grade will be used if any toxicity event is reported multiple times on the same participant. Adverse events will be summarized according to grade, overall and by treatment arm, as number and percentage of participants. All adverse events resulting in discontinuation, dose modification, and/or dosing interruption, and/or treatment delay of drug will also be summarized by treatment arm.

12.7 Reporting and Exclusions

The following Analysis Populations are planned for this study:

Full analysis set (FAS): The FAS will include all randomized patients with treatment groups assigned in accordance with the randomization, regardless of the treatment actually received or any dosing error. Patients who are randomized but do not subsequently receive treatment are included in the FAS. The FAS will be used for all efficacy analyses.

Safety analysis set: The safety population will include all patients who receive at least one dose of study treatment. Patients will be analyzed in the treatment group according to the study treatment they actually receive. The safety population will be used for the analysis of safety data in this study.

13. ETHICS

13.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by the DFCI IRB and by the IRB of record for each outside site.

The sponsor investigator, Dr. Anthony V. D'Amico is responsible for informing the DFCI IRB and all external sites of any amendment to the protocol. The site investigator is responsible for informing the local IRB of any amendment to the protocol in accordance with local

requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

13.2 Ethics Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

13.3 Informed Consent Procedures

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

14. PUBLICATION PLAN

The data will be collected and analyzed by the study team. It is anticipated that the results will be made public within 12 months of the end of data collection. A manuscript is planned to be published in a peer-reviewed journal, however initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three (3) years after the end of data collection, and a final report will be sent to Janssen within 3 months of completion of data collection.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

DF/HCC Protocol #: 18-530

APPENDIX B

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

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16. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1. Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Policies and Operations.

17. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1. Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain CTEP, FDA or OBA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to External Sites as needed.
- Oversee the data collection process from External Sites.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by External Sites and provide to the DF/HCC Sponsor for timely review and submission to the IRB of record, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the reporting requirements for the IRB of record to all External Sites.
- Provide External Sites with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor External Sites either by on-site or remote monitoring.
- Maintain Regulatory documents of all External Sites which includes but is not limited to the following: local IRB approvals/notifications from all External Sites, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all External Sites (conference calls, emails, etc) and maintain documentation all relevant communications.

2.2. External Site

An External Site is an institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC investigator. The External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document.

The general responsibilities for each External Site may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their IRB of record. For studies under a single IRB, the Coordinating Center will facilitate any study-wide submissions.
- Maintain regulatory files as per ICH GCP and federal requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required.
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.
- Submit Serious Adverse Event (SAE) reports to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to the Sponsor, Coordinating Center, and IRB of record as applicable.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.
- Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.

18. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1. Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- **Protocol revisions:** External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions should be IRB approved and implemented within a timely manner from receipt of the notification.

- **Protocol closures and temporary holds:** External Sites will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.2. Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites must send their version of the informed consent document to the Coordinating Center for sponsor review and approval. If the HIPAA authorization is a separate document, please submit to the sponsor for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In these cases, the approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

3.3. IRB Re-Approval

Verification of IRB re-approval for the External Sites is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received for the External Site on or before the anniversary of the previous approval date.

3.4. DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.5. Participant Registration and Randomization

To register a participant, the following documents should be completed by the External Site and faxed or e-mailed to the Coordinating Center:

- Copy of screening test results, including imaging and pathology results
- Signed participant consent form
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility checklist
- Clinic note, covering screening requirements and baseline AEs
- Additional screening assessments

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the External Site and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. External Sites should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

Subjects will be randomized by DF/HCC Office of Data Quality (ODQ) in a 1:1 ratio to either ARM 1 (Standard of Care) or ARM 2 (Experimental). Cycle 1 Day 1 is considered the first day of treatment. Following registration and randomization, subjects may begin protocol treatment. Issues that would cause treatment delays should be discussed with the sponsor-investigator.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

3.6. Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the External Site receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and IRB of record must be notified of any violations to this policy.

3.7. Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without IRB approval will be permitted. All External Sites are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8. Data Management

DF/HCC develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC provides a web based training for all eCRF users.

3.4.1. Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

If study forms are not submitted on schedule, the External Sites will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

3.9. Protocol Reporting Requirements

3.9.1. Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor and to the IRB of record.

3.9.2. Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

3.9.3. Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

4. MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.1. Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents to the Coordinating Center for monitoring. External Sites may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

External Sites will be required to participate in monthly Coordinating Center initiated teleconferences.

4.1.1. Remote Monitoring

DFCI CTO will virtually monitor sites throughout the study. The coordinating center will review 100% of participants' consent and eligibility for registration, and the DFCI CTO will review consent and eligibility for about 10% of participants within approximately 60 days of enrollment. The DF/HCC Lead Institution will request source documentation from External Sites as needed to complete virtual monitoring activities. External sites will be asked to forward de-identified copies of participants' medical record and source documents to the DF/HCC Lead Institution to aid in the source documentation verification process. A remote closeout visit will be conducted once per site at the end of study to verify resolution or previous monitoring findings and reconcile collected regulatory documents. Pharmacy records will be reviewed approximately once per year. Study visit documentation and CRFs will be reviewed for 10% of participants approximately every 6 months.

4.2. Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.3. Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each External Site. Accrual will be monitored for each External Site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

As this is a Phase III trial, 3 patients per site/annually is the minimum target for each site. However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site/annually should be a minimum target for each site..

5. AUDITING: QUALITY ASSURANCE

5.1. DF/HCC Internal Audits

All External Sites are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

5.2. Audit Notifications

It is the External Site's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

5.3. Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the IRB as applicable.

5.4. External Site Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.

APPENDIX C: DRUG DIARY

Study Participant Self-Administration Study Drug Diary

Participant Identifier: _____ ARM2 - Cycle Number: _____ Protocol #: _____
Your MD_____Phone_____
Your RN_____Phone_____

Treatment Plan:

Agent	Pre-medications; Precautions	Dose	Route	Schedule
Apalutamide**	Can be taken with or without food	Take _____ 60 mg tablets	Orally	Once daily Take all at once Example: 8am
Abiraterone Acetate*	No food at least two hours before the dose and for at least one hour after the dose	Take_____ 250 mg tablets	Orally	Once daily Take all at once Example: 8pm
Prednisone	Take with food, preferred to be taken in the morning	Take_____ 5 mg tablets	Orally	Twice daily -Once in AM -Once in PM

* Abiraterone acetate should **NOT** be taken at the same time as Apalutamide or prednisone.
** Apalutamide may be taken with prednisone (and food).

INSTRUCTIONS TO THE PATIENT:

1. All medications should be taken at the same time every day.
2. If a dose of study medication is skipped, missed or vomited, it should not be taken (or retaken if vomited) on the day of the missed dose but dosing should be resumed the following day. Doses should be taken no later than 12 hours after the scheduled time for dosing
3. Your study medications should not be crushed, chewed, or dissolved in water.
4. You may not consume grapefruit or grapefruit-containing products while taking the study medications.
5. Please bring your pill bottle and this form to your physician when you go to your next appointment.
6. Store at 68°F to 77°F. Keep out of reach of children.

Please record how many tablets you take of abiraterone acetate, apalutamide, and prednisone, the time you take them and any comments here below and bring the completed Diary as well as your study drug supply, including empty bottles, to every study visit. This will help us keep track of your study drug and how well you are tolerating it.

Protocol #_____Patient Name: _____ Patient Study ID_____

Date	Day	Number of Tablets or Capsules/Time of Day				Comments
		Apalutamide (All 4 tablets unless your MD reduced dose)	Abiraterone Acetate (All 4 tablets unless your MD reduced dose)	Prednisone (AM)	Prednisone (PM)	
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	13					
	14					
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	27					
	28					
	29					
	30					

Patient's Signature: _____ Date: _____