ALLIANCE FOUNDATION TRIALS (AFT)

PROTOCOL
NUMBER AFT – 19

A Phase 3 Study of Androgen Annihilation in High-Risk Biochemically Relapsed Prostate Cancer

Protocol Version: 5.0
Protocol Version Date: 5/17/2019

Investigational Products: apalutamide, abiraterone acetate/prednisone

IND Sponsor: Alliance Foundation Trials, LLC
IND#: 131411
Investigational Product Supplier and Funding Support: Janssen Scientific Affairs, LLC
Biomarker Funding and Analysis: Janssen R&D, LLC

ClinicalTrials.gov Identifier: NCT03009981

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Study Resources

Adverse Event Reporting accessible via the AFT website, https://alliancefoundationtrials.org/
IRT – Randomization System accessible via the AFT website, https://alliancefoundationtrials.org/
Site Zone https://sitezone.mywingspan.com/sitezone/trials For Site Zone Help: [redacted]
Medidata Rave→ iMedidata Portal https://login.imedidata.com
BiOMS AFT Resource Site https://cbmiapps.wustl.edu/confluence/display/AB/AFT+BioMS+Home

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Synopsis and Study Schema

Study Title	**A Phase 3 Study of Androgen Annihilation in High-Risk Biochemically Relapsed Prostate Cancer**
Study Number	AFT-19
Study Type/Phase	Interventional Phase III
Clinical Indication	Biochemically recurrent prostate cancer after prior radical prostatectomy
ClinicalTrials.gov Identifier	NCT03009981
IND Number	131411
Number of Trial Patients	504 patients
Estimated Duration of Trial	6 years
Rationale	Biochemically recurrent prostate cancer with a short PSA doubling time (≤ 9 months) represents a high-risk subpopulation with significant risk of prostate-cancer related mortality. The median prostate cancer-specific survival for patients with rapidly rising serum PSA is approximately 5 years, which is comparable to patients with limited metastatic castration-sensitive disease (< 4 bone metastases and/or node-only soft tissue involvement). A frequently applied standard of care in this setting is intermittent androgen deprivation therapy (IADT). Though IADT is initially effective in lowering PSA and reducing tumor burden, disease progression to castration-resistant prostate cancer is a uniform event, often caused by enhanced intra-tumoral ligand production and androgen receptor amplification. Potent androgen signaling inhibitors including androgen synthesis inhibitors and next generation androgen receptor (AR) antagonists have transformed the management of metastatic castration-resistant prostate cancer (mCRPC), with significant improvements in progression-free and overall survival with both treatment approaches.

Rationale (continued)	Combining the two treatment strategies was well tolerated in prior phase 2 studies in the castration-resistant disease setting, and an ongoing study of abiraterone acetate in combination with apalutamide (NCT02123758) in mCRPC has provided additional safety data supporting the use of the combination with minimal impact of apalutamide on the pharmacokinetic (PK) profile of abiraterone acetate. The application of potent androgen signaling inhibitors as single agents, which includes abiraterone acetate, enzalutamide, and apalutamide, in castration-sensitive prostate cancer has led to impressive preliminary results in durable PSA suppression and disease control, including initial data from an ongoing study of apalutamide alone and in combination with a LHRH agonist in biochemically relapsed prostate cancer (NCT01790126). Combining potent androgen synthesis inhibition with AR blockade in the castration-naïve disease setting with limited disease burden offers the potential to durably suppress or even eradicate disease with a finite duration of therapy. This hypothesis has not been previously evaluated in the biochemically recurrent castration-naïve disease setting. The current proposal, a randomized phase 3 study, will be the first to investigate the potential of combined potent androgen signaling blockade to lead to durable relapse-free survival in the castration-sensitive setting. Positive results from the current study would justify the implementation of potent androgen signaling inhibition in high-risk biochemically recurrent prostate cancer.

Primary Objective	To compare PSA progression-free survival in each of the experimental arms versus the control arm of luteinizing hormone releasing hormone (LHRH) analogue monotherapy.
Secondary Objectives	▪ To compare PSA progression-free survival in testosterone-evaluable population in each experimental arm versus the control arm. Testosterone-evaluable population includes all patients who achieve serum testosterone recovery to > 50 ng/dL with subsequent PSA measurements sufficient for evaluation. ▪ To compare the 36-month PSA progression-free survival rate in each experimental arm versus the control arm. ▪ To compare the time to recovery of serum testosterone to greater than 50 ng/dL in each experimental arm versus the control arm. ▪ To compare the time to castration resistance in each experimental arm versus the control arm. ▪ To compare the metastasis-free survival in each experimental arm versus the control arm. ▪ To compare the overall survival in each experimental arm versus the control arm. ▪ To characterize the safety profile in each treatment arm. ▪ To compare short-term and long-term health-related quality of life (HRQOL) in each experimental arm versus the control arm. ▪ To compare the quality-adjusted PSA progression-survival (PSA progression-free survival multiplied by utility score) of patients in each experimental arm versus the control arm.
Translational Science Objectives	▪ To investigate whether higher levels of expression of gene pathways associated with resistance to AR pathway inhibition, including but not limited to ARV7, neuroendocrine signaling, and glucocorticoid receptor (GR), as detected by analysis of whole blood RNA, will be associated with early resistance to potent AR signaling inhibition.

Translational Science Objectives (continued)	▪ To investigate whether baseline and/or depth of circulating serum testosterone suppression is associated with improved clinical outcomes including PSA progression-free survival and metastasis-free survival. ▪ To investigate whether application of previously validated prognostic gene expression signatures in archival primary prostate cancer tissue can identify a more homogenous high-risk group of biochemically relapsed patients as compared with clinical characteristics alone. ▪ To investigate whether application of other gene expression signatures, including androgen response and neuroendocrine signaling, to primary prostate cancer tissue is predictive of treatment outcomes among men treated with apalutamide with or without abiraterone acetate for biochemical relapse. ▪ To characterize the frequency of detection of AR- V7 using IHC in FFPE archival tissue and association with clinical outcomes including PSA progression-free survival and metastasis-free survival.
Trial Design and Schema	Randomized, open-label, three-arm, phase 3 study in men with biochemically recurrent prostate cancer and PSA doubling time ≤ 9 months at the time of study entry. Patients will be stratified by PSA doubling time (< 3 months vs. 3-9 months) and randomized in 1:1:1 fashion to one of three treatment arms: (1) Control arm consisting of LHRH analogue monotherapy, (2) Experimental arm consisting of apalutamide in combination with LHRH analogue, and (3) Experimental arm consisting of apalutamide, abiraterone acetate + prednisone, and LHRH analogue. Patients will be treated for a maximum duration of 52 weeks and then enter follow up phase until the time of PSA progression. Patients with PSA progression will be followed long term for development of castration resistance, first metastasis, and death.

Inclusion Criteria	▪ Histologically confirmed prostate adenocarcinoma ▪ Prior radical prostatectomy ▪ Biochemically recurrent prostate cancer with PSA doubling time ≤ 9 months at the time of study entry. Calculation of PSA doubling time should include the use of all applicable PSA values obtained within past 6-12 months prior to randomization, with a minimum of 3 values separated by at least 2 weeks apart. The PSA values used to calculate the PSA doubling time must all be ≥ 0.1 ng/mL, and should be measured in the same laboratory whenever feasible. PSA values obtained prior to therapeutic interventions (e.g. salvage radiation) will be excluded from the determination of PSA doubling time. PSA doubling time to be estimated using Memorial Sloan Kettering Cancer Center online calculator (https://www.mskcc.org/nomograms/prostate/psa_doubling_time) ▪ Prior adjuvant or salvage radiation or not a candidate for radiation based upon clinical assessment of disease characteristics and patient co- morbidities. ▪ Screening PSA > 0.5 ng/mL ▪ No definitive evidence of metastases on screening CT or MRI of abdomen/pelvis and radionuclide whole body bone scan per the judgment of the investigator. Abdominal and/or pelvic lymph nodes measuring 2 cm or less in short axis diameter are allowed. Lesions identified on other imaging modalities (e.g. PSMA or choline PET) that are not visualized on CT and/or MRI or radionuclide bone scan are allowed. Equivocal lesions on bone scan should be followed up with additional imaging as clinically indicated. ▪ Screening serum testosterone > 150 ng/dL. ▪ Eastern Cooperative Oncology Group (ECOG) Performance Status grade 0 or 1 or Karnofsky Performance Status ≥ 70 ▪ Age ≥ 18 years ▪ Medications known to lower the seizure threshold (see Appendix 1) must be discontinued or substituted at least 4 weeks prior to Cycle 1 Day 1.

Inclusion Criteria (continued)	▪ 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. ▪ Adequate organ function as defined by the following laboratory values at screening: • Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) < 2.5 x upper limit of normal (ULN) • Total serum bilirubin ≤1.5 x ULN. In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, subject may be eligible) • Serum potassium ≥ 3.5 mmol/L. Supplementation and re-screening is allowed. • Estimated creatinine clearance > 45 ml/min using Cockroft-Gault equation • Platelets ≥ 100,000/mL independent of transfusion and/or growth factors within 3 months prior to randomization • Hemoglobin ≥ 9.0 g/dL independent of transfusion and/or growth factors within 3 months prior to randomization • -Serum albumin ≥ 3.0 g/dL

Exclusion Criteria	▪ Prior systemic treatment with androgen deprivation therapy and/or first-generation anti-androgen (e.g. bicalutamide, nilutamide, flutamide) for biochemically recurrent prostate cancer. Prior ADT and/or first-generation anti-androgen in the (neo)adjuvant and/or salvage setting in conjunction with radiation or surgery is allowed provided last effective dose of ADT and/or first-generation anti-androgen is > 9 months prior to date of randomization and total duration of prior therapy is ≤ 36 months. ▪ Prior treatment with CYP17 inhibitor (e.g. ketoconazole, abiraterone acetate, galeterone) or next generation androgen receptor antagonist including apalutamide or enzalutamide ▪ Prior chemotherapy for prostate cancer except if administered in neoadjuvant or adjuvant setting ▪ Use of 5-alpha reductase inhibitor within 42 days prior to randomization ▪ Use of investigational agent within 28 days prior to randomization ▪ Use of other prohibited medications within 7 days prior to Cycle 1 Day 1 on study (Arms B and C only) (see Appendix 1 for list of prohibited medications) ▪ Prior bilateral orchiectomy ▪ Seizure or known condition that may pre-dispose to seizure (e.g. prior stroke within 1year to randomization, brain arteriovenous malformation, Schwannoma, meningioma, or other benign CNS or meningeal disease which may require treatment with surgery or radiation therapy) ▪ Uncontrolled hypertension ▪ Gastrointestinal disorder affecting absorption or the ability to swallow tablets ▪ Baseline severe hepatic impairment (Child-Pugh Class B & C) ▪ Intercurrent illness that is not controlled such as active infection, psychiatric illness/social situations that would limit compliance with study requirements ▪ Any chronic medical condition requiring a higher dose of corticosteroid than equivalent of 10 mg prednisone/prednisolone per day

SCHEMA

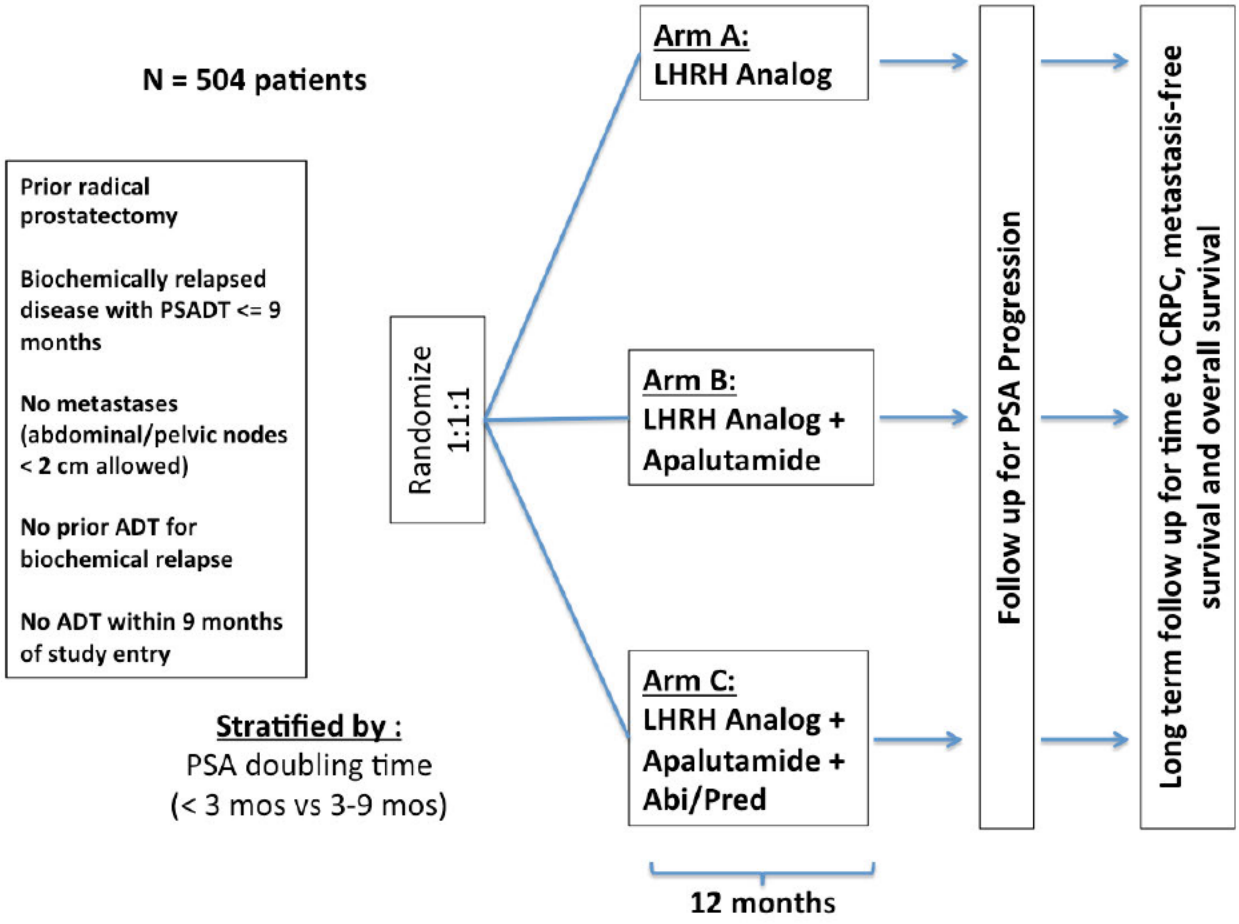

N = 504 patients
Prior radical prostatectomy
Biochemically relapsed disease with PSADT <= 9 months
No metastases (abdominal/pelvic nodes < 2 cm allowed)
No prior ADT for biochemical relapse
No ADT within 9 months of study entry
Stratified by :
PSA doubling time
(< 3 mos vs 3-9 mos)
Randomize 1:1:1
Arm A:
LHRH Analog
Arm B:
LHRH Analog + Apalutamide
Arm C:
LHRH Analog + Apalutamide + Abi/Pred
12 months
Follow up for PSA Progression
Long term follow up for time to CRPC, metastasis-free survival and overall survival

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1 Background Information

1.1 Overview of Biochemically Recurrent Prostate Cancer

1.1.1 Risk Stratification and Treatment for Biochemical Relapse

Prostate cancer is the second most common cancer in men worldwide, with an estimated incidence of 1,100,000 cases and 307,000 deaths in 2012 [1]. In the United States, approximately

220,000 cases were diagnosed in 2015 [2], of which an estimated two-thirds undergo radical prostatectomy or definitive radiation therapy (RT). Approximately 25%-35% of patients treated with definitive operative or radiation therapy for localized adenocarcinoma of the prostate will recur in the form of rising serum PSA without overt metastatic disease, which is called biochemical recurrence (BCR) [3,4]. An estimated 40,000 - 50,000 men in the U.S develop biochemically relapsed prostate cancer each year, yet treatment of men in this disease state is far from standardized. The optimal time to initiate treatment and the choice of specific therapy for such patients remains controversial and highly variable in clinical practice. This may be due to several potential reasons, which include (1) a dearth of prospective randomized trial data demonstrating an overall survival advantage for one particular therapeutic approach and (2) a biologically heterogeneous population with a variable natural disease course.

The kinetics of PSA change over time have emerged as an important independent prognostic factor for patients with BCR, with respect to both the time to development of metastases and risk of prostate cancer-specific mortality. In a cohort study of 8,669 men treated with localized therapy, of the 1,451 men with PSA recurrence, a PSA doubling time (PSADT) less than 3 months was associated with an approximately 50% chance of prostate-cancer specific mortality at 5 years. In contrast, those with a PSADT greater than 12 months had less than 10% prostate cancer-specific mortality during the same time interval [5]. In another study of 1,650 patients previously treated with external beam radiotherapy, at the time of PSA recurrence, the 3 year risk of distant metastases for PSADT 0-3 months, 3-6 months, 6-12 months, and > 12 months was 49%, 41%, 20%, and 7%, respectively (P <0 .001) [6]. For patients with PSA doubling times 9 months or less, the median prostate cancer-specific survival is approximately 5 years, which is similar to patients with limited extent metastatic castration-naïve disease [7].

Risk stratifying patients with BCR may allow for individualized selection of treatment. A prolonged PSADT, Gleason grade 3+3 at the time of diagnosis, positive surgical margins, and pre-treatment PSA level < 2.0 ng/mL, may help predict which patients benefit from localized salvage therapy such as radiotherapy after prior prostatectomy [8]. Patients with a PSADT greater than 12 months active surveillance may best be observed, especially in elderly patients with other potentially life-limiting co-morbidities who are not candidates for locally directed salvage therapy. Patients with a very short PSADT are at significant risk of prostate-cancer specific mortality over the next 5-10 years. Early treatment with

androgen deprivation therapy (ADT), in the form of luteinizing hormone releasing hormone (LHRH) agonists (e.g. goserelin, leuprolide acetate) with or without an androgen receptor (AR) antagonist (e.g. flutamide, bicalutamide), has been one standard approach.

There are no randomized data in this higher risk population that demonstrate an overall survival advantage for early continuous ADT versus deferred therapy until the time of progression to metastatic disease. Nevertheless, retrospective data and extrapolation from randomized clinical trials of patients with high-risk localized disease (e.g. node positive after radical prostatectomy or high-risk radiation therapy patients) favor earlier treatment with ADT [9-11]. For example, in a prior clinical trial of 98 men with node-positive prostate cancer who underwent prior radical prostatectomy and lymph node dissection, randomized to receive either immediate ADT or deferred until detection of distant metastases or symptomatic recurrences (i.e. not started at the time of rising PSA only), men randomized to the immediate ADT arm showed significant improvement in overall survival after a median follow up of 11.9 years (hazard ratio [HR] 1.84; 95% confidence interval [CI] 1.01-3.35, p = 0.04; median overall survival [OS] 13.9 vs. 11.3 years) [10]. In clinical trial RTOG 85-31, 173 prostate cancer patients with either clinical stage T3 or positive regional lymph nodes (radiographically or histologically) were randomized to receive radiation therapy + immediate long-term continuous ADT vs. RT + deferred ADT initiated at the time of disease relapse [9]. On multivariate analysis, RT + immediate ADT had a significant impact on absolute survival (p = 0.030), disease-specific failure (p = 0.014), metastatic failure (p = 0.005). While these studies are generally underpowered, and don't directly test the hypothesis of early vs. deferred ADT in the biochemically relapsed patient population, they do raise a provocative question as to whether early ADT provides a clinical benefit in these patients with lower volume disease.

1.1.2 Intermittent Androgen Deprivation Therapy is a Standard Therapeutic Approach in Biochemically Relapsed Prostate Cancer

The toxicities of long-term continuous ADT include risk of osteoporosis, diabetes, cognitive effects, and increased risk of cardiovascular disease. To potentially mitigate such toxicities, more contemporary treatment strategies involving intermittent ADT (IADT) are commonly used in BCR. The threshold at which to stop and start ADT during the course of IADT varies in prior clinical trials and clinical practice [12-15]. Numerous Phase 2 and 3 trials comparing IADT to continuous ADT, though not adequately powered for non-inferiority, have shown comparable overall and prostate cancer-specific survival and improved quality of life (QOL) [12-15]. More recently, a randomized Phase 3, non-inferiority trial of continuous vs. IADT in 1,386 patients with BCR after definitive radiation treatment was conducted by the NCIC [16]. There was no difference in overall survival after a median follow up of 6.9 years (HR = 1.02, 95% CI 0.86 – 1.21) and significantly better QOL with IADT. The results of this trial further justify finite treatment with IADT as a standard treatment approach in men with high-risk biochemically relapsed prostate cancer.

1.1.3 Study Rationale

Though ADT is initially effective in lowering PSA in the vast majority of patients, disease progression to metastatic castration-resistant prostate cancer is a frequent event in men with high-risk biochemically relapsed prostate cancer, due to enhanced intra-tumoral ligand production and androgen receptor amplification. Potent androgen signaling inhibitors including androgen synthesis inhibitors and next generation androgen receptor (AR) antagonists have transformed the management of metastatic castration-resistant prostate cancer (mCRPC), with improvements in progression-free and overall survival with both treatment approaches [17,18].
Combining the two treatment strategies has been demonstrated to be well tolerated in prior phase 2 studies in the castration-resistant disease setting, and an ongoing study of abiraterone acetate in combination with apalutamide (NCT02123758) provides evidence of tolerability with the two agents and minimal impact on pharmacokinetic (PK) profile [19, 20].

The application of potent androgen signaling inhibitors as single agents, including abiraterone acetate, enzalutamide, and apalutamide, in castration-naïve prostate cancer has led to impressive preliminary results with respect to durable PSA suppression and disease control, including initial data from an ongoing study of apalutamide alone and in combination with Lupron in biochemically relapsed prostate cancer (NCT01790126), as well as from a previously reported single arm phase 2 study of enzalutamide [21].

It is hypothesized that combining potent androgen synthesis inhibition with AR blockade in men with biochemically relapsed prostate cancer offers the potential to durably suppress or even eradicate disease with a finite duration of therapy. This hypothesis has not been previously evaluated in the biochemically recurrent castration-naïve disease setting. The current proposal, a randomized phase 3 study, will be the first to investigate the potential of combined potent androgen signaling blockade to lead to durable relapse-free survival in the castration-sensitive setting. Positive results from the current study would justify implementation of potent androgen signaling inhibition in high-risk biochemically relapsed prostate cancer.

1.2 Study Design

This is a randomized, open-label, three-arm, phase 3 study in men with BCR and PSA doubling time ≤ 9 months at the time of study entry. Patients will be stratified by PSA doubling time (< 3 months vs. 3-9 months) and randomized in 1:1:1 fashion to one of three treatment arms: (1) Control arm consisting of LHRH analogue monotherapy; (2) Experimental arm consisting of apalutamide in combination with LHRH analogue; and (3) Experimental arm consisting of apalutamide, abiraterone acetate + prednisone, and LHRH analogue. Patients will be treated for a maximum duration of 52 weeks and then enter follow up phase until the time of PSA progression, development of metastasis, or patient withdrawal from study, whichever occurs first. Patients with PSA progression will be treated per investigator discretion and will be followed long term until the development of castration resistance, first metastasis, and death.

The primary endpoint of the study is PSA progression-free survival in the intent-to-treat patient population. PSA progression during the 52-week treatment period is defined as a rising PSA confirmed on repeat measurement, and at least 25% and 2 ng/mL above nadir or baseline, whichever is lower. PSA progression during post-treatment follow up defined as PSA > 0.2 ng/mL confirmed by repeat measurement at least 2 weeks later. Secondary study endpoints include PSA progression-free survival in testosterone-evaluable population, 36-month PSA progression-free survival rate in both intent-to-treat and testosterone-evaluable populations, time to testosterone recovery, time to castration resistance, metastasis-free survival, quality of life, and safety. Each experimental arm will be compared against the control arm in pair-wise fashion. The study is not powered to detect differences in primary or secondary endpoints between the two experimental arms.

1.3 Study Design Rationale

1.3.1 Rationale for LHRH analogue Control Arm

There is no universally accepted standard of care for the form of ADT in men with biochemically recurrent prostate cancer. Either LHRH agonists such as leuprolide acetate with short term anti-androgen therapy in the form of bicalutamide, or degarelix, a luteinizing hormone releasing hormone (LHRH) antagonist, would be considered standard androgen therapies for androgen deprivation in this setting.

1.3.2 Rationale for the Combination of Apalutamide + LHRH analogue in Non-Metastatic Prostate Cancer

Apalutamide is FDA approved for the treatment of non-metastatic castration resistant prostate cancer. It is considered investigational in this trial setting. It is a potent AR antagonist that has demonstrated significant clinical activity in both the castration-resistant and castration-naive settings. Apalutamide in combination with leuprolide acetate is currently being evaluated in an ongoing randomized phase 2 study in men with biochemically recurrent prostate cancer. Initial results suggest potent suppression of PSA which is durable upon cessation of treatment. Apalutamide was also evaluated in combination with LHRH agonist therapy in a randomized, phase 3, placebo-controlled study in non-metastatic castration-resistant prostate cancer. In both studies, it is hypothesized that potent blockade of AR signaling via the combination of LHRH analogue + apalutamide will lead to more potent and durable suppression of cancer that may have an impact on time to PSA progression and metastasis-free survival. In the current study, we aim to demonstrate that treatment with the addition of apalutamide + LHRH analogue (with or without abiraterone acetate/prednisone) will potently suppress or even eradicate minimal residual disease among men with biochemically recurrent prostate cancer.

1.3.3 Rationale for the Combination of Apalutamide + Abiraterone Acetate/Prednisone + LHRH Analogue

We hypothesize that the addition of potent CYP17 antagonist abiraterone acetate (in combination with low dose prednisone 10 mg daily) to LHRH antagonist + potent AR antagonist apalutamide will produce complete shutdown of the androgen signaling pathway, translating into durable disease suppression or even eradication of residual burden of disease in patients with biochemically recurrent prostate cancer. This would translate into a clinically meaningful and beneficial delay or avoidance of further systemic therapy and potentially development of metastatic disease among men with high-risk BCR.

The combination of abiraterone acetate + apalutamide in men with mCRPC (who are also receiving continuous LHRH analogue therapy) has been recently evaluated [20]. The treatment combination was well tolerated, and tumor responses were observed in patients with abiraterone acetate and/or enzalutamide-refractory cancer, providing preliminary support of the hypothesis of additional efficacy with more complete androgen deprivation therapy. There was minimal impact of apalutamide on reducing exposure to abiraterone acetate in PK analyses; therefore, no significant drug-drug interactions between the two agents are expected in the current study. The toxicity profile was manageable (see Section 1.5 below).

1.3.4 Rationale for the Treatment Schedule

The study design utilizes the backbone of what can be regarded as the first "cycle" of IADT, a standard treatment option in men with biochemically recurrent prostate cancer. The duration of treatment, 12 months, is consistent with prior studies of intermittent ADT conducted in this disease setting, including an ongoing randomized phase 2 study of LHRH analog +/- apalutamide in biochemically relapsed prostate cancer [24-26]. A treatment duration of 12 months is hypothesized to be of sufficient duration to durably suppress or even eradicate residual disease in a subset of patients, yet not too long as to have detrimental impact on patient adherence and quality of life in this asymptomatic patient population.

1.3.5 Rationale for the Study Endpoints

PSA progression-free survival is the primary endpoint of the study. Though not validated as a surrogate for metastasis-free or overall survival in the biochemically recurrent setting, previous retrospective analyses of phase 3 studies conducted in both the castration-sensitive and castration-resistant setting have demonstrated that PSA progression-free survival (using PCWG2 definition) is significantly associated with overall survival [27]. In a retrospective analysis of the SWOG 9346 study of men receiving continuous versus intermittent ADT for metastatic castration-naive prostate cancer, the risk of death increased by 2.4 fold if PSA progression occurred within the first 7 months of treatment [27]. PSA progression-free survival was likewise chosen as the primary endpoint of the TAX3503 study of ADT +/- docetaxel in biochemically relapsed prostate cancer [28]. The definition of PSA progression employed in the current study is similar to that used in TAX3503. No standardized definition

of PSA progression has been accepted in the biochemically recurrent setting. A stringent definition of PSA progression as defined by rise of serum PSA to > 0.2 ng/mL during the follow up phase is justified in a trial with the aim of delaying or preventing disease relapse.

Sustained suppression of PSA can be reasonably expected to translate into longer durations of overall disease control and may translate into improved long-term outcomes including metastasis-free survival with longer follow up. Long-term endpoints including metastasis-free survival and time to castration resistance will be captured in the current study.

The addition of the androgen synthesis inhibitor abiraterone acetate to one of the experimental treatment arms poses the potential risk of delayed time to testosterone recovery, which may in turn impact time to PSA progression during the follow up phase. We will assume a 20% inevaluable rate for the purposes of study design, and also measure time to testosterone recovery and PSA progression-free survival in the testosterone-evaluable patient populations as key secondary endpoints of the study.

The study design is predicated around the hypothesis that more intense androgen deprivation therapy for a finite treatment period will translate into a longer duration off treatment, a clinically meaningful result that may result in improved overall quality of life across the spectrum of the disease course. Quality of life will be assessed using a series of validated instruments focusing on items relevant to the patient experience when receiving ADT. Severity of fatigue, hot flashes, cognitive changes, and overall health status will be measured at pre-specified time points, which include at baseline, during, and following completion of protocol therapy.

1.3.6 Rationale for the Correlative Studies

Archival tissue analysis

In patients with biochemically relapsed prostate cancer, there are validated clinical characteristics that can be used to identify a high-risk group of patients, including PSA doubling time, time interval from local therapy to biochemical relapse, and disease characteristics at the time of initial diagnosis. However, even within a clinically-defined high-risk group of patients, there exists significant heterogeneity with respect to long term outcomes including metastasis- free survival and prostate cancer-related mortality. Recent evidence supports the potential use of gene expression signatures from archival primary prostate cancer tissue in predicting time to metastasis among men with biochemical relapse [29, 30] **(Figure 1)**. In one particular study, the androgen signaling subgroups of the various platforms may have specific prognostic and/or predictive utility when applied to men receiving hormone therapy in this setting. The androgen signaling subgroup of OncotypeDx platform has been shown to be associated with clinical recurrence among men receiving androgen deprivation therapy for biochemical relapse in a prior retrospective study.

In addition, approximately 200 patients are expected to have DECIPHER testing performed prior to study enrollment, and give consent for access to genomic data in the DECIPHER

GRID database. This platform provides high density human exon array data for detailed assessment of the landscape of genes being transcribed within a population of cancer cells, and provides insights into potential resistance mechanisms.

An AR response signature based upon CYP17 and its co-factors along with AR regulated genes *AKR1C3* and *PCNA* has been shown to be associated with radiographic progression-free survival (rPFS) in the prior phase 3 study of abiraterone acetate in mCRPC [31] and can also be applied to archival tissue in the hormone sensitive setting to investigate association with outcomes. Finally, detection of AR- V7 in FFPE primary prostate cancer and HGPIN tissue using IHC assay is feasible [32]. Detection of AR-V7 in CTCs has been shown to be predictive of response to AR pathway therapy in the mCRPC setting [33]. Therefore, the potential predictive utility of detecting AR-V7 expression in archival tumor tissue in the castration sensitive setting will be explored in the current proposal.

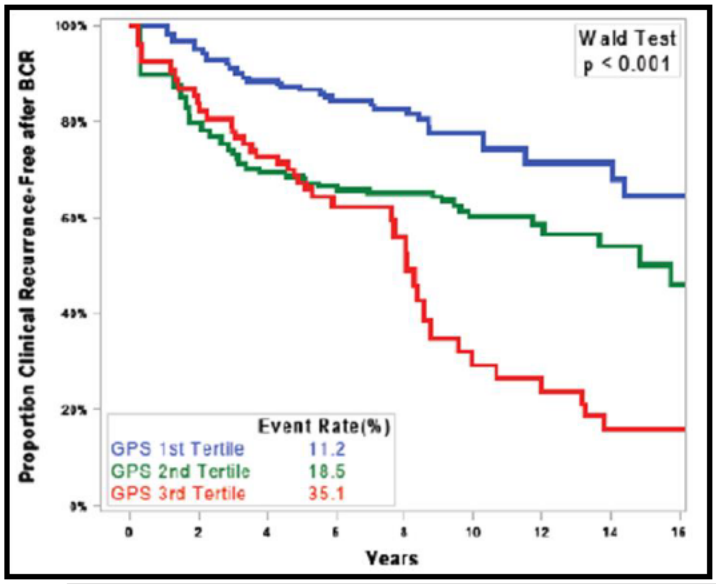


Figure 1

Circulating Biomarkers

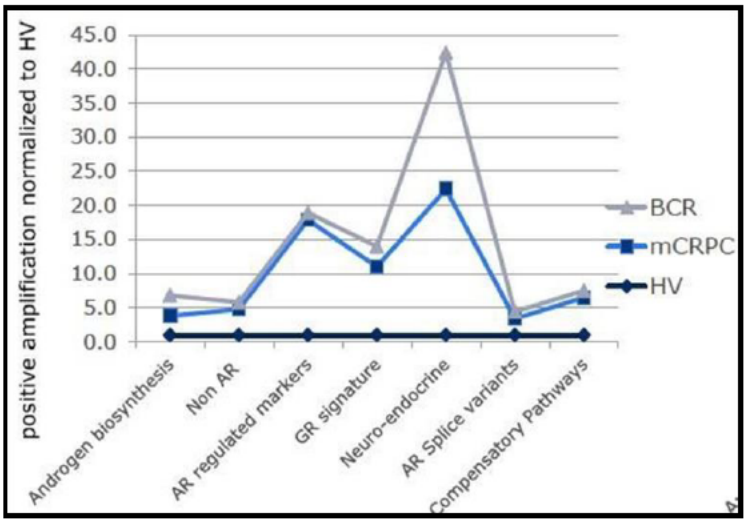


Figure 2

Analysis of circulating nucleic acids relevant to androgen receptor signaling as well as those implicated in putative mechanisms of resistance may offer the ability to identify subgroups of patients with biochemical relapse most likely to respond or develop early resistance to potent suppression of the androgen signaling pathway. Using internal data, Janssen has developed a whole blood RNA assay containing 38 genes comprising many of the pathways relevant to AR signaling and resistance, including AR-V7, androgen biosynthetic pathway, AR regulated genes, markers of neuroendocrine differentiation, and GR signature genes. In collaboration with Janssen, we have analyzed 17 samples from the ongoing randomized phase 2 study of Lupron +/- apalutamide in men with biochemically relapsed prostate cancer (NCT01790126). The analysis thus far has demonstrated that detection of circulating tumor RNA (normalized to healthy volunteers) is feasible across the gene groups, including, interestingly, 70% of patients with overexpression of the neuroendocrine marker NPY (neuropeptide Y) (Figure 2). We hypothesize that patients with higher baseline levels of expression of genes within putative resistance pathways of AR signaling, including AR-V7 and neuroendocrine signaling, will develop early resistance to AR signaling blockade translating into shorter time to PSA progression and castration resistance.

The depth of serum testosterone suppression on hormone therapy has been shown to be associated with treatment outcomes in patients receiving androgen deprivation therapy for castration sensitive disease. In a prior study of 153 patients treated with LHRH analogue therapy for metastatic disease (N = 54) or biochemical relapse (N = 99), achievement of serum testosterone level < 20 ng/dL after 6 months of therapy was associated with improved long-term outcomes [34]. In the current proposal, we hypothesize that more potent suppression of circulating testosterone levels will be associated with improvement in subsequent outcomes including PSA progression-free survival and metastasis-free survival.

1.3.7 Rationale for the Quality of Life Assessments

The health related quality-of-life (HRQOL) effect of more intense androgen deprivation therapy is unknown, and may be more prevalent and/or severe than that reported for LHRH analog monotherapy – this trial offers an important opportunity to assess this important issue.

1) Expanded Prostate Cancer Index Composite (EPIC): This is a validated prostate cancer-specific HRQOL instrument that measures urinary, bowel, sexual, and hormonal symptoms related to prostate cancer treatments, including prostatectomy, radiotherapy, and hormonal therapy [35]. Summary and subscale scores were derived by content and factor analyses.
   Test-retest reliability and internal consistency were high for EPIC urinary, bowel, sexual, and hormonal domain summary scores (each $r \geq 0.80$ and Cronbach's alpha ≥ 0.82) and for most domain-specific subscales. Correlations between function and bother subscales within domains were high $r > 0.60$). Correlations between different primary domains were consistently lower, indicating that these domains assess distinct HRQOL components.

2) Hot Flash Related Daily Interference Scale (HFRDIS): Hot flashes are another common side effect from ADT, and in some patients can be very bothersome [36]. HFRDIS is a 10-item scale that assesses the degree to which hot flashes interfere with a variety of daily activities and quality of life. Interference is rated on an 11-point scale (0=not interfere; 10=completely interfere). The validity of the HFRDIS has been demonstrated in breast cancer survivors and healthy women [36]. As the only hot-flash-specific HRQOL instrument, HFRDIS has also previously been used in prostate cancer patients receiving ADT [37].

3) EQ-5D-5L: This is a 6-item validated utility assessment instrument [38-41]. The first part consists of 5 items covering 5 dimensions including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 health states to which unconsciousness and death are added [42]. The sixth item is a visual analogue scale for overall health. The 5-item index score is transformed into a utility score between 0, “Worst health state,” and 1, “Best health state.” The index score can be used in a quality adjusted survival analysis [43]. For this study, the measured utility values for each patient will be combined with overall survival to calculate the quality-adjusted survival, and compared between each experimental arm versus control.

4) PROMIS Fatigue Scale: Fatigue is a well-described side effect from androgen deprivation therapy. The relative effects on fatigue and depression of luteinizing hormone releasing hormone analogues vs. more intense hormonal treatments is not currently known. In this trial, we will use measures from the Patient-Reported Outcomes Measurement Information System (PROMIS), part of the NIH Roadmap Initiative, which was developed to provide a publicly available resource of standardized, accurate, and efficient measures of symptoms, distress, and functioning [44-46]. The PROMIS fatigue measure [47] (8 items), which

includes two content domains of fatigue, experience and impact, were identified by a panel of experts. An initial item pool of 58 fatigue experience and 54 fatigue impact items were developed. The psychometric properties of these items were evaluated in a sample of 450 individuals from the general US population using classical test theory indices, monotonicity, and scalability.

*PROMIS® was funded with cooperative agreements from the National Institutes of Health (NIH) Common Fund Initiative. See www.nihpromis.org for additional information on the PROMIS initiative.

1.4 Study Agents

1.4.1 Apalutamide

Summary:

Apalutamide (also known as ARN-509, JNJ-56021927) is a potent and specific antagonist of the androgen receptor (AR) that is being developed for the treatment of men with prostate cancer. Apalutamide is FDA approved for the treatment of non-metastatic castration resistant prostate cancer. It is considered investigational in this trial setting. The tablet formulation of apalutamide is an immediate release oral tablet containing 60 mg of drug substance that will be used in the current study. The recommended starting dose of apalutamide, established in the phase 1 study and used in all subsequent studies, is 240 mg dosed orally once daily.

Nonclinical studies:

The mechanism of action of apalutamide is antagonism of AR signaling through inhibition of AR nuclear translocation and deoxyribonucleic acid (DNA) binding to androgen response elements, a mechanism that is distinct from the first-generation anti-androgen, bicalutamide. Unlike bicalutamide, apalutamide shows no significant agonist properties in an in vitro model of castration-resistant prostate cancer (CRPC) (e.g. AR-overexpressing prostate cancer cells; LNCaP/AR cells). In murine tumor models of CRPC, apalutamide showed tumor growth inhibition and tumor regression that were superior to bicalutamide.

Apalutamide and its major human plasma metabolite JNJ-56142060 (M3) are inducers of human CYP2B6 and CYP3A4 in cultured hepatocytes at concentrations up to 30 µM. In vitro, apalutamide is a moderate inhibitor of human cytochrome P450 isozyme CYP2C8 and CYP2B6 with IC50 values of 13.9 µM and 36 µM, respectively. Apalutamide is also a weak inhibitor of CYP2C9, 2C19, and 3A4 with IC50 values ranging from 54 µM to 67 µM. Metabolite JNJ-56142060 (M3) is a moderate CYP2B6, 2C8, and 2C9 inhibitor with IC50 values ranging from 38 to 49 µM in vitro.

Repeat dose toxicology studies up to 26 weeks of duration in male rats and 39 weeks duration in male dogs were conducted with once daily administration of apalutamide. The no observed adverse effect level (NOAEL) in the 26-week rat study was 25 mg/kg/day; corresponding apalutamide steady-state (Day 182) plasma Cmax and AUC from time 0 to time 24 hours post dose (AUC0-24h) values were 7.20 µg/mL and 135 µg•h/mL, respectively. The NOAEL in the

39-week dog study was below 2.5 mg/kg/day based upon lower body weight performance from 2.5 mg/kg/day onwards. At 2.5 mg/kg/day, apalutamide steady-state (Day 273) plasma Cmax and AUC0-24h values were 3.82 µg/mL and 86.6 µg•h/mL, respectively. The majority of clinical pathology and target organ changes observed in the rat and dog were attributed to the pharmacologic (anti-androgen) activity of apalutamide and included effects on prostate, epididymis and testes, progressing to benign interstitial adenomas in the 26-week rat study, as well as an increase in serum cholesterol associated with decreases in red cell parameters in rats. In the liver, multifocal bile duct/oval cell hyperplasia was observed in the 39-week dog study. Findings were either completely or partially reversible following a treatment-free recovery period (reversibility of bile duct/oval cell hyperplasia in dogs and interstitial adenomas in rats was not assessed). High-dose (25 mg/kg/day) daily administration of apalutamide resulted in tremors and seizures in dogs in the second week of dosing in a 28-day study. The average apalutamide concentration at the time of first observation of CNS toxicity was 30.2 µg/mL, which was about 4-fold higher than the mean apalutamide steady-state Cmax (7.55 µg/mL) at 240 mg/day measured during repeated dosing in patients with CRPC. When exposure is corrected for the difference in protein binding between species, the unbound concentration of apalutamide at which seizures were observed in dogs is about 6- fold higher than the estimated unbound steady-state Cmax at a dose of 240 mg in CRPC patients. No seizures have been observed in patients treated with apalutamide up to 480 mg/day (apalutamide steady-state Cmax=11.2 µg/mL).

Dose range finding studies have been conducted in female animals. The NOAEL was 100 mg/kg/day in a 28-day study in female rats, while 10 mg/kg/day was the maximum tolerated dose in a 21-day study in female dogs. Doses up to 100 mg/kg/day were well tolerated in a preliminary 10-day toxicity study in male and female mice.

Preclinical studies have demonstrated the absence of mutagenic, clastogenic, and phototoxic properties for apalutamide and its pharmacologically active metabolite JNJ-56142060 (M3). JNJ- 56142021 (M4), an inactive metabolite of apalutamide, tested negative in an in vitro bacterial reverse mutation (Ames) assay, but was weakly positive in an in vitro chromosome aberration test in human peripheral blood lymphocytes. However, the totality of nonclinical data, including absence of clastogenic activity in an in vivo bone marrow micronucleus test in the rat with adequate exposure to M4, supports the lack of an in vivo genotoxic potential of JNJ-56142021 (M4). The NOAEL for paternal toxicity and reproductive performance in the male rat was 25 mg/kg/day. Apalutamide administered at 150 mg/kg/day was associated with adverse, but reversible effects on sperm concentration, sperm motility and secondary sex organs that resulted in a lower copulation rate, a lower fertility rate, and a reduced potential for generating viable offspring.

Clinical Studies:

As of 22 June 2017, 324 men with prostate cancer have been treated with apalutamide across 7 ongoing clinical studies in the open-label clinical program: Studies ARN-509-001, ARN-509-002, ARN-509-004, 56021927PCR1008, 56021927PCR1010, 56021927PCR1019, and 56021927PCR1020. Additionally, 3,902 subjects were either treated with apalutamide or placebo in 4 ongoing placebo-controlled Phase 3 clinical studies: ARN-509-003, 56021927PCR3001, 56021927PCR3002, and 56021927PCR3003. Studies PCR3001, PCR3002 and PCR3003 are double-blinded studies, and Study ARN-509-003 is a double-blinded study which was unblinded 22 July 2017 as recommended by the Independent Data Monitoring Committee (IDMC). Subjects randomized to placebo in Study ARN-509-003 have the option to switch to active treatment with apalutamide.Therefore, of the 3,902 treated subjects in the ongoing double-blinded Phase 3 studies, 803 subjects with prostate cancer were identified as having been treated with apalutamide in Study ARN-509-003 after the safety reporting period. Studies ARN-509-004, 56021927PCR1010, and 56021927PCR3001 are evaluating the combination of apalutamide with abiraterone acetate and prednisone (AA-P).

As of 22 June 2017, 398 healthy men have received single doses of apalutamide (either as a single dose of 240 mg or 2 single doses of 60 mg) across 7 completed studies (ARN-509-006, 56021927PCR1007, 56021927PCR1011, 56021927PCR1012, 56021927PCR1015, 56021927PCR1017, and 56021927PCR1018). Study 56021927PCR1018 enrolled subjects with mild or moderate hepatic impairment (16 subjects) and subjects with normal hepatic function (8 subjects). Key efficacy and safety information for apalutamide are summarized in this IB, and include data available from clinical studies and the safety database as of 22 June 2017.

Pharmacokinetics and Product Metabolism

Clinical pharmacology studies demonstrate that apalutamide is rapidly absorbed with measureable plasma concentrations within 30 minutes after administration as either softgel capsules or tablets. The median peak plasma concentrations occurred 2 to 3 hours after administration. The bioavailability of apalutamide was comparable between softgel capsules and tablets. In subjects with CRPC, the increases in plasma Cmax and AUCs after repeated doses were approximately linear and dose-proportional over the dose range of 30 to 480 mg per day. The mean terminal half-life of apalutamide in healthy subjects after a single oral dose is approximately 7 days. The steady-state half-life of apalutamide in subjects with CRPC is approximately 4 days. Plasma trough concentrations of apalutamide increased steadily with time and in proportion to dose across cohorts. Based on these trough levels, most subjects had reached steady-state exposure by Week 4 (ie, following 3 weeks of continuous administration).

A high-fat meal did not alter the AUC of apalutamide and its metabolite JNJ-56142060 (M3) following a single 240 mg oral dose of apalutamide.

Efficacy

Study ARN-509-001:

Anti-tumor activity, as measured by 12-week prostate-specific antigen (PSA) percentage change response (defined as ≥50% decline from baseline), was shown in 48% of the Phase 1 subjects across all dose levels. In the Phase 2 portion of the study, the 12-week PSA percentage change (50% decline from baseline) in the high risk non-metastatic castration- resistant prostate cancer (NM-CRPC) cohort (Cohort 1), the metastatic CRPC (mCRPC) cohort (no previous abiraterone acetate, enzalutamide or chemotherapy for mCRPC; Cohort 2), and the post-abiraterone acetate mCRPC cohort (Cohort 3), was 89%, 88%, and 22%, respectively. Median time to PSA progression was 24 months, 18.2 months, 3.7 months for Cohorts 1, 2,and 3 respectively. Metastasis-free survival (MFS) in Cohort 1 was not reached after median follow up of 28 months (range: 1.0, 39.8 months). Similarly, progression-free survival (PFS) in Cohorts 2 and 3 was not reached after median follow up of 22.1 months (range: 2.7, 37.5 months) and 5.6 months (range: 1.9, 24.3 months), respectively.

Safety and Tolerability

Single Agent Studies in Prostate Cancer

Study ARN-509-001:

In the Phase 1 portion of Study ARN-509-001 in subjects with CRPC, 1 dose-limiting toxicity (DLT) observed in the 300 mg cohort: the subject experienced Grade 3 abdominal pain that resolved upon study drug interruption and subsequent dose reduction. As a result of this DLT, an additional 3 subjects were enrolled in the 300 mg cohort. No additional DLTs were observed.

As of 31 December 2014, for the Phase 2 portion of Study ARN-509-001, across the 3 cohorts, the majority of the AEs were of Grade 1 or 2 severity. Most Grade 3 AEs were reported in 1 subject each. Grade 3 AEs reported in >1 subject included constipation, back pain, spinal cord compression, rash erythematous, hypocalcemia, contusion, anemia, hypertension, malignant melanoma, and fatigue. No Grade 3 AE was reported in more than 3 subjects. Grade 4 AEs reported in 1 subject each included duodenal ulcer, abdominal adhesions, asthenia, anemia, and brain neoplasm malignant. Drug-related AEs observed across the 3 cohorts in >10% of subjects were fatigue (47%), diarrhea (28%), nausea (27%), abdominal pain (13%), hot flush, hypothyroidism and dysgeusia (11% each). Drug-related AE of blood thyroid stimulating hormone (TSH) increased was reported in 8 subjects (8%). Decreased appetite and weight loss were reported as drug-related AEs in 8 subjects (8%) and 5 subjects (5%), respectively. Nineteen (20%) subjects had reported drug-related AEs under the system organ class (SOC) of skin and subcutaneous disorders, which included pruritus (7 subjects [7%]), rash (7 subjects [7%]), rash erythematous (3 subjects [3%]), and rash macular (3 subjects [3%]). Serious adverse events were experienced by 31% of subjects and 15% had AEs leading to discontinuation of study treatment. Two deaths due to progressive disease were reported in the mCRPC cohort (Cohort 2).

The side effect profile had not changed at the time of the safety cutoff for this IB (22 June 2016).

Study ARN-509-002:

As of 22 June 2016, AEs reported in subjects receiving apalutamide as monotherapy or in combination with LHRHa were mainly in the SOCs of General Disorders and Administrative Site Conditions (63%; mainly fatigue), Gastrointestinal Disorders (56%; mainly diarrhea, nausea and abdominal pain or discomfort), Vascular Disorders (54%; mainly hot flush), Nervous System Disorders (49%; mainly headache, dysguesia, and memory impairment), Musculoskeletal and Connective Tissue Disorders (42%; mainly arthralgia and muscle weakness), Reproductive System and Breast Disorders (37%; mainly nipple pain and gynecomastia), and Psychiatric Disorders (29%; mainly insomnia). Adverse events of rash were reported in 11% of subjects. Adverse events of fall and hypothyroidism were each reported in 5% of subjects. In the LHRHa monotherapy group, AEs reported in >10% of subjects were hot flush (69%), fatigue (55%), and arthralgia (17%). Anemia was reported in 10% of subjects.

Studies in Healthy Men

Safety data are available from the 6 completed studies in healthy men and 1 ongoing study (56021927PCR1018). Subjects in Studies ARN-509-006, 56021927PCR1007, 56021927PCR1011, and 56021927PCR1012, and 56021927PCR1018 received or are receiving a single dose of 240 mg of apalutamide. For studies 56021927PCR1015 and 56021927PCR1017, the subjects received 2 doses of apalutamide at 60 mg each and at an interval of 8 weeks to 9 weeks apart.

Most AEs were Grade 1 in severity. Drug-related AEs of Grade 2 or higher included nausea (ARN-509-006), Grade 3 vasovagal syncope (56021927PCR1007), Grade 2 neutrophil count decreased and white blood cell count decreased in 1 subject (56021927PCR1011). In Study 56021927PCR1012, drug-related AEs of Grade 2 upper respiratory tract infection (5 subjects), headache, testicular swelling, viral illness, nervousness, constipation, back pain, and generalized pruritis were reported (each 1 subject). In Study 56021927PCR1015, drug-related AEs of Grade 2/3 neutropenia and Grade 2 leukopenia (1 subject), Grade 4 blood creatinine phosphokinase increased (2 subjects), Grade 2 headache (1 subject). In Study 56021927PCR1017 Grade 2 headache (1 subject) and Grade 3 alanine aminotransferase increased (1 subject) were reported as drug-related. Based on the mechanism of action of apalutamide and administration of the therapeutic dose of 240 mg, a transient increase in mean from baseline was sometimes observed for testosterone and LH in healthy men.

1.4.2 Abiraterone acetate + Prednisone

Abiraterone acetate in combination with prednisone is approved in the treatment of patients with mCRPC and in patients with high-risk metastatic castration sensitive prostate cancer. Abiraterone acetate is a selective, irreversible inhibitor of androgen biosynthesis that potently

blocks CYP17, which is critical to testosterone synthesis by the adrenals, testes, and within the prostate tumor. In phase 1-2 trials, treatment with abiraterone acetate resulted in significant antitumor activity in both taxane naïve and taxane treated patients. The most common adverse events were associated with increased mineralocorticoid levels, including hypokalemia, fluid retention, and hypertension; these were largely abrogated by co-administering low-dose glucocorticoids. Two phase III trials have been undertaken with abiraterone acetate. In study COU-AA-301, patients with progressive mCRPC following treatment with docetaxel were treated with abiraterone acetate and prednisone or prednisone alone. A total of 1195 men were randomized, with a primary endpoint of overall survival. Men who received the abiraterone acetate enjoyed a significant reduction in the risk of death, with a hazard ratio of 0.65, associated with a median survival of 14.8 months as opposed to 10.9 months (P<0.0001). As a result, abiraterone acetate and prednisone were approved by the FDA for patients with mCRPC who have progressed despite prior treatment with docetaxel in April 2011.

In study COU-AA-302, 1088 patients with mCRPC who were chemotherapy naïve were randomized to abiraterone acetate and prednisone vs. prednisone alone. On March 8, 2012, the independent data monitoring committee (IDMC) unblinded the study as a planned interim analysis. In the most recent survival analysis, patients who received a placebo and prednisone had a median survival of 30.3 months versus 34.7 months for those receiving abiraterone acetate and prednisone (HR 0.81 (0.70-0.93, p = 0.0033). The FDA has expanded the indication of abiraterone acetate to include patients with mCRPC who are chemotherapy naïve.

In the LATITUDE study, 1199 patients were randomly assigned to receive either androgen-deprivation therapy plus abiraterone acetate (1000 mg daily, given once daily as four 250-mg tablets) plus prednisone (5 mg daily) (the abiraterone group) or androgen-deprivation therapy plus dual placebos (the placebo group). The two primary end points were overall survival and radiographic progression-free survival. After a median follow-up of 30.4 months at a planned interim analysis (after 406 patients had died), the median overall survival was significantly longer in the abiraterone group than in the placebo group (not reached vs. 34.7 months) (hazard ratio for death, 0.62; 95% confidence interval [CI], 0.51 to 0.76; P<0.001). The median length of radiographic progression-free survival was 33.0 months in the abiraterone group and 14.8 months in the placebo group (hazard ratio for disease progression or death, 0.47; 95% CI, 0.39 to 0.55; P<0.001).

The most common adverse reactions (≥10%) of abiraterone acetate are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

The most common adverse reactions related to prednisone are fluid retention, adrenal insufficiency, loss of bone density, hyperglycemia, muscle weakness, insomnia, mood swings including depression and euphoria.

1.4.3 Degarelix and LHRH Agonists (e.g. Lupron)

Degarelix is a GnRH receptor antagonist approved for the treatment of patients with advanced prostate cancer. The starting dose is 240 mg given as two 120 mg subcutaneous injections, followed by maintenance dose of 80 mg administered as a single subcutaneous injection every 28 days. Lupron is an LHRH agonist administered intramuscularly at various dosing schedules (e.g. 22.5 mg every 3 months).

A total of 1325 patients with prostate cancer received degarelix either as a monthly treatment (60-160 mg) or as a single dose (up to 320 mg). A total of 1032 patients (78%) were treated for at least 6 months and 853 patients (64%) were treated for one year or more. The most commonly observed adverse reactions during degarelix therapy included injection site reactions (e.g. pain, erythema, swelling or induration), hot flashes, increased weight, fatigue, and increases in serum levels of transaminases and gamma glutamyltransferase (GGT). The majority of the adverse reactions were Grade 1 or 2, with Grade 3/4 adverse reaction incidences of 1% or less.

Degarelix was studied in an active-controlled trial (N = 610) in which patients with prostate cancer were randomized to receive degarelix (subcutaneous) or Lupron monthly for 12 months. Adverse reactions reported in 5% of patients or more are shown in the table below:

	TRADENAME 240/160 mg (subcutaneous) N = 202	TRADENAME 240/80 mg (subcutaneous) N = 207	leuprolide 7.5 mg (intramuscular) N = 201
	%	%	%
Percentage of subjects with adverse events	83	79	78
Body as a whole			
Injection site adverse events	44	35	<1
Weight increase	11	9	12
Fatigue	6	3	6
Chills	4	5	0
Cardiovascular system			
Hot flash	26	26	21
Hypertension	7	6	4
Musculoskeletal system			
Back pain	6	6	8
Arthralgia	4	5	9
Urogenital system			
Urinary tract infection	2	5	9
Digestive system			
Increases in Transaminases and GGT	10	10	5
Constipation	3	5	5

The most frequently reported adverse reactions at the injection sites were pain (28%), erythema (17%), swelling (6%), induration (4%) and nodule (3%). These adverse reactions were mostly transient, of mild to moderate intensity, occurred primarily with the starting dose and led to few discontinuations (<1%). Grade 3 injection site reactions occurred in 2% or less of patients receiving degarelix.

Hepatic laboratory abnormalities were primarily Grade 1 or 2 and were generally reversible. Grade 3 hepatic laboratory abnormalities occurred in less than 1% of patients.

In 1-5% of patients the following adverse reactions, not already listed, were considered related to degarelix by the investigator:

Body as a whole: Asthenia, fever, night sweats;

Digestive system: Nausea;

Nervous system: Dizziness, headache, insomnia.

The following adverse reactions, not already listed, were reported to be drug-related by the investigator in ≥1% of patients: erectile dysfunction, gynecomastia, hyperhidrosis, testicular atrophy, and diarrhea.

Changes in bone density:
Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist. It can be anticipated that long periods of medical castration in men will result in decreased bone density.

Anti-degarelix antibody development has been observed in 10% of patients after treatment with degarelix for 1 year. There is no indication that the efficacy or safety of degarelix treatment is affected by antibody formation.

1.5 Anticipated Risks and Safety Considerations of Combination

As of 14 January 2015, safety data were available from 29 subjects in a Phase 1b combination study of apalutamide with abiraterone acetate plus prednisone (AA-P) in mCRPC (Study 56021927PCR1010). The median treatment duration (exposure) was 12.1 weeks (approximately 3 treatment cycles) (range: 4 to 24 weeks [approximately 1 to 6 treatment cycles]). Most of the drug-related AEs were of toxicity Grade 1 (15 subjects [52%]) or Grade 2 (8 subjects [28%]). Drug-related AEs of Grade 3 toxicity were reported in 3 subjects (10%) and included fatigue, hepatic function abnormal, hypokalemia, and hyponatraemia. One subject (3%) experienced a drug related AE of Grade 4 hypokalemia. Serious adverse events were reported in 4 subjects (13.8%): Grade 3 hyponatremia and Grade 2 atrial fibrillation (same subject), Grade 4 hypokalemia (1 subject), Grade 3 influenza (1 subject), and Grade 3 viral infection (1 subject). One death was reported due to progressive disease.

As of 22 June 2016, 57 subjects were enrolled in Study 56021927PCR1010 and are included in

the preliminary safety analysis. The highest incidence of AEs were in the SOC of Gastrointestinal Disorders (83%), including nausea (40%), vomiting (40%), constipation (30%), and diarrhea (25%). Other AEs commonly reported with apalutamide and AA-P combination treatment included fatigue (56%), back pain (33%), arthralgia and decreased appetite (28% each), hypokalemia (25%), dysgeusia (16%), hot flush, rash, and fall (12% each), insomnia (9%), hypertension (7%), alanine aminotransferase increased (5%), and aspartate aminotransferase increased (4%). Drug related Grade ≥3 AE included fatigue (7%), hypokalemia (5%), hyponatremia (4%), rash (2%), hypertension (4%), ALT increased (2%), anemia (2%) and pneumonia (2%).

The safety profile of combination treatment of apalutamide with AA-P is as expected based on known side effects observed to date with apalutamide and AA-P.

2 Objectives and Endpoints

2.1 Primary Objectives

To compare PSA progression-free survival in each of the experimental arms (LHRH analogue + apalutamide; LHRH analogue + apalutamide +abiraterone acetate) versus the control arm (LHRH analogue) among all randomized patients (intent-to-treat population).

2.2 Secondary Objectives

- To compare PSA progression-free survival in testosterone-evaluable population in each experimental arm versus the control arm. Testosterone-evaluable population includes all patients who achieve serum testosterone recovery to > 50 ng/dL with subsequent PSA measurements sufficient for evaluation.
- To compare the 36-month PSA progression-free survival rate in each experimental arm versus the control arm in both the intent-to-treat and testosterone-evaluable populations.
- To compare the time to recovery of serum testosterone to greater than 50 ng/dL in each experimental arm versus the control arm.
- To compare the time to castration resistance in each experimental arm versus the control arm.
- To compare metastasis-free survival in each experimental arm versus the control arm.
- To compare overall survival in each experimental arm versus the control arm.
- To characterize the safety profile in each treatment arm.
- To compare short-term and long-term health-related quality of life (HRQOL) in each experimental arm versus the control arm.
- To compare the quality-adjusted survival (overall survival multiplied by utility score) of patients in each experimental arm versus the control arm.

2.3 Exploratory Objectives

- To investigate whether higher levels of expression of gene pathways associated with resistance to AR pathway inhibition, including but not limited to ARV7, neuroendocrine signaling, and GR, as detected by analysis of whole blood RNA, will be associated with early resistance to potent AR signaling inhibition.
- To investigate whether baseline and/or depth of circulating serum testosterone suppression is associated with improved clinical outcomes including PSA progression- free survival and metastasis-free survival.
- To investigate whether application of previously validated prognostic gene expression signatures to archival primary prostate cancer tissue can identify a more homogenous high-risk group of biochemically relapsed patients as compared with clinical characteristics alone.
- To investigate whether application of other gene expression signatures, including androgen response and neuroendocrine signaling, is predictive of treatment outcomes among men treated with apalutamide with or without abiraterone acetate for biochemical relapse.
- To characterize the frequency of detection of AR-V7 using IHC in FFPE archival tissue and association with clinical outcomes including PSA progression-free survival and metastasis-free survival.

2.4 Study Endpoints

Primary endpoint: PSA progression-free survival.

PSA progression is defined as time from date of randomization to first date of PSA progression in all randomized patients (ITT population). PSA progression during the 52-week treatment period defined as a rising PSA confirmed on repeat measurement and at least 25% and 2 ng/mL above nadir or baseline, whichever is lower. PSA progression during the follow up phase (post- 52 weeks) is defined as the first date of serum PSA > 0.2 ng/mL, confirmed by repeat measurement at least 2 weeks later.

Secondary endpoints:

- PSA progression-free survival in testosterone-evaluable population. Testosterone- evaluable defined as recovery of serum T to > 50 ng/dL with subsequent PSA measurements sufficient for evaluation.
- 36-month PSA progression-free survival rate in ITT and testosterone-evaluable patient populations.
- Time to testosterone recovery (serum T > 50 ng/dL)
- Time to castration resistance. Castration resistance defined as PSA increase > 25% and more than 2 ng/mL above nadir with concomitant serum T < 50 ng/dL

- Metastasis-free survival
- Overall survival and prostate-cancer specific survival
- Safety
- Quality of life and quality-adjusted overall survival

Exploratory endpoints:

- Association of whole blood RNA pathway signatures including AR signaling, GR, and neuroendocrine pathways with clinical outcomes including PSA progression-free survival and metastasis-free survival.
- Association between serum testosterone levels at baseline and on treatment with subsequent clinical outcomes including PSA progression-free survival, metastasis-free survival, and time to castration resistance.
- Association between gene expression prediction scores derived from archival primary prostate cancer tissue analysis with clinical outcomes including PSA progression-free survival, time to castration resistance, and metastasis-free survival.
- Association between gene expression signatures including androgen response and neuroendocrine signaling applied to archival primary prostate cancer tissue analysis with clinical outcomes among men treated with apalutamide +/- abiraterone acetate for biochemically relapsed prostate cancer.
- Frequency of detection of AR-V7 by immunohistochemical analysis of archival prostate cancer tissue and association with clinical outcomes among men with biochemical relapse including PSA progression-free survival, time to castration resistance, and metastasis-free survival.

3 Patient Selection/Population

Five-hundred and four (504) men with biochemically relapsed prostate cancer following radical prostatectomy with a PSA doubling time ≤ 9 months will be enrolled across multiple investigational sites in the United States. All screening labs must be performed within 28 days of randomization. Screening scans must be completed within 42 days of date of randomization.

AFT does not grant eligibility waivers. Investigators must carefully consider any condition that in the opinion of investigator would interfere with participation in the study. Please contact the study team for eligibility questions.

3.1 Inclusion Criteria

- Histologically confirmed prostate adenocarcinoma
- Prior radical prostatectomy
- Biochemically recurrent prostate cancer with PSA doubling time ≤ 9 months at the time of randomization.
    - Calculation of PSA doubling time should include the use of all applicable PSA values obtained within past 6-12 months prior to randomization, with a minimum of 3 values separated by at least 2 weeks apart.
    - The PSA values used to calculate the PSA doubling time must all be ≥ 0.1 ng/mL, and should be measured in the same laboratory whenever feasible.
    - PSA values obtained prior to therapeutic interventions (e.g. salvage radiation) will be excluded from the determination of PSA doubling time.
    - PSA doubling time to be estimated using Memorial Sloan Kettering Cancer Center online calculator (https://www.mskcc.org/nomograms/prostate/psa_doubling_time)
- Prior adjuvant or salvage radiation or not a candidate for radiation based upon clinical assessment of disease characteristics and patient co-morbidities.
- Screening PSA > 0.5 ng/mL
- No definitive evidence of metastases on screening CT or MRI of abdomen/pelvis and radionuclide whole body bone scan per the judgment of the investigator. Abdominal and/or pelvic lymph nodes measuring 2 cm or less in short axis diameter are allowed. Lesions identified on other imaging modalities (e.g. PSMA or choline PET) that are not visualized on CT and/or MRI or radionuclide bone scan are allowed. Equivocal lesions on bone scan should be followed up with additional imaging as clinically indicated.
- Screening serum testosterone > 150 ng/dL.
- Eastern Cooperative Oncology Group (ECOG) Performance Status grade 0 or 1 or Karnofsky performance status ≥ 70 (Appendix 6)
- Age ≥ 18 years
- Medications known to lower the seizure threshold (see Appendix 1) must be discontinued or substituted at least 4 weeks prior to Cycle 1 Day 1 (C1D1).
- 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.
- Adequate organ function as defined by the following laboratory values at screening:
    - Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum

glutamic pyruvic transaminase [SGPT]) < 2.5 x upper limit of normal (ULN)
    - Total serum bilirubin ≤1.5 x ULN. In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, subject may be eligible)
    - Serum potassium ≥ 3.5 mmol/L. Supplementation and re-screening is allowed.
    - Estimated creatinine clearance > 45 ml/min using Cockroft-Gault equation
    - Platelets ≥ 100,000/mL independent of transfusion and/or growth factors within 3 months prior to randomization
    - Hemoglobin ≥ 9.0 g/dL independent of transfusion and/or growth factors within 3 months prior to randomization
    - Serum albumin ≥ 3.0 g/dL
- Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

- Prior systemic treatment with androgen deprivation therapy and/or first generation anti-androgen (e.g. bicalutamide, nilutamide, flutamide) for biochemically recurrent prostate cancer. Prior ADT and/or first generation anti-androgen treatment in the (neo)adjuvant and/or salvage setting in conjunction with radiation or surgery is allowed provided last effective dose of ADT and/or first-generation anti-androgen is > 9 months prior to date of randomization and total duration of prior therapy is ≤ 36 months.
- Prior treatment with CYP17 inhibitor (e.g. ketoconazole, abiraterone acetate, galeterone) or next generation androgen receptor antagonist including apalutamide or enzalutamide
- Prior chemotherapy for prostate cancer except if administered in neoadjuvant or adjuvant setting
- Use of 5-alpha reductase inhibitor within 42 days prior to Cycle 1 Day 1
- Use of investigational agent within 28 days prior to Cycle 1 Day 1
- Use of other prohibited medications within 7 days prior to Cycle 1 Day 1 (Arms B and C only) (see Appendix 1 for list of prohibited medications)
- Prior bilateral orchiectomy
- Seizure or known condition that may pre-dispose 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
- Uncontrolled hypertension as defined by SBP > 160 and/or DBP > 100. Patient's blood pressure may be controlled on appropriate antihypertensive regimen and rescreening is permitted.
- Gastrointestinal disorder affecting absorption or the ability to swallow tablets

- Baseline severe hepatic impairment (Child-Pugh Class B & C)
- Intercurrent illness that is not controlled such as active infection, psychiatric illness/social situations that would limit compliance with study requirements
- Any chronic medical condition requiring a higher dose of corticosteroid than equivalent of 10 mg prednisone/prednisolone per day

3.3 Inclusion of Minorities

Men of all races and ethnic groups are eligible for this trial.

4 Method of Treatment Assignment

4.1 Site Enrollment Requirements

Site must submit to AFT all required essential documents including:

- IRB/Regulatory Approval Letter
- Investigator Form 1572 and CV
- Institutional IRB approved informed consent form and protocol
- Essential documents must be submitted to the AFT electronic Trial Master File, accessible via the AFT website, https://alliancefoundationtrials.org/.

4.2 Patient Enrollment and Randomization Procedure

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form are required prior to patient consent and enrollment.

Patient enrollment will be facilitated using the AFT web-based IRT (interactive response technology) system, accessible via the AFT website, https://alliancefoundationtrials.org/.

Patient must be enrolled prior to submission of biospecimens. After written informed consent has been obtained, the study site will obtain a unique patient identifier, which will stay the same throughout the entire study. Patients enrolled but not randomized for any reason have to be documented as a Screening Failure in IRT.

Prior to accessing IRT, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form

The AFT IRT system will provide the site with a confirmation of enrollment and treatment randomization information. Please retain this confirmation for your records.
Patients will be stratified according to the PSA doubling time submitted as part of screening

tests (< 3 months versus 3-9 months). Patients will be randomized with equal probability to one of the three treatment arms from within each of the two strata. Balance in treatment assignment will be achieved using a randomized block design. Randomization will be carried out via computer generated random assignment. All patients must commence treatment within 7 calendar days from date of randomization.

4.3 Treatment Blinding

This is an open-label study.

5 Treatment Plan

5.1 Treatment Regimen

Protocol treatment is to begin within 7 days of randomization on IRT. Treatment will continue until the development of PSA progression, unacceptable toxicity, patient withdrawal, or completion of 52-week treatment, whichever occurs first. Protocol therapy will consist of 28-day cycles (13 cycles total) of treatment.

Arm A: LHRH Analogue Monotherapy

Patients randomized to Arm A will receive investigator's choice of LHRH analogue therapy, following one of the treatment schedules shown below:

a) Degarelix subcutaneous injections every 28 days (+/- 3 days). Patients will receive loading dose of 240 mg (two 120 mg injections) on Cycle 1 Day 1, followed by maintenance dose of 80 mg subcutaneous injection on Day 1 of subsequent cycles for a total of 13 treatment cycles (52 weeks of therapy).

OR

b) Leuprolide acetate 7.5 mg intra-muscular injection (or equivalent LHRH agonist) on Cycle 1 Day 1 in combination with bicalutamide 50 mg orally once daily starting on Cycle 1 Day 1 and continuing for 28 days through completion of Cycle 1. Starting Cycle 2 Day 1, patients will continue leuprolide acetate 7.5 mg IM injections (or equivalent LHRH agonist) on Day 1 of every treatment cycle thereafter for a total of 13 treatment cycles (52 weeks), without concurrent bicalutamide.

OR

c) Leuprolide acetate 7.5 mg intra-muscular injection (or equivalent LHRH agonist) on Cycle 1 Day 1 in combination with bicalutamide 50 mg orally once daily starting on Cycle 1 Day 1 and continuing for 28 days through completion of Cycle 1. Starting Cycle 2 Day 1, patients will receive leuprolide acetate 22.5 mg intra-muscular injection (or equivalent LHRH agonist) on Cycle 2 Day 1, Cycle 5 Day 1, Cycle 8 Day 1, and Cycle 11 Day 1 without concurrent bicalutamide.

Arm B: LHRH Analogue + Apalutamide

Patients randomized to Arm B will receive LHRH analogue therapy as specified above. In addition, patients will be instructed to take apalutamide 240 mg (four 60 mg tablets) orally once daily starting on Cycle 1 Day 1 and continuing throughout 52-week treatment period. Patients will not take bicalutamide at any point in the treatment course.

Arm C: LHRH Analogue + Apalutamide + Abiraterone acetate + Prednisone

Patients randomized to Arm C will receive LHRH analogue therapy and apalutamide as specified above. In addition, patients will be instructed to take abiraterone acetate 1000 mg (four 250 mg tablets) orally once daily starting on Cycle 1 Day 1 and continuing throughout 52-week treatment period. Patients randomized to Arm C will also be instructed to take prednisone 5 mg twice daily starting on Cycle 1 Day 1 and continuing throughout the 52-week treatment period. Patients will not take bicalutamide at any point in the treatment course.

Following completion of treatment period, patients will taper off prednisone per institutional guidelines.

Suggested tapering plan: prednisone 5 mg daily for 7 days, then 2.5 mg daily for 7 days, then discontinue.

LHRH Analogue Administration
Degarelix and LHRH agonists will be administered per package insert.

Apalutamide Administration
Apalutamide tablets will be administered orally on a continuous daily dosing regimen at a starting dose of 240 mg per day (4 x 60-mg tablets) with or without food.

Based on its mechanism of action, apalutamide may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle apalutamide without protection, e.g., gloves.

Abiraterone acetate + Prednisone Administration
Abiraterone acetate will be administered as per package insert. Abiraterone acetate will be administered at a starting dose of 1000 mg (four 250 mg tablets) once daily. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before abiraterone acetate and for at least one hour after abiraterone acetate. The tablets should be swallowed whole with water; tablets should not be crushed or chewed. Prednisone 5 mg should be taken twice a day with food. If dosing of either abiraterone acetate or prednisone is missed on one day for any reason, double dosing should NOT occur the following day. Following completion of 52-week treatment period or subject withdrawal

(whichever occurs first), prednisone should be tapered off over a maximum period of 2 weeks per institutional guidelines.

Based on its mechanism of action, abiraterone acetate may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection, e.g., gloves.

5.2 Supportive Care and Concomitant Medications

Concomitant medications will be recorded at each study visit. Bone health should be considered. Supportive therapy with calcium/vitamin D, bisphosphonates or denosumab should be used as appropriate and in accordance with label indications.

Prohibited Concomitant Medications

No concomitant use of any anti-cancer therapy will be permitted prior to development of PSA progression. Prohibited anti-cancer therapies include surgery, radiation therapy, non-protocol hormonal therapy, immunotherapy, chemotherapy, or other investigational agents. Start of any of these therapies prior to PSA progression will result in discontinuation from the study. The use of prednisone or other systemic corticosteroids is prohibited except for patients randomized to Arm C (abiraterone acetate-containing study arm). Patients who require short course of steroids for treatment of non-cancer related conditions may be permitted to do so only after discussion and approval of Study Chair.

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 (eg, chlorpromazine, mesoridazine, thioridazine)
- Tricyclic antidepressants (eg, amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)

Apalutamide is metabolized primarily by human CYP3A4, thus co-administration with strong inhibitors or inducers of CYP3A4 should be avoided for patients randomized to receive apalutamide. Examples of the strong CYP3A4 inhibitors and inducers include the following:

Strong CYP3A4 inhibitors: itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir,

telithromycin, voriconazole, grapefruit juice (or grapefruits); co-administration with any of these agents may increase apalutamide plasma concentrations

Strong CYP inducers: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, efavirenz, tipranivir, St. John's wort; co-administration with any of these agents may decrease apalutamide plasma concentrations

Please see Appendix 1 for a more complete listing of prohibited medications.

Restricted Concomitant Medications

Apalutamide may also induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have a narrow therapeutic index.

The potential for drug-drug interaction between apalutamide and warfarin (eg, Coumadin) 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.

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 alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug. 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.

6 Dose and Treatment Modifications

6.1 Dose/Delays Modifications

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Treatment plans should explicitly identify when treatment (typically dose) modifications are appropriate. Treatment modifications/dosing delays and the factors predicating treatment modification should be explicit and clear.

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

Any patient requiring > 28-day delay in treatment due to adverse events attributable to the study regimen should be discontinued from study treatment and enter follow up phase. Patients who require treatment delay > 28 days for reasons not related to toxicity of study therapy may be permitted to resume study therapy only after approval by Study Chair.

No intra-patient dose escalations will be permitted following dose reduction unless permission is granted by Study Chair.

In patients randomized to combination treatment (Arm B or Arm C), investigators should try whenever possible to attribute adverse events as specifically as possible with a particular study drug. In cases where this is not possible, attribution should be assigned to treatment regimen.

Dose Modifications for Degarelix and other LHRH Analogues

Dosing will be interrupted for grade 3 injection site reactions until resolution to Grade 1.

Treatment must be permanently discontinued for related Grade 4 adverse events, with the exception of clinically insignificant laboratory abnormalities that resolve within two days of optimal treatment. Unanticipated adverse events that the investigator attributes to LHRH analogue, and if Grade 3 or higher in severity for a duration > 28 days, will lead to treatment discontinuation and entry into follow up phase of study.

Dose Modifications for Toxicity Attributed to Apalutamide Except for Rash:

Toxicity	Dose of Abiraterone acetate	Dose of Apalutamide	Dose of prednisone
Grade 1 or 2	No change	No change	No change
≥Grade 3 or higher*	No change	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)	No change
First Recurrence ≥Grade 3*	No change	Hold until Grade 1 or baseline, resume at 120 mg (2 tablets)	No change
Second Recurrence ≥ Grade 3*	No change	Discontinue	No change
First occurrence of Grade 4*	No change	Discontinue	No change

* Excludes clinically insignificant laboratory abnormalities that resolve within two days on optimal treatment

Dose Modifications for Rash Attributed to Apalutamide

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]	• Consider holding apalutamide for up to 28 days • Initiate dermatological treatment[a] o Topical steroid cream AND o Consider Oral Antihistamines • Monitor for change in severity[a] o 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 28 days • Initiate dermatological treatment[a] o Topical steroid cream AND o Oral Antihistamines AND o 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 o Reinitiate apalutamide at a 1 dose level reduction[c] when rash is Grade ≤ 1. o If the dose reduction will lead to a dose less than 120mg, the study drug must be stopped (discontinued). • If after 28 days, rash has not resolved to Grade ≤ 1, contact Study Chair 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 4.03 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 study chair

Dose Modifications for LFT Abnormalities

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 to 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 Study Chair	Hold until return to Grade 1 or baseline, resume at 240 mg	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 Study Chair	Hold until return to Grade 1 or baseline, resume at 240 mg	No change
Second recurrence Grade 3 or Grade 4	Discontinue	Discontinue	Taper off

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

Dose Modifications for Hypokalemia Attributed to Abiraterone Acetate

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	No change. 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 and initiate PO/IV potassium and cardiac monitoring as clinically indicated, resume only after discussion and approval by Study Chair	No change	Taper off if abiraterone acetate permanently discontinued

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

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	No change	No change	No change
Grade 3 Note: Grade 3 hypertension defined as SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg	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	Taper off
First Occurrence Grade 4	Discontinue	No change	Taper off

Dose Modifications for Other Toxicities Attributable to Abiraterone acetate

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	No change	No change	No change
First Occurrence 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	Discontinue	Taper off
First occurrence of Grade 4	Discontinue	Discontinue	Taper off

Dose Modifications for Prednisone

There are no mandated dose reductions and/or delays for adverse events attributed to prednisone. For grade 3 and intolerable grade 2 adverse events that are clearly related to prednisone and not to other study drugs, reduction of prednisone dose to 5 mg daily (dose level -1) and 2.5 mg daily (dose level -2) may be permitted per investigator discretion after approval of Study Chair. Patients will not be allowed to discontinue prednisone while taking abiraterone acetate.

7 Study Assessment Types

7.1 Serum PSA

Serum PSA will be measured at a local laboratory (using the same laboratory when feasible) during Screening, Day 1 of each treatment cycle, and during Follow Up as specified below. For serum PSA tests, ultrasensitive assay is preferred when possible, but it is not mandatory.

7.2 Imaging

Baseline radionuclide bone scan and CT or MRI of the abdomen and pelvis will be obtained during the Screening period. Scans performed as routine clinical management are acceptable for use as the baseline scan as long as they are completed within 42 days prior to randomization.

Follow-up staging scans will be performed within 8 weeks following first date of PSA progression, and every 6 months (+/- 2 months) thereafter until the development of first metastasis or the patient withdraws from the study, whichever occurs first.

7.3 Safety and Tolerability Assessments

All patients will be assessed for adverse events on Day 1 visit of each treatment cycle, and at the End of Treatment visit (30 days after last dose of study drug taken).

Laboratory assessments obtained during treatment will vary depending upon treatment arm assignment:

- Arm A (LHRH Analogue monotherapy):
  - CBC + diff and platelets at Cycle 1 Day 1, and Day 1 of every third cycle thereafter
  - Liver function tests at Cycle 1 Day 1, and Day 1 of every third cycle thereafter
- Arm B (LHRH Analogue + Apalutamide):
  - CBC + diff and platelets at Cycle 1 Day 1, and Day 1 of every third cycle thereafter
  - Liver function tests at Cycle 1 Day 1, and Day 1 of every third cycle thereafter
  - TSH (with reflex free T3/free T4 if TSH abnormal) on Day 1 of the first four cycles and Day 1 of every fourth cycle thereafter

- Arm C (LHRH Analogue + Apalutamide + Abiraterone acetate/Prednisone):
  - CBC + diff and platelets at Cycle 1 Day 1, and Day 1 of every third cycle thereafter
  - Liver function tests and serum potassium on Days 1 and 15 for Cycles 1-3 and Day 1 of every cycle thereafter
  - TSH (with reflex free T3/free T4 if TSH abnormal) on Day 1 of first four cycles, and every fourth cycle thereafter
  - Serum chemistry panel (sodium, creatinine, and fasting glucose) on Day 1 of every third cycle

Clinical Laboratory Assessments:

CBC + differentials and platelets	Liver function test	Chemistry	Other
Hemoglobin White blood cell count Neutrophil count Platelet count	ALT AST total bilirubin alkaline phosphatase	Albumin (Screening only) Creatinine Potassium Sodium TSH Testosterone (local lab)	Fasting glucose (Arm C only)

7.4 Biomarkers/Correlative Studies

Archival Tumor Collection (If Tissue Available)

Archival tumor tissue will be collected for the following analyses:

- Analysis of AR response gene expression signature
- Analysis of AR-V7 expression by immunohistochemistry

In addition, for patients who had genomic testing of test of archival prostate cancer tissue (e.g. DECIPHER® and/or GenomeDX) performed as standard of care prior to study enrollment and give consent for optional retrieval of data, the gene expression data will be extracted from the database and analyses will be performed as outlined below. Please see Section 12 for details on correlative studies.

Circulating Biomarkers

Peripheral blood will be collected for the following analyses:

- Analysis of whole blood RNA expression signatures involving AR, GR, and neuroendocrine signaling at baseline, end of treatment, and at time of PSA progression
- Testosterone measurement using ultrasensitive assay on Cycle 1 Day 1 and Cycle 3 Day 1.

7.5 Patient Reported Outcomes

Patient reported outcomes will be collected at pre-specified time points during the study, including Cycle 1 Day 1, Cycle 7 Day 1, end of treatment, and after 12 months of follow up. The specific health related quality of life instruments to be utilized include:

- Expanded Prostate Cancer Index Composite (EPIC) (Appendix 2): This is a validated prostate cancer-specific HRQOL instrument that measures urinary, bowel, sexual, and hormonal symptoms related to prostate cancer treatments, including prostatectomy, radiotherapy, and hormonal therapy. Summary and subscale scores

were derived by content and factor analyses. Test-retest reliability and internal consistency were high for EPIC urinary, bowel, sexual, and hormonal domain summary scores (each $r \geq 0.80$ and Cronbach's alpha ≥ 0.82) and for most domain-specific subscales. Correlations between function and bother subscales within domains were high $r > 0.60$). Correlations between different primary domains were consistently lower, indicating that these domains assess distinct HRQOL components.

- Hot Flash Related Daily Interference Scale (HFRDIS) (Appendix 3): Hot flashes are another common side effect from ADT, and in some patients can be very bothersome.[2] HFRDIS is a 10-item scale that assesses the degree to which hot flashes interfere with a variety of daily activities and quality of life. Interference is rated on an 11-point scale (0=not interfere; 10=completely interfere). The validity of the HFRDIS has been demonstrated in breast cancer survivors and healthy women. As the only hot-flash- specific HRQOL instrument, HFRDIS has also previously been used in prostate cancer patients receiving ADT.
- EQ-5D-5L (Appendix 4): This is a 6-item validated utility assessment instrument. The first part consists of 5 items covering 5 dimensions including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 health states to which unconsciousness and death are added. The sixth item is a visual analogue scale for overall health. The 5-item index score is transformed into a utility score between 0, "Worst health state," and 1, "Best health state." The index score can be used in a quality adjusted survival analysis. For this study, the measured utility values for each patient will be combined with overall survival to calculate the quality-adjusted survival, and compared between each experimental arm versus control.
- PROMIS Fatigue (Appendix 5): The PROMIS fatigue measures 8 items, which includes two content domains of fatigue, experience and impact, were identified by a panel of experts. An initial item pool of 58 fatigue experience and 54 fatigue impact items were developed. The psychometric properties of these items were evaluated in a sample of 450 individuals from the general US population using classical test theory indices, monotonicity, and scalability.

8 Study Assessments and Procedures

SCREENING PERIOD/PRESTUDY EVALUATION

All subjects must sign a written informed consent form before study-specific screening procedures are performed. Screening procedures to evaluate subject eligibility will be conducted within 28 days prior to randomization. Re-screening is permitted. The measurements collected at screening will be considered the baseline values except for PSA. Serum PSA measurements at Day 1 will be considered as baseline for PSA endpoints.

Clinical Assessments (within 28 days of date of randomization)

- Complete history including current medications and prostate cancer treatment history, consisting of:
  - Date of diagnosis
  - PSA and Gleason grade at time of diagnosis
  - Date of prior radical prostatectomy
  - Gleason grade and pathologic stage at radical prostatectomy
  - Date of first biochemical relapse (defined as date of first serum PSA > 0.2 ng/mL following radical prostatectomy)
  - Prior adjuvant or salvage radiation therapy
  - Prior ADT/anti-androgen therapy including type, duration, indication, and date of last dose prior to study entry
  - Prior chemotherapy including type, duration, indication, and date of last dose prior to study entry
- Physical Exam including vital signs (blood pressure and heart rate)
- Baseline demographics
- Height, weight, and body mass index
- ECOG or Karnofsky Performance Status (Appendix 6)

Laboratory Assessments (within 28 days of date of randomization)

- Complete blood count including differential and platelet count (hemoglobin, WBC count, Neutrophil count)
- Total bilirubin, alkaline phosphatase, AST, ALT
- Serum creatinine including estimated GFR by Cockroft-Gault equation
- Serum potassium
- Serum PSA
- Serum albumin
- Calculation of PSA doubling time, using all known PSA levels within the past 6-12 months including screening PSA level (but not Cycle 1 Day 1 PSA). There must be a minimum of 3 values spaced at a minimum of 2 weeks apart. PSA values obtained prior to localized therapy will be excluded. The PSA doubling time can be calculated from the website: https://www.mskcc.org/nomograms/prostate/psa_doubling_time

Laboratory assessments obtained within 16 days of C1D1 may be used for pre-treatment evaluation and approval to treat on C1D1 visit. Serum PSA will be repeated on C1D1 and will be used as the baseline value for all PSA-based endpoints.

Radiographic Studies (performed within 42 days of date of randomization)

- Whole body radionuclide bone scan
- CT or MRI of the abdomen/pelvis

TREATMENT PERIOD (C1D1 until completion of 52 Weeks of Treatment = 13 cycles)

During the Treatment Period patients will receive protocol therapy. The study timeline is defined as Cycle 1 Day 1 = first dose of study treatment.

Subsequent study time points will be defined based on study calendar, irrespective of subsequent dose delays/interruptions.

Subjects will be treated with protocol therapy until disease progression (either by PSA or radiographic), unacceptable toxicity, subject/physician withdrawal, initiation of non-protocol therapy, or completion of 52-weeks of treatment (13 cycles), whichever occurs soonest. After the 52 weeks (13 cycles) of treatment are completed, the patient will be scheduled for an End of Treatment (EOT) visit 30 days (+/- 3 days) after Cycle 13 Day 1 prior to beginning the post-treatment phase. If the patient stops treatment during the on-therapy period, the EOT visit will be scheduled 30 days (+/- 3 days) after the last Cycle Day 1.

PSA progression during the on-therapy period is defined as an increase in PSA to > 25% and > 2 ng/mL above the nadir or baseline, whichever is lower, confirmed by repeat measurement at least 2 weeks later.
Radiographic progression is defined as the detection of new metastasis on either bone scan or cross-sectional imaging (CT or MRI). If subjects develop progressive disease (either by PSA or radiographic) while receiving protocol therapy, they will discontinue protocol therapy and will be treated as per individual investigator discretion, and enter the follow up phase of the study.

POST-TREATMENT PHASE: (Off Treatment until PSA Progression)

Patients will undergo monthly PSA (ultrasensitive if possible) and total serum testosterone (standard assay) measurements using local laboratory until the time of PSA progression, defined in follow up phase as the date of first serum PSA > 0.2 ng/mL, confirmed by repeat measurement at least 14 days after initial measurement. Patients should not start any non-protocol treatment for prostate cancer prior to PSA progression. Any treatment applied for prostate cancer (see Prohibited Medications section) prior to PSA progression will be considered non-protocol therapy and will result in transition to long term follow up.

At the time of PSA progression, patients will undergo restaging scans including radionuclide bone scan and CT or MRI of the abdomen and pelvis.

Patients will complete HRQOL assessments at the end of treatment visit and after 12 months of post-treatment follow up. These questionnaires may be sent and returned via mail or electronically.

LONG TERM FOLLOW UP: (Post-PSA Progression Until Study Completion)

Following PSA progression, patients will enter long-term follow up phase, consisting of the following:

- Bone scan + CT or MRI of the abdomen/pelvis every 6 months (+/- 2 months) until the development of first metastasis
- Review of medical records and/or telephone calls every 6 months to document:
    - Anti-cancer therapies including start and stop dates of each therapy
    - Documentation of date of castration resistance, defined as rising PSA on consecutive measurements with absolute PSA > 2 ng/mL with concomitant serum testosterone < 50 ng/dL
    - Survival status and cause of death (if applicable)

Patients will continue on-study in long-term follow up, until patient withdrawal, death, or study termination, whichever occurs first.

9 Schedule of Events

	Pre-Study[1]	Cycle 1 Day 1	Day 1 of Each Subsequent Cycle (+/- 3 days)	End of Treatment Visit (+/- 3 days)	Post-Treatment Phase[20]	Upon PSA Progression	Long Term Follow Up
LHRH Analogue administration[2]		X[3]	X				
Apalutamide administration (Arms B and C)		Daily Administration					
Abiraterone + Prednisone (Arm C only)		Daily Administration					
Drug Diary Collection[4]		X	X	X			
Informed Consent	X						
Demographics	X						
Medical History	X						
Physical Exam including injection site monitoring and vital signs (heart rate, blood pressure)[5]	X	X	X[5]	X[5]			
Adverse Event Assessment		X	X	X			
Concomitant Medications	X	X	X	X			
Height	X						
Weight	X	X	X	X			
ECOG or Karnofsky Performance Status (Appendix 6)	X	X	X	X			

	Pre-Study[1]	Cycle 1 Day 1	Day 1 of Each Subsequent Cycle	End of Treatment Visit (+/- 3 days)	Post-Treatment Phase	Upon PSA Progression	Long Term Follow Up
CT or MRI of abd/pelvis	X					X[6]	X[6]
Whole body bone scan	X					X[6]	X[6]
HRQOL Assessments[7]		X[7]	X[7]	X[7]	X[7]		
CBC w/diff and platelets[8]	X	X[9]	X	X			
Liver Function Tests (ALT, AST, AlkP, total bilirubin[10])	X	X[9]	X	X			
Serum Albumin	X						
Serum chemistry panel[11]	X	X[9]	X	X			
TSH (with reflex free T3/free T4 if TSH abnormal)[12] (Arm B and C only)		X	X	X			
PSA[13]	X	X[14]	X	X	X	X	X

	Pre-Study[1]	Cycle 1 Day 1	Day 1 of Each Subsequent Cycle (+/-3 days)	End of Treatment Visit (+/- 3 days)	Post-Treatment Phase	Upon PSA Progression	Long Term Follow Up
Serum testosterone with standard assay using local laboratory[15]	X[15]				X[15]	X[15]	
Serum testosterone ultrasensitive, using central lab LC/MS/MS assay[16]		X[16]	X[16]				
Archival tumor tissue collection (if tissue available)[17]	X						
Whole blood collection for RNA analysis[18]		X[18]		X[18]		X[18]	

abd = abdomen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AlkP = alkaline phosphatase; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; HRQOL = health-related quality of life questionnaires; ICF = informed consent form; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; TSH=thyroid stimulating hormone;

[1] Pre-study assessments need to be completed within 28 days prior to randomization, except for scans which must be completed within 42 days prior to randomization. The screening window begins the day of the first screening assessment performed on site. Informed consent is not governed by the 28 day window.

[2] See Section 5.1 for treatment schedule. Choice of LHRH analogue is per investigator discretion.

[3] Arm A only: if administering leuprolide, lead-in of 50mg bicalutamide to be taken in conjunction for C1D1-D28

[4] Drug diary is to be dispensed to Arm B and C patients only. Patients are to start completing diary on a daily basis to capture IP administration. IP compliance must be documented in the medical record by any member of the care team.

[5] Physical exam changes will not be collected in the eCRF, any significant change in physical exam from baseline needs to be recorded on the adverse event page.

[6] Whole body radionuclide bone scan and CT or MRI of the abdomen/pelvis will be obtained at the time of PSA progression (within 8 weeks), and every 6 months thereafter from date of PSA progression (+/- 2 months) until the time of first metastasis or patient withdrawal from study, whichever occurs first. Scans may also be performed as clinically indicated in patients suspected of developing metastatic disease based upon signs/symptoms of disease. Scans at time of PSA progression and subsequent time points may be omitted if performed within 3 months of the scheduled time point. The detection of metastasis on scan should be followed up with confirmatory scan performed at least 4 weeks after initial scan demonstrating metastase(s).

[7] HRQOL assessments include EPIC, hot flash related daily interference scale, EQ-5D-5L, and PROMIS Fatigue scale. HRQOL assessments will be completed on Cycle 1 Day 1, cycle 7 Day 1, end of treatment, and after 12 months of follow up. Each HRQOL time point assessment has a window of +/- 2 weeks for completion. The date of completion should be recorded on eCRF. Patients should be encouraged to complete all items on each questionnaire. Assessments are optional for non-English speaking patients when a translated version is not available.

[8] CBC + differential will be collected at Screening, C1D1, and Day 1 of every third cycle (e.g. C4D1, C7D1, etc) thereafter.

[9] C1D1 safety labs may be omitted if Screening labs were obtained within 16 days prior to C1D1. Subsequent cycles, labs, scans, tests, and observations may be obtained ≤ 72 hours prior to Day 1 of each treatment cycle.

[10] Liver function tests (AST, ALT, total bilirubin, and alkaline phosphatase) will be collected at Screening and C1D1 for all patients, Day 1 of every third cycle for patients randomized to Arms A and B. For patients randomized to Arm C, liver function tests will be collected on Day 1 and 15 of cycles 1-3 and Day 1 of every cycle thereafter.

[11] Potassium and creatinine levels will be collected at Screening for all patients. For patients randomized to Arm C only, potassium will be collected on Day 1 and 15 of cycles 1-3, Day 1 of every treatment cycle thereafter, and at End of Treatment. For patients randomized to Arm C only, sodium, creatinine will be collected on Day 1 of every third cycle (C1D1, C4D1, C7D1, C10D1, C13D1) and at End of Treatment.) Fasting glucose levels will be collected on C4D1, C7D1, C10D1, C13D1, and End of Treatment.

[12] Arm B and C patients only: TSH (with reflex free T4 testing if TSH is abnormal) will be collected from patients on Day 1 of the first four treatment cycles and then every fourth cycle thereafter (C1D1, C2D1, C3D1, C4D1, C8D1, C12D1).

[13] PSA laboratory evaluations are recommended (but not required) to be performed using an ultrasensitive assay and at the same local laboratory for all assessments on study. Serum PSA sample on Day 1 should be taken pre-dose. There is a /- 3 day window for Cycle 1 Day 1 PSA measurement. In the Post-Treatment Phase, PSA will be measured on a monthly basis (+/- 7 days) until PSA progression. Following PSA progression and during Long Term Follow Up, PSA will be measured at intervals per investigator discretion.

[14] +/- 3 day window permitted for C1D1 PSA measurement

[15] Serum total testosterone will be measured at the local laboratory using standard assay at Screening and then during the Post-Treatment Phase. During Post-Treatment Phase, total testosterone will be measured on a monthly basis (+/- 7 days) until the first date of PSA progression. The Screening serum testosterone value will be used for eligibility determination.

[16] Serum testosterone will be measured at the central laboratory using ultrasensitive LC/MS/MS assay on Cycle 1 Day 1 and Cycle 3 Day 1 (+/- 2 weeks).

[17] See Section 7.4 and Section 12.1 for details on archival tumor tissue collection.

[18] Whole blood for RNA analysis will be collected on C1D1, end of treatment, and at PSA progression (+/- 2 weeks).

19 Patients should not start any non- protocol treatment for prostate cancer prior to PSA progression. This will result in transition to long-term follow-up.

10 Adverse Events

10.1 Adverse Events – General Overview

Per the International Conference of Harmonisation (ICH) guidelines, an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal
product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. 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.

10.2 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 abiraterone acetate, the link to the package insert is:
http://www.zytiga.com/sites/default/files/pdf/full_product_information.pdf
For apalutamide, the link to the package insert is:
http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ERLEADA-pi.pdf
For degarelix, the link to the package insert is:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022201lbl.pdf
For leuprolide, the link to the package insert is:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020517s036_019732s041lbl.pdf
For prednisone, the link to the package insert is:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202020s000lbl.pdf

10.3 Expected Toxicities

Please refer to package insert for degarelix and other LHRH analogues for expected toxicities.

Apalutamide:

The most frequent, treatment-emergent, all causality, AEs were fatigue, arthralgia, rash, falls, weight loss, and fracture. Most adverse events were Grades 1 and 2 in severity. In the ongoing clinical studies of apalutamide in men with CRPC, continuous treatment with a GnRHa (or previous surgical castration) is required during treatment with apalutamide or

placebo. The possible risks and side effects related to administration of apalutamide along with continuous GnRHa therapy (or surgical castration) include the following:

Adverse Drug Reactions Coded by MedDRA (Version 19.1) Associated With Apalutamide

MedDRA System Organ Class (SOC)	Frequency	Preferred term(s)
General disorders and administration site conditions	Very Common	**Fatigue**
Musculoskeletal and connective tissue disorders	Very Common	**Arthralgia**
Skin and subcutaneous tissue disorders	Very Common	**Rash*#**
	Common	**Pruritus**
Nervous system disorder	Uncommon	**Seizure***
Metabolism and nutrition disorders	Common	**Hypercholesterolemia**
	Common	**Hypertriglyceridemia**
Injury, poisoning and procedural complications	Very Common	**Fracture*#**
	Very Common	**Fall***
Investigations	Very Common	**Weight decreased***
Endocrine disorders	Common	**Hypothyroidism*#**

IB Edition 10 Addendum 1, Effective Date 21 August 2017.
ADRs are based on 803 subjects treated with 240 mg of apalutamide with a cut-off date of 19 May 2017.
All events in this table were reported in more than 1 subject.
*Events with a life-threating outcome (defined as at least 1 subject with an SAE)
No events in this table have resulted in a fatal outcome.
The frequency of occurrence is defined as: Very common (≥10%); Common (≥1% to <10%); Uncommon (≥0.1% to <1%); Rare (≥0.01% to <0.1%); Very rare (<0.01%).
#Indicates a grouping of preferred terms (PT)
Rash includes PTs of Rash, Rash maculo-papular, Rash generalized, Urticaria, Rash pruritic, Rash macular, Conjunctivitis, Erythema multiforme, Rash papular, Skin exfoliation, Genital rash, Rash erythematous, Stomatitis, Drug eruption, Mouth ulceration, Rash pustular, Blister, Papule, Pemphigoid, Skin erosion, Rash vesicular.
Fracture includes PTs of Rib fracture, Lumbar vertebral fracture, Spinal compression fracture, Spinal fracture, Foot fracture, Hip fracture, Humerus fracture, Thoracic vertebral fracture, Upper limb fracture, Femur fracture, Fractured sacrum, Hand fracture, Pubis fracture, Acetabulum fracture, Ankle fracture, Compression fracture, Costal cartilage fracture, Facial bones fracture, Lower limb fracture, Osteoporotic fracture, Wrist fracture, Avulsion fracture, Fibula fracture, Fractured coccyx, Pelvic fracture, Radius fracture, Sternal fracture, Stress fracture, Traumatic fracture, Cervical vertebral fracture, Femoral neck fracture, Pathological fracture, Tibia fracture.
Hypothyroidism includes PTs of Hypothyroidism, Blood thyroid stimulating hormone increased, Thyroxine decreased, Goitre, Autoimmune thyroiditis, Blood thyroid stimulating hormone abnormal, Blood thyroid stimulating hormone decreased, Thyroxine free decreased, Tri-iodothyronine decreased.

Source: Apalutamide Investigator's Brochure, version 10.0 Addendum 1 21 Aug 2017

Abiraterone acetate:

The most common adverse reactions (≥10%) of abiraterone acetate are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyper- glycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

In the combined data for studies COU-AA-301 and COU-AA-302, cardiac failure occurred more commonly in patients treated with abiraterone acetate compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients

taking abiraterone acetate and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In COU-AA-301 and COU-AA-302, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the abiraterone acetate arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the abiraterone acetate arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the abiraterone acetate arms.

Prednisone:

The most common adverse reactions related to prednisone are fluid retention, adrenal insufficiency, loss of bone density, hyperglycemia, muscle weakness, insomnia, mood swings including depression and euphoria.

10.4 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Baseline conditions will be recorded as part of medical history during Screening. Any new AEs or increase of a documented baseline condition after screening/history will be recorded from the time of signed consent through 30 days following cessation of treatment. All adverse events are entered into the eCRF in Rave® Electronic Data Capture (EDC) system.

10.5 Expedited Adverse Event Reporting

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Investigators are required to notify the AFT and their Institutional Review Board if a patient has a reportable serious adverse event.

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at:

ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTCAE. SAEs must be entered into the eCRF in Rave EDC within 24 hours of learning of the event.
Novella will submit expedited adverse event reports to Janssen using the MedWatch form within 24 hours of becoming aware of the event.

Note: All deaths on study require both routine reporting and reporting via the EDC regardless of causality. Attribution to treatment or other cause should be provided.

10.6 Serious Adverse Event Reporting Requirements

REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

NOTE: Investigators **MUST** immediately report to the sponsor (AFT) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours

II. 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.]

4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

Life-Threatening Conditions

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

5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to AFT and Novella via Rave EDC within the timeframes detailed in the table below. Novella will send SAE reports to Janssen within 24 hours of becoming aware of the event.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grades 3 Timeframes	Grades 4 & 5 Timeframes
Resulting in hospitalization > 24 hrs	Enter in Rave EDC within 24 hours of the sites awareness of the event			
Not resulting in hospitalization ≥ 24 hrs	Not required to enter into Rave EDC		Enter into Rave EDC within 24 hours of the site's awareness of the event.	

Expedited AE reporting timelines are defined as:

- "All Grade 3, 4 and 5 AEs: 24-Hour; 4 Calendar Days" - The AE must initially be reported via Rave EDC ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ **4** calendar days of the initial 24-hour report.
- "All Grade 1 and 2 AEs resulting in hospitalization or prolonged hospitalization: 24-Hour; 10 Calendar Days" - The AE must initially be reported via Rave EDC ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 10 calendar days of the initial 24-hour report.

All serious adverse events that occur up to 30 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the investigational product, require reporting into Rave EDC within 24 hours of awareness of the event.

NOTE: 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

NOTE: Deaths occurring outside of the serious adverse event reporting period that are clearly due to progressive disease should **NOT** be reported as a Serious Adverse Event, but rather should be reported via routine reporting methods in the Rave data capture system. Deaths occurring within the reporting window, even if considered to be related to disease progression as the cause of death should be reported within Rave EDC as a serious adverse event with death noted as the outcome of the event.

10.7 Adverse Events of Special Interest

10.7.1 Adverse Events of Special Interest

Adverse events of special interest are events that are being actively monitored as a result of a previously identified signal (even if non-serious). There are no adverse events of special interest identified for apalutamide or abiraterone acetate.

10.7.2 Adverse Events of Special Interest Reporting

All non-serious adverse events should be reported to AFT in a routine manner at scheduled times according to the study calendar. All adverse events are entered into the eCRF in Rave. Clinically insignificant laboratory abnormalities do not need to be reported per standard AE reporting guidelines.

On a quarterly basis, AFT will report to Janssen an up-to-date summary of non-serious adverse events.

10.8 Special Reporting Requirements

Safety events of interest for a Janssen medicinal product that require expedited 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
- For Abiraterone acetate only, failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product 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
- For Abiraterone acetate only, unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

10.8.1 Adverse Events and Special Situation Reporting

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 study investigational product/ Janssen medicinal product.

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 should be recorded as such on the Adverse Event case report forms/worksheets and reported by sites within 24 hours of becoming aware of the event(s) within Rave EDC, and AFT **will report to Janssen within 24 hours of becoming aware of the event.**

All serious adverse events that occur up to 30 days after the last administration of investigational agent/intervention, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the investigational product, require reporting into Rave EDC within 24 hours of awareness of the event and Novella will report to Janssen using MedWatch form within 24 hours of becoming aware of the event.

Sites will record all SAEs and special situations following exposure to an investigational product under study on the Adverse Event case report forms/worksheets and reported **within 24-hours of becoming aware of the event** in EDC Rave, and Novella will report to Janssen using the MedWatch form within 24 hours of becoming aware of the event.

10.9 Pregnancy

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.

10.9.1 Pregnancy Reporting

Because the study drug(s) may have an effect on sperm, pregnancies in partners of male subjects exposed to a study investigational/Janssen medicinal product will be reported by sites **within 24 hours of their knowledge of the event** using the Adverse Event pregnancy casereport forms/worksheets within Rave EDC. AFT will report the pregnancy to Janssen using the MedWatch form within 24 hours of becoming aware of the pregnancy.

10.10 Product Quality Reporting (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 patient. 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

10.10.1 PQC Reporting

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 patient. Lot and batch numbers are of high significance and need to be collected whenever available.

Sites must report all initial PQCs involving a Janssen medicinal product under study to Janssen **within 24 hours after being made aware of the event.** Additional information regarding reporting within Rave EDC and the forms to be completed will be provided to sites. AFT will report to Janssen within 24 hours of becoming aware of the PQC event.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the AFT must report the PQC to the 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.

10.11 Adverse Event/Safety Reporting Requirements

A valid safety report must contain the four minimum criteria required to meet regulatory reporting requirements.

1. an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
2. an identifiable reporter (investigational site)
3. an investigational product
4. an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected investigational/Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- patient details (patient 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)
- protocol ID

10.12 Follow-Up for SAEs and Special Interest Reporting Situations

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

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)

10.13 Assessment of Severity of Adverse Events

Signs or symptoms should be graded and recorded by the Investigator according to the NCI-CTCAE (Version 4.03).

Any adverse event not listed in the CTCAE will be graded as follows:

Grade 1, Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Grade 2, Moderate: Sufficient discomfort is present to cause interference with normal activity.

Grade 3, Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Grade 4, Life-threatening: Urgent intervention indicated.

Grade 5, Death: Death.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

10.14 Assessment of Causality of Adverse Events

A suspected adverse reaction means any adverse event for which there is reasonable possibility that the study drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. The Investigator will assign attribution of the possible association of the event with the study drug using the following definitions:

Not Related

An adverse event that is not related to the use of the drug.

Unlikely (doubtful)

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Definitely (Very Likely)

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by de-challenge and re-challenge).

11 Drug Information

11.1 Apalutamide

Drug Substance: Apalutamide drug substance is an almost white to slightly brown powder

Chemical Name: (4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7- diazaspiro [3.4]oct-5-yl]-2-fluoro-*N*-methylbenzamide)

Molecular Formula: C21H15F4N5O2S

Molecular Weight: 477.44

Formulation: The apalutamide tablet supplied for this study contains 60 mg of apalutamide. It will be manufactured and provided under the responsibility of Janssen Scientific Affairs, LLC. Refer to the Investigator's Brochure for a list of excipients.

Apalutamide is rapidly absorbed in humans, with measurable plasma concentrations within 30 minutes after ingestion as tablets. The median peak plasma concentrations occurred 2 to 3 hours after oral administration. The bioavailability of apalutamide was comparable between softgel capsules and tablets. In CRPC patients, the increases in plasma Cmax and AUCs after repeated doses were approximately linear and dose proportional over the dose range of 30 to 480 mg per day. A single 240 mg oral dose of apalutamide as the tablet formulation was administered to healthy subjects with a high-fat meal or in the fasted condition. A high-fat meal did not alter the AUC of apalutamide and its metabolite JNJ-56142060 (M3). The mean terminal half-life of apalutamide in healthy subjects after a single oral dose is approximately 7 days. The steady-state half-life of apalutamide in CRPC patients is approximately 4 days. No relationship was

apparent between dose group and half-life, time to steady-state or accumulation ratio, although half-life did decrease significantly with repeated administration in all dose groups. Plasma trough concentrations of apalutamide increased steadily with time and in proportion to dose across cohorts. Based on examination of these trough levels, most patients had reached steady-state exposure following 21 days of continuous administration (ie, by Week 4).

11.1.1 Form

The apalutamide 60-mg tablets will packaged in 120-count, 160 cc high-density polyethylene (HDPE) bottles with child-resistant caps. Study drug labels will contain information to meet the applicable regulatory requirements

11.1.2 Storage and Stability

Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C. Do not discard dessicant. Protect from light and moisture. (59°F to 86°F).

11.1.3 Handling

Apalutamide should at all times be kept in original packaging until time of administration. Based on its mechanism of action, apalutamide may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle apalutamide without protection, e.g., gloves.

11.1.4 Availability

Apalutamide will be provided free of charge to subjects enrolled on this study by Janssen Scientific Affairs, LLC.

11.1.5 Administration

Apalutamide is to be taken 240 mg (four 60-mg tablets) orally once daily with or without food. Tablets should be stored at room temperature. Apalutamide should be taken as close as possible to the same time each day. Apalutamide can be taken with or without food. If dosing is missed on one day for any reason, double dosing should NOT occur the following day. Apalutamide will be dispensed on Day 1 of each study cycle for the duration of the 52-week treatment period.

11.1.6 Ordering

Apalutamide is to be ordered manually via drug order form. Sufficient study drug for the next cycle of therapy will be provided to subjects randomized to one of the two apalutamide treatment arms at each monthly study visit.

11.1.7 Accountability

Study drug used for this study must be maintained under adequate security and stored in the pharmacy at the study site until dispensing or destruction at each site's pharmacy. Investigators may not supply apalutamide to any person not enrolled in this study or to any person not named

as an investigator or sub-investigator. In addition, the site research staff must maintain an accurate, running inventory of all drug supplies received and dispensed during the conduct of the study.

Patients will be required to keep a drug diary to record dose and time of apalutamide, abiraterone acetate, and prednisone administration during the treatment period, and will be instructed to bring the diary and used pill bottles to each study visit.

Upon completion or termination of study treatment, all used and unused study drug bottles, whether empty or containing study drug, should be destroyed at each study site's pharmacy (or site's authorized destruction unit) following their site-specific procedures on drug destruction. Any return shipments must provide proof of delivery accompanied by the Drug Accountability Form and a memo noting the number of bottles and quantity of study drug being returned in the site's drug accountability records.

11.2 Abiraterone Acetate

Abiraterone acetate, the active ingredient of abiraterone, is the acetyl ester of abiraterone. Abiraterone acetate is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains 250 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl) androsta-5, 16-dien-3-yl acetate.

Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is C26H33NO2 and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the tablets are colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic castration-resistant prostate cancer (CRPC). *In vivo*, abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (<0.2 ng/mL) in >99% of the analyzed samples. Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate. At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of Cmax were 226 ± 178 ng/mL and of AUC were 993 ± 639 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg. However, the exposure was not significantly increased when the dose was doubled from 1,000 to 2,000 mg (8% increase in the mean AUC). Systemic exposure of

abiraterone is increased when abiraterone acetate is administered with food. In healthy subjects abiraterone Cmax and AUC0-∞ were approximately 7- and 5-fold higher, respectively, when a single dose of abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal compared to overnight fasting. Abiraterone AUC0-∞ was approximately 7-fold or 1.6-fold higher, respectively, when a single dose of abiraterone acetate was administered 2 hours after or 1 hour before a medium fat meal (25% fat, 491 calories) compared to overnight fasting. Systemic exposures of abiraterone in patients with metastatic CRPC, after repeated dosing of abiraterone acetate were similar when abiraterone acetate was taken with low-fat meals for 7 days and increased approximately 2-fold when taken with high-fat meals for 7 days compared to when taken at least 2 hours after a meal and at least 1 hour before a meal for 7 days.

11.2.1 Form

Abiraterone will be supplied as 250 mg white to off-white, oval-shaped tablets debossed with AA250 on one side.

11.2.2 Storage and Handling

Abiraterone acetate 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. Abiraterone acetate 250 mg tablets are available in high- density polyethylene bottles of 120 tablets.

NDC Number 57894-150-12

Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F).

Based on its mechanism of action, abiraterone acetate may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection, e.g., gloves.

11.2.3 Availability

Abiraterone acetate will be provided free of charge by drug manufacturer Janssen Scientific Affairs, LLC.

11.2.4 Administration

The starting dose of abiraterone acetate is 1000 mg (4 250-mg tablets) taken orally once daily. Given the normal variation in the content and composition of meals, taking abiraterone acetate with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. The tablets should be swallowed whole with water.

11.2.5 Ordering

Abiraterone acetate is to be ordered manually via drug order form. Sufficient study drug for the next cycle of therapy will be provided to subjects randomized to the abiraterone acetate treatment arm at each monthly study visit.

11.2.6 Accountability

Study drug used for this study must be maintained under adequate security and stored in the pharmacy at the study site until dispensing or destruction at each site's pharmacy. Investigators may not supply apalutamide or abiraterone acetate to any person not enrolled in this study or to any person not named as an investigator or sub-investigator. In addition, the site research staff must maintain an accurate, running inventory of all drug supplies received and dispensed during the conduct of the study.

Patients will be required to keep a drug diary to record dose and time of apalutamide, abiraterone acetate, and prednisone administration during the treatment period, and will be instructed to bring the diary and used pill bottles to each study visit.

Upon completion or termination of study treatment, all used and unused study drug bottles, whether empty or containing study drug, should be destroyed at each study site's pharmacy (or site's authorized destruction unit) following their site-specific procedures on drug destruction. Any return shipments must provide proof of delivery and will be accompanied by the Drug Accountability Form and a memo noting the number of bottles and quantity of study drug being returned in the site's drug accountability records.

11.3 Prednisone

Investigators should refer to the package insert for the form, stability, storage and handling, and detailed instructions on the administration of prednisone. Store at controlled room temperature at 25 degrees C (77 degrees F), with excursion permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from moisture.

11.3.1 Availability

Prednisone will be obtained and provided to sites by AFT. Janssen Scientific Affairs, LLC is providing funding for prednisone supply for this trial.

11.3.2 Administration

The starting dose of prednisone is 5 mg twice daily. Patients will take one 5mg tablet orally twice per day with food.

11.3.3 Ordering

Prednisone is to be ordered manually via drug order form. Sufficient study drug for the next cycle of therapy will be provided to subjects randomized to the abiraterone acetate treatment arm at each monthly study visit.

11.3.4 Accountability

Study drug used for this study must be maintained under adequate security and stored in the pharmacy at the study site until dispensing or destruction at each site's pharmacy. Investigators may not supply prednisone to any person not enrolled in this study or to any person not named as an investigator or sub-investigator. In addition, the site research staff must maintain an accurate, running inventory of all drug supplies received and dispensed during the conduct of the study.

Patients will be required to keep a drug diary to record dose and time of prednisone administration during the treatment period, and will be instructed to bring the diary and used pill bottles to each study visit.

Upon completion or termination of study treatment, all used and unused study drug bottles, whether empty or containing study drug, should be destroyed at each study site's pharmacy (or site's authorized destruction unit) following their site-specific procedures on drug destruction. Any return shipments must provide proof of delivery, and will be accompanied by the Drug Accountability Form and a memo noting the number of bottles and quantity of study drug being returned in the site's drug accountability records.

11.4 LHRH Analogue

LHRH analogue will be administered per package insert and will be made available via commercial supply. Choice of LHRH analogue is per investigator discretion and will be administered according to one of the schedules outlined in Section 5.1 of the protocol.

12 Data Collection and Management/Data and Specimen Submission

12.1 Biospecimen Collection and Submission

Data collection for this study will be done through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in AFT CTMS System. Access to samples and study data will be available to research and study staff at AFT, Washington University, Janssen, and to the FDA in the event of a safety audit.

12.1.1 Biospecimen Collection

Screening/Registration

Tissue Specimens:

Tissue block (preferred) and/or unstained slides from the archival radical prostatectomy tumor specimen will be collected from clinical sites and shipped in ambient temperature to

the AFT Biorepository and stored at ambient temperature until subsequent processing and batched shipment to the respective testing laboratories.

Please refer to the Correlative Science Procedure Manual for details regarding specimen collection and shipping instructions to the AFT Biorepository.

Research Blood Samples:

Cycle 1 Day 1

- Whole blood for measurement of total testosterone using ultrasensitive assay
- Whole blood for genomic analysis

Cycle 3 Day 1

- Whole blood for measurement of total testosterone using ultrasensitive assay

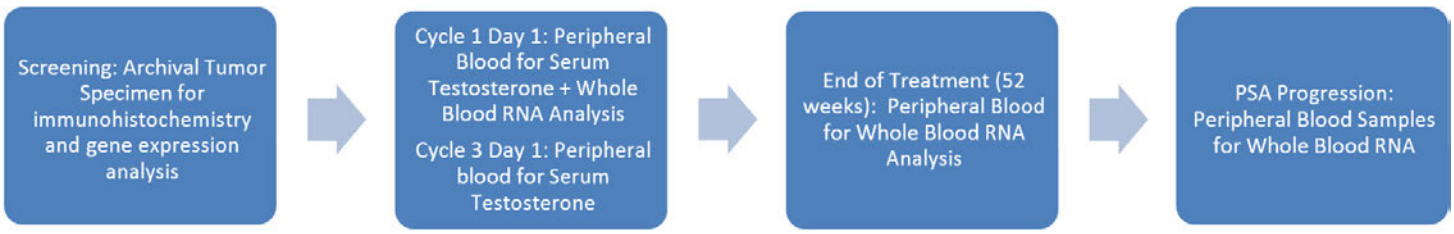
End of Treatment

- Whole blood for genomic analysis

At PSA Progression

- Whole blood for genomic analysis

12.1.2 Biospecimen Collection Schema



12.2 Biospecimen Logging and Tracking (AFT BioMS)

AFT Biospecimen Management System (AFT.BioMS) will be used for this study, and all specimens will be logged and shipped via this system. AFT BioMS is a web- based system for logging and tracking all biospecimens collected on AFT trials. Authorized individuals may access AFT.BioMS at the following URL: https://aftbioms.wustl.edu using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the AFT.BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-642-4667or aftbiomshelp@email.wustl.edu. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-642-4667 or aftbiomshelp@email.wustl.edu.

Staff members should familiarize themselves with the AFT.BioMS system and confirm that they are able to log into the system, prior to registering patients to the trial.

After logging collected specimens in AFT.BioMS, the system will create a shipping manifest. This shipping manifest will be printed and placed in the shipment container with the specimens.

12.3 Biospecimen Shipping

Upon entry of patients by sites into the AFT IRT, biospecimen shipping kits will be made available at the clinical sites for collecting and shipping biospecimens at baseline and follow up collection time points. It is important for the clinical research coordinators or designee to contact the AFT Biorepository in a timely manner prior to registering patients, to obtain kit(s). Upon return of kits containing biospecimens, additional new, empty kits will be sent to the site. Additional 'unscheduled visit' kits will also be sent to clinical sites for collection of samples as indicated (e.g. as back-up in case of expired kits).

All submitted biospecimens must be physically labeled with the AFT patient number, patient's initials, date of specimen collected and study time point. A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens. A printed, de-identified copy of the institutional surgical pathology report should also be included with the shipment. Please be sure to use a method of shipping that is secure and traceable. Ship specimens on Monday through Thursday only. Shipping by overnight service to assure receipt is required. Do not ship specimens on Fridays or Saturdays. All specimens should be sent upon collection to the following address:

AFT Biorepository at Washington University

c/o Siteman Cancer Center Tissue Procurement Core

425 S. Euclid Ave. BJCIH Building, Room 5120

St. Louis, MO 63110-1005

[redacted]

13 Correlative Science

13.1 Archival Tumor Analysis

As described above and in the lab manual, archival tumor tissue (if available) will be collected from all patients for the analysis of AR response gene expression signature and of AR-V7 expression by immunohistochemistry. In addition, for patients who had genomic testing of archival prostate cancer tissue (e.g. DECIPHER® and/or GenomeDX) performed as standard of care prior to study enrollment and who give consent for optional retrieval of data, the gene expression data will be extracted from the database and analyses will be performed per the methods outlined below.

OncotypeDx Testing:

Approximately 200 patients who have had OncotypeDx testing prior to enrollment are estimated to provide consent for optional retrieval of data. For the OncotypeDx assay, qPCR is applied to generate overall GPS score, as well as expression levels of AR-responsive subsets of genes including *KLK2*.

DECIPHER Testing:

Approximately 100-200 patients who have had DECIPHER testing performed prior to study enrollment and give consent for access to genomic data in the DECIPHER GRID database.

Decipher gene expression score in the GenomeDX assay is based upon purified RNA hybridized to the human exon (HuEX) 1.0 ST gene chip (Affymatrix). For these patients, the genomic classifier score will be obtained, which is a continuous score from 0 (lowest risk) to 1 (highest risk). Application of additional signatures of interest including AR response and neuroendocrine signaling to the complete gene expression data contained within the DECIPHER GRID database will also be performed.

Gene Expression Signature:

Approximately 300 archival FFPE archival prostate cancer tissue samples are estimated to be available for analysis of AR response signature derived from the AA-302 phase 3 study. A qPCR assay has been developed by Janssen to analyze gene expression levels of the target genes in this signature, including CYP17 and its cofactors (CYP17A1, CYB5A, CYP3A5, DUSP5, HNF1A, NROB1, and POR), as well as AR-regulated genes (AKR1C3, FKBP5, and PCNA).

AR-V7 IHC Testing:

An estimated 300 of the planned 500 patients enrolled on study will have FFPE archival prostate cancer tissue collected and stained for presence of AR-V7 by IHC using validated antibody at central laboratory. Quantification of AR-V7 expression by IHC will be performed using H-score as previously reported [49].

13.2 Circulating Biomarkers

Peripheral blood samples will be collected for analysis of whole blood RNA expression signatures involving AR, GR, and neuroendocrine signaling. The frequency of detection of ARV7 and expression levels of other gene sets of interest in whole blood RNA will be descriptively reported, normalized to RNA levels detected in healthy volunteers by means of ROC analysis and threshold C1 cut-off.

Serum testosterone will be measured using ultrasensitive assay at C1D1 and on C3D1 during treatment. The association between depth of serum testosterone suppression and clinical outcomes will be analyzed using Cox regression using dichotomized cohort at the median observed level.

13.3 Future Biomedical Research

All collected biospecimens will be stored in the Alliance Foundation Biorepository (AFB), a CAP-accredited biorepository at Washington University in St. Louis, until biospecimen accrual and clinical follow-up is sufficiently complete to allow for the design and execution of specific correlative analyses using 'state-of-the-art' analytical platforms that will be available at that time. Samples may be stored for up to 5 years after study closeout, or up to 11 years.

Such biomarker research will address emergent questions not described elsewhere in this protocol and will only be conducted on specimens from appropriately consented patients. The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of disease and/or their therapeutic treatments in the context of this trial. Proposals for future correlative research will undergo rigorous scientific, programmatic, and statistical review by AFT, and biospecimens will only be released to those investigators who have obtained appropriate regulatory approval and demonstrate adequate funding to successfully complete proposed research aims. AFT will ensure that all collected specimens are used only for approved research protocols.

Anonymized (de-identified) data generated from biospecimens used for future correlative research, including somatic and constitutional (germline) genomic data, may be shared with other researchers or deposited in a publicly accessible or controlled-access data repositories. Correlative study results and data will never be returned to individual patients.

14 Measurement of Effect

14.1 PSA Progression-Free Survival

PSA progression is defined as time from date of randomization to first date of PSA progression. PSA progression during the 52-week treatment period defined as a rising PSA confirmed on repeat measurement and at least 25% and 2 ng/mL above nadir or baseline, whichever is lower. PSA progression during the follow up phase (post-52 weeks) is defined as the first date of serum PSA > 0.2 ng/mL, confirmed by repeat measurement at least 2 weeks later.

14.2 Time to Castration Resistance

Time to castration resistance is defined as time from date of randomization to first date of PSA increase > 25% and more than 2 ng/mL above nadir on study with concomitant serum testosterone level < 50 ng/dL, confirmed by repeat measurement at least 2 weeks later.

14.3 Metastasis-Free Survival

Metastasis-free survival is defined as time from date of randomization to first date of metastatic lesion on whole body radionuclide bone scan and/or cross-sectional imaging, confirmed by repeat imaging performed at least 4 weeks after initial scan, or death, whichever occurs first.

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor. However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate progressive disease. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, date of metastasis should be declared using the date of the initial scan on which the lesion was discovered.

14.4 Overall Survival

Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause.

15 Statistical Considerations

15.1 Overview of the Study Design

This is a randomized, open-label, three-arm, phase 3 study in men with biochemically relapsed prostate cancer. The primary endpoint is PSA progression-free survival (PSA PFS) defined as time from date of randomization to date of PSA progression or death, whichever occurs first. Patients will be randomized with equal allocation to one of three treatment arms: LHRH analogue alone (control arm; Arm A); LHRH analogue + apalutamide (Experimental arm; Arm B), or LHRH analogue + apalutamide + abiraterone acetate + prednisone (Experimental Arm; Arm C).

Patients will be treated for a maximum duration of 52 weeks and then enter follow up phase until the time of PSA progression, development of metastasis, or patient withdrawal from study, whichever occurs first. Patients with PSA progression will be followed until the development of castration resistance and first metastasis.

15.2 Sample Size Determination, Accrual Time and Study Duration

The target sample size is 504 patients for comparing both experimental arms to control or 168 patients per arm. This sample size is adjusted for 20% inevaluable rate to account for in part the expected proportion of patients without testosterone recovery. The planned analyses for PSA progression-free survival consist of two independent comparisons of each experimental combination treatment arm versus LHRH analogue monotherapy. Each hypothesis will be tested using a two-sided type I error rate = 0.025. The null and alternative hypotheses can be written as H0:

Δ=1 or Ha: Δ=0.63, where Δ= is the hazard ratio defined as λ_{ArmB} / λ_{ArmA} (or λ_{ArmC}) λ_{ArmA} represents the hazard of PSA progression or death for Arm A and λ_{ArmB} represents the hazard of PSA progression or death for Arm B (or Arm C). Under the alternative hypothesis, the expected full information for each comparison is 205 PFS events. With 205 PFS events, assuming a one- sided type I error rate = 0.0125 and an exponential PFS distribution, the log-rank test has 85% power to detect a hazard ratio of 0.63 taking into account the planned schedule of the interim analyses.
The PSA progression-free survival rates at 36 months are 7% and 12% in patients with PSA doubling times of <3 months and 3-9 months, respectively (based on TAX 3503). Thus, the median PSA progression-free survival in patients randomized to the control arm is assumed=11.2 months. A clinically meaningful median PSA PFS in patients receiving treatment in either arm B or C months is considered to be 17.9 months (HR=0.63).
With an accrual rate of about 14 patients per month for 36 months, a minimum of 15 months follow-up period is needed to achieve the target number of 297 PFS events (205 PFS events for each comparison).

The total study duration is anticipated to be approximately six years from first patient enrolled.

15.3 Stratification Factors

Randomization will be stratified on PSADT (<3 months, 3-9 months).

15.4 Accrual

Based upon prior phase 3 studies conducted in high-risk biochemically relapsed prostate cancer, the anticipated accrual rate is approximately 14 patients/month, leading to an estimated accrual period of 36 months.

15.5 Analysis of the Primary Endpoint

The planned analyses for PSA PFS consist of two independent comparisons of the combination arms (Arm B versus Arm A; Arm C versus Arm A). Each hypothesis will be tested using a one- sided type I error rate of 0.0125. An intent-to-treat approach will be used in this phase III study to analyze the primary endpoint of PSA PFS. PSA progression is defined as time from

date of randomization to date of first PSA progression. PSA progression during the 52- week treatment period defined as a rising PSA confirmed on repeat measurement and at least 25% and 2 ng/mL above nadir or baseline, whichever is lower. PSA progression during the follow up phase (post- 52 weeks) is defined as the first date of serum PSA > 0.2 ng/mL, confirmed by repeat measurement at least 2 weeks later. Patients who receive non-protocol therapy prior to PSA progression will be censored for analysis of the primary endpoint of PSA progression-free survival.

No formal hypothesis to compare Arm B and Arm C will be performed. However, if both null hypotheses are rejected, the hazard ratio comparing arm B versus arm C will be estimated and 95% CI for the HR between Arms B and C with respect to PSA PFS will be reported.

Patients who withdraw consent for treatment or withdraw from the study due to toxicity will continue to be followed for analysis of secondary endpoints including OS, even if they begin another therapy. The stratified log-rank statistic will be the primary analysis to compare the two arms on PFS adjusting on the stratification factor (PSADT). The Kaplan-Meier product-limit estimator will be used to estimate the PSA PFS. In addition, the proportional hazards model will be used to assess the importance of each comparison adjusting on the stratification variable (PSADT) and other important covariates in predicting PSA PFS.

15.6 Interim Analysis Design for Primary Endpoint

Analyses of efficacy (PSA PFS) results will be conducted when the protocol- specified number of PFS events has occurred and interim analyses will be presented to the AFT Independent Data and Monitoring Committee (IDMC). The following description of group sequential methods applies to each comparison. Under the alternative hypothesis, 205 PFS events are expected at the end of the follow-up period. The first interim analysis for PFS will be performed at about 50% of the full information (approximately 30 months after study activation). Other interim analyses will be performed at 75% (approximately 38 months after study activation). The final analysis will occur when each comparison achieve the target 205 PFS event (approximately 46 months after study activation).

A Lan-Demets spending function analogue of a one-sided O'Brien-Fleming will be used to stop the trial early to reject the null hypothesis. Assuming the above percent information available at each look and a one-sided type I error rate =
0.0125, the z-score boundaries, HR and nominal, HRnominal significance boundaries for stopping for superiority or futility under the alternative hypothesis using Friedlin et al futility guidelines presented in the table below.
Should any boundary be crossed, accrual to the trial may be stopped. These rules have a negligible impact on the type I and II error rates of this trial.

Interim Analysis (approximate time)	Percent information (Number of PFS events)	One-sided Boundaries for Interim Analysis for the PFS endpoint Z-values, hazard ratio, nominal significance level	
		For Superiority	For Futility
1 (30 months)	50% (102)	3.224 0.674 0.0006	-0.016 0.981 0.494
2 (38 months)	75% (153)	2.632 0.769 0.004	
3 (Final)	100% (205)	2.274 0.821 0.011	2.274 0.821 0.011

The trial has randomization between three arms. If one comparison crosses a boundary, then that arm may be dropped.

15.7 Toxicity Monitoring

Extensive clinical data is available on apalutamide and abiraterone acetate/prednisone, alone and in combination, when administered in conjunction with LHRH analogue. We have no reason to believe that the combination of the two drugs will lead to increased toxicity, and there is no plan to do a separate phase I/II study of the combination. Given that the safety of LHRH analogue monotherapy is well established, safety parameters will apply to the combination arms. Monthly conference calls (including the Study Chair, Committee Chair, study statisticians, data coordinator, protocol coordinator, and Alliance

Executive Officer) will be held to monitor the first 120 patients randomized to the trial treated for 4 cycles due to unacceptable treatment- related events. Unacceptable toxicity will be defined as: treatment-related death and seizures. It is assumed that the incidence of unacceptable toxicity in patients treated with apalutamide is < 1%. Unacceptable toxicity rates will be compared by the two experimental arms versus control arm for the first 120 randomized patients to the study. We expect to accrue the first 120 patients at about 8.6 months after FPI. Three analyses at 50% (60 patients), 80% (72 patients), and 100% (120 patients) will be performed and will be discussed at all scheduled conference calls. If at any

scheduled time of analysis the lower boundary of a one-sided 90% confidence interval for the difference in unacceptable toxicity exceeds 10%, accrual to the trial will be immediately suspended. The trial will remain closed until the review of all toxicity data is completed and a decision is made about whether it is safe to resume accrual. This decision will be made by consensus of the study team and the AFT IDMC.

15.8 Data Analysis Plan for the Secondary Endpoints

PSA Progression-Free Survival in Testosterone-Evaluable Population

The planned analyses for PSA PFS consist of two independent comparisons of the combination arms (Arm B versus Arm A; Arm C versus Arm A). Each hypothesis will be tested using a one- sided type I error rate of 0.0125. The testosterone-evaluable patient population is defined as the cohort of patients who includes all patients who achieve serum testosterone recovery to > 50 ng/dL with subsequent PSA measurements sufficient for evaluation of PSA progression. The stratified log-rank statistic will be the primary analysis to compare the two arms on PSA PFS in the testosterone-evaluable patient population adjusting on the stratification factor (PSADT). The Kaplan-Meier product-limit estimator will be used to estimate the PSA PFS in the testosterone- evaluable patient populations in each treatment arm. In addition, the proportional hazards model will be used to assess the importance of each comparison adjusting on the stratification variables (PSADT) and other important covariates in predicting PSA PFS in testosterone- evaluable patient populations.

36-month PSA progression-free survival rate in ITT and testosterone- evaluable patient populations

The Kaplan-Meier will be used to estimate the PSA PFS rate at 36 months. In addition, the chi-square statistic will be used to test each hypothesis (each experimental arm vs control). Subjects who withdraw from the study prior to 36 months after randomization will be censored in this analysis.

Time to testosterone recovery (serum T > 50 ng/dL)

The time to serum testosterone recovery to > 50 ng/dL after the cessation of protocol therapy at 12 months will be compared between each experimental arm and the control arm. The log-rank statistic will be used to compare the arms on the distribution of time to testosterone recovery. Subjects who discontinue study drug prior to 12 months for disease progression, unacceptable toxicity, or study withdrawal, as well as subjects who receive non-protocol therapy prior to testosterone recovery will be censored.

Time to castration resistance.

The time to castration resistance will be defined as the first date of PSA increase > 25% and more than 2 ng/mL above nadir with concomitant serum testosterone < 50 ng/dL. The log-rank statistic will be used to compare the time to castration resistance distribution for each hypothesis (experimental arm vs control).

Metastasis-free survival

Metastasis-free survival is defined as time from date of randomization to the first date of metastatic lesion on whole body radionuclide bone scan and/or cross-sectional imaging, or death whichever occurred first. The log-rank test will be used to compare the two arms on the distribution of metastasis-free survival.

Overall survival

Overall survival is defined as the time from date of randomization to death. The log-rank test will be used to compare the two arms (each experimental arm vs. control) on the overall survival distribution.

Safety

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

Specifically, the following adverse events will be summarized:

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

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

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

Quality of life and quality-adjusted PSA progression-free survival

Change from baseline in each HRQOL instrument will be analyzed using a mixed-model for repeated measures (MMRM). The model will include baseline scale, treatment, month (categorical), and treatment-by-month interaction as covariates. An unstructured variance-covariance matrix will
be used to model within-subject errors, but simpler structures (eg, compound symmetry) may be used to ensure estimation convergence. Change from baseline will be estimated using least squares means with factor levels weighted according to overall baseline sample means. Data up to 72 months from date of randomization will be included in the analysis.

Contrasts will be set up to compare LHRH analogue monotherapy control arm versus each of

the experimental arms. The estimated least-squares mean (+/- SE) over time will be presented using a line plot.

The measured utility values for each patient will be combined with PSA progression-free survival to calculate the quality-adjusted PSA progression-free survival, and compared between control arm and each experimental arm.

15.9 Analytic Plan for the Correlative Study Endpoints

Association between previously validated prognostic gene expression signature score with outcomes on study:

Association of GPS score with clinical endpoints will be evaluated for the subset of patients with available GPS scores from primary prostate cancer tissue who have consented to access of their data. The patient cohort will be divided into two groups based upon the GPS score (<0.4= low risk; >=0.4 = high risk). The difference in PSA progression-free survival and metastasis- free survival between groups will be measured using the log-rank test. In addition, association of GPS score measured as a continuous value with time to event will be estimated using cox proportional hazards

For the subset of patients with available DECIPHER scores from primary prostate cancer tissue who have consented to access of their data, the patient cohort will be divided into tertiles based upon DECIPHER genomic classifier score (0 – 0.45 = low risk; 0.45-0.60 = intermediate; 0.60-1.0 high risk). The difference in PSA progression-free survival and metastasis-free survival between tertiles will be compared using log-rank test.

Association between androgen response and other gene signatures of interest with clinical outcomes on study:

Gene expression signatures will be evaluated in exploratory or validation contexts to the subset of patients with RT-PCR expression data available. Signatures evaluated in an exploratory context will be evaluated as continuously measured variables and/or dichotomized variables as appropriate. Association with biomarker status, treatment and PSA-progression free survival or metastasis-free survival will be evaluated using the log rank test or cox proportional hazards as appropriate. Signatures evaluated in a validation context will be dichotomized based on pre-defined thresholds. Association with biomarker status, treatment and PSA-progression free survival or metastasis- free survival will be evaluated using the log-rank test.

Additional gene expression signatures of interest, including AR transcriptional signature and neuroendocrine signaling, will be applied in an exploratory fashion to the subset of patients with gene expression data available within the DECIPHER GRID database. Subjects will be either dichotomized into appropriate categories based on specific signature (e.g. positive score vs negative score; above vs. below median) as appropriate. Differences in PSA progression-free survival and metastasis-free survival between dichotomized subgroups will be analyzed using log-rank test.

Frequency and association of AR-V7 expression in archival tumor tissue with clinical outcomes:

Frequency of ARV7 expression will be determined using pre-defined thresholds for positive expression. Confidence intervals for the frequency of expression will be estimated using Wilson's score method. Association of ARV7 with clinical outcomes will be evaluated for both dichotomized and continuously measured expression values using log rank test or cox proportional hazards as appropriate.

Whole blood RNA expression of genes of interest:

Expression of RNA transcripts of interest from whole blood collected at baseline will be evaluated to identify associations with prognosis and response to treatment. Signatures will be evaluated in an exploratory context as dichotomized or continuously measured values. For prognostic analysis, association with clinical outcome will be evaluated using the log-rank test or cox proportional hazards as appropriate. For association with response to treatment, the relationship between biomarker status, treatment and response will be evaluated using cox proportional hazards analysis.

Serum testosterone analysis by ultrasensitive LC/MS/MS assay

The mean and standard deviation in baseline and percent change from baseline serum testosterone will be descriptively reported for patients in each of the three treatment arms and across the entire study cohort. Differences between study arms will be compared using paired t-test. The study population will be dichotomized by baseline and percent change from baseline in serum testosterone above and below the median for the entire study cohort. A log-rank test will be used to compare.

15.10 Criteria for Taking a Patient off Protocol Therapy

Patients will continue study therapy until one of the following, whichever occurs first:

- PSA progression
- Unacceptable toxicity
- Patient/physician withdrawal
- Completion of 52-week treatment period
- Development of metastasis

The reason for treatment discontinuation except for completion of 52- week treatment period must be entered into the eCRF.

Patients who discontinue treatment will remain on study in Follow Up Phase.

15.11 Duration of Follow-Up

Patients will remain in study follow-up until one of the following, whichever occurs first:

- Patient Withdrawal
- Death
- Study Termination

In the long-term follow-up phase, patients and/or providers may be contacted via telephone at 6-month intervals to ascertain survival status and details of prostate cancer treatment course including date of castration resistance, first metastasis, and subsequent therapies.

15.12 Criteria for Taking a Patient Off Study

Patients will be removed from study for one of the following:

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

The date of death or last known alive should be entered into the eCRF when a patient is removed from study.

15.13 Primary Endpoint Completion Time

With accrual rate of about 14 patients per month for 36 months, a minimum of 15 months after the accrual period is needed to achieve the target number of 297 PFS events (205 PFS events for each comparison). The total study duration is anticipated to be approximately 72 months.

16 General Regulatory Considerations and Credentialing

16.1 Compliance with Trial Enrollment and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

16.2 Regulatory and Ethical Compliance

By signing the Protocol the investigator agrees to treat all of the information that is provided with the strictest confidentiality and to require the same of his personnel as well as the IRB. Study documents (protocols, investigator`s brochures, eCRFs, etc.) provided by the AFT will

be stored in an appropriate manner in order to ensure confidentiality. The information provided to the investigator by AFT must not be made available to other parties without a direct written authorization by the aforesaid parties, with the exception of the extent to which disclosure is necessary in order to obtain informed consent from the patients who wish to participate in the study.

This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines, if applicable. These documents ensure that the ICH E6 guideline for Good Clinical Practice is maintained as well as compliance with the principles of the Declaration of Helsinki (World Medical Association), or the laws and regulations of the country in which the research is conducted, whichever afford the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulation and applicable local, state and federal laws.

By signing the study protocol the investigator agrees to comply with the instructions and procedures described therein and thus to adhere to the principles of good clinical practice, which these instructions and procedures reflect.

16.3 Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Informed Consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any trial-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study).

For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patients and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Furthermore, it is the investigator's responsibility to obtain the signed Informed Consent Form, and a signature from the person conducting the informed consent discussion, prior to undertaking any trial-related procedure. The proposed Informed Consent Form must comply with the ICH GCP guideline and regulatory requirements.

16.4 Responsibilities of the Investigator IRB/IEC/REB

The regulatory requirements for the Investigator can be found in Subpart D of 2121 CFR 312 (21CFR 312.60: General Responsibilities of Investigators) and in ICH E6 Section 4.

Additional requirements are also outlined in the Statement of Investigator Responsibilities (Form FDA 1572) and the Site Services Agreement. Alliance Foundation Trials, LLC (AFT) will supply the protocol and subsequent amendments.

The Investigator is responsible for ensuring all patients and/or parents or legal guardian of each patient, if applicable, are informed about the study and that written consent is obtained prior to the conduct of any study related procedures.

In addition, the Investigator is responsible for reviewing all health- related information collected for each study patient in order to identify any safety related issues/adverse events (AE) or Infusion Associated Reactions (IAR). All Serious Adverse Events (SAEs) and IARs are to be reported within 24 hours to Novella via the Argus Safety Management System of becoming aware of the event. If this is not reported within 24 hours, a Protocol Deviation will be documented.

As specified in 21CFR 312.62 (Investigator Record Keeping and Record Retention) and ICH E6 Sections 4.9 and 8, the Investigator is responsible for ensuring that their study staff maintains and retains all study related documentation, including but not limited to: signed Informed Consent forms, medical records that are applicable for this study and source documents, the AFT-19 protocol, Institutional Review Board (IRB) approvals, relevant IRB and Sponsor correspondence, and assorted regulatory documents. The Investigator is responsible for retaining and keeping safe all patient related documentation. In order to do this, the site staff will complete electronic case report forms (eCRFs) in a timely manner.

16.5 Financial Disclosures

Investigators will provide AFT with adequate and accurate financial information in accordance with local regulations and laws in order to allow AFT to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing updated information on financial interests during the course of the study as well as for 1 year after completion of the study.

16.6 Protocol Deviations

The investigator is responsible to document and explain any deviations from the approved protocol. The investigator should promptly report any deviations that might impact patient safety and data integrity to AFT and if locally applicable, to the respective IRB in accordance with local IRB policies and procedures.

A deviation is a departure from the protocol. If deviations are discovered by the monitor or data manager, other member of study staff or otherwise, they will be discussed with the Investigator and study staff. AFT does not provide waivers for protocol deviations.

16.7 Protocol Amendments

Any modifications to the protocol or the Informed Consent Form which may impact the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by AFT, agreed by the investigator(s) and Janssen, and approved by relevant IRBs prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the Informed Consent Form have been approved by relevant IRBs must be provided to AFT before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the AFT, agreed by the investigator(s) and notified to the IRB.

16.8 Retention of Records (Study Documentation, Record Keeping, and Retention of Records)

Any records and documents relating to the conduct of this study and the distribution of investigational drug must be retained by the study chair until notification by AFT, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of AFT. Written notification should be provided to AFT prior to transferring any records to another party or moving them to another location.

Correlative study samples will be stored at AFT Biorepository for up to 5 years following study completion.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), AFT should be prospectively notified. The study records must be transferred to a designee acceptable to AFT, such as another investigator, another institution, or to AFT itself.

16.9 Data Confidentiality

Patient medical information both, associated with biologic specimens or not, is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law. Data derived from biologic specimen analysis on

individual patients will in general not be provided to study investigators unless a request for research use is granted. The overall results of any research conducted using biologic specimens will be available in accordance with the effective AFT policy on study data publication.

16.10 Database Management and Quality Control

The Site Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate patient case histories with observations and data pertinent to the study.

Rave EDC will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF.

The Clinical Research Coordinator (CRC) or designated study site personnel will complete the eCRFs in a timely manner after the information is collected. The Investigator will review and approve the completed eCRFs. Patients will not be identified by name in the study database or on any study documents to be collected by the AFT (or designee), but will be identified by a site number, subject number.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto eCRFs.

At study completion, when the database has been declared to be complete and accurate, the database will be locked.

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

AFT will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to AFT; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources. Queries are entered, tracked, and resolved through the EDC system directly. All changes to the study database will be documented.
At critical junctures of the protocol (e.g., production of interim and final reports), data for analysis is locked and cleaned per established procedures.

AFT Biorepository will be responsible for ensuring proper methods of specimen collection, tracking shipment of samples from individual sites to AFT Biorepository, specimen processing, and subsequent batched shipment to testing labs at the required shipping conditions (e.g. frozen, ambient temperature). Janssen R&D Oncology Translational Research (OTR) group will be performing correlative analyses as outlined in Section 12. AFT Biorepository will provide monthly (and upon request) sample inventory reports to Janssen OTR group.

16.11 Site Monitoring

Monitoring visits will be conducted by representatives of the Alliance Foundation according to the US CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to AFT (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. Sites will be monitored at least annually during the treatment phase of the trial. The first monitoring visit at each site will occur after the first patient enrolled has completed two cycles of study treatment.

16.12 Data Safety and Monitoring Board

The Alliance Foundation Trials Data Safety Monitoring Board will be monitoring this study.

16.13 Regulatory Reporting

Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, AFT's guidelines, and Institutional Review Board (IRB) policy.

16.14 Audits and Inspections

To enable evaluations and/or audits from regulatory authorities or AFT, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). In the event that the investigator or other site personnel are notified of a Health Authority's intent to inspect the site(s), notification will be sent to compliance@alliancefoundationtrials.org immediately upon awareness. Investigator sites will be audited by AFT under the AFT site audit program. Sites will be audited within eighteen (18) months of first patient in (FPI) on any AFT sponsored study. Affiliate and satellite sites are subject to audit by AFT but in most cases will be centrally audited at the main member site.

16.15 Early Discontinuation of the Study

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

16.16 Publication of Study Protocol and Results

Alliance Foundation Trials, LLC prioritizes the timely presentation and publication of study results. Publications and any kind of presentations of results from the study shall be in accordance with accepted scientific practice, academic standards and customs and must be approved in writing by AFT as the sponsor of this trial. No investigator may present or publish any portion of this trial without written approval from AFT.

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18 Appendices

18.1 Appendix 1: List of Prohibited and Restricted Medications

Medications/Supplements which are PROHIBITED while on study:

- Medications known to lower seizure threshold, including:
  - Aminophylline/theophylline
  - Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone)
  - Buproprion
  - Lithium
  - Meperidine and pethidine
  - Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
  - Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
- Strong CYP3A4 inhibitors: itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit
- Strong CYP3A4 inducers: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, efavirenz, tipranivir, St. John's wort
- Systemic corticosteroids (except treatment arm C)
- 5-alpha reductase antagonists
- Anti-cancer therapies other than those specified in protocol

Medications/Supplements, which are NOT RECOMMENDED while on study (monitor for increased toxicity/potential drug interactions):

- Apalutamide may also induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have a narrow therapeutic index
- The potential for drug-drug interaction between apalutamide and warfarin (e.g., Coumadin) is unknown at present. If a patient is taking warfarin, re-assess PT/INR as clinically indicated and adjust the dose of warfarin accordingly.
- Whenever possible, 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
- Whenever possible, avoid co-administration of abiraterone acetate with CYP2C8 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2C* substrate
- Avoid pomegranate, saw palmetto, megestrol, milk thistle as these supplements/medications may affect serum PSA levels.

18.2 Appendix 2: EPIC-26

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number)
   About once a week..... 4
   Rarely or never..... 5

2. Which of the following best describes your urinary control **during the last 4 weeks?**

   No urinary control whatsoever..... 1
   Frequent dribbling..... 2 (Circle one number)
   Occasional dribbling..... 3
   Total control..... 4

3. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks?**

   None 0
   1 pad per day..... 1
   2 pads per day..... 2 (Circle one number)
   3 or more pads per day..... 3

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks?**

   (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Dripping or leaking urine	0	1	2	3	4
b. Pain or burning on urination.....	0	1	2	3	4
c. Bleeding with urination.....	0	1	2	3	4
d. Weak urine stream or incomplete emptying.....	0	1	2	3	4
e. Need to urinate frequently during the day.....	0	1	2	3	4

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks?**

   No problem..... 1
   Very small problem..... 2
   Small problem..... 3 (Circle one number)
   Moderate problem..... 4
   Big problem..... 5

6. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Urgency to have a bowel movement	0	1	2	3	4
b. Increased frequency of bowel movements	0	1	2	3	4
c. Losing control of your stools	0	1	2	3	4
d. Bloody stools	0	1	2	3	4
e. Abdominal/ Pelvic/Rectal pain	0	1	2	3	4

7. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number)
Moderate problem..... 4
Big problem..... 5

8. How would you rate each of the following **during the last 4 weeks**? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good
a. Your ability to have an erection?	1	2	3	4	5
b. Your ability to reach orgasm (climax)?	1	2	3	4	5

9. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all..... 1
Not firm enough for any sexual activity..... 2
Firm enough for masturbation and foreplay only..... 3 (Circle one number)
Firm enough for intercourse..... 4

10. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one..... 1
I had an erection LESS THAN HALF the time I wanted one..... 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number)
I had an erection MORE THAN HALF the time I wanted one..... 4
I had an erection WHENEVER I wanted one..... 5

11. Overall, how would you rate your ability to function sexually **during the last 4 weeks?**

Very poor	1	
Poor	2	
Fair	3	(Circle one number)
Good	4	
Very good	5	

12. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks?**

No problem	1	
Very small problem	2	
Small problem	3	(Circle one number)
Moderate problem	4	
Big problem	5	

13. How big a problem **during the last 4 weeks**, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Hot flashes	0	1	2	3	4
b. Breast tenderness/enlargement	0	1	2	3	4
c. Feeling depressed	0	1	2	3	4
d. Lack of energy	0	1	2	3	4
e. Change in body weight	0	1	2	3	4

18.3 Appendix 3: Hot Flash Related Interference Scale

Hot Flash Related Daily Interference Scale (HFRDIS)

Please circle one number to the right of each phrase to describe how much DURING THE PAST WEEK hot flashes have INTERFERED with each aspect of your life. Higher numbers indicate more interference with your life. If you are not experiencing hot flashes or if hot flashes do not interfere with these aspects of your life, please mark zero to the right of each question.

	Do not interfere									Completely interfere
1. Work (work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
2. Social activities (time spent with family, friends, etc.)	0	1	2	3	4	5	6	7	8	9	10
3. Leisure activities (time spent relaxing, doing hobbies, etc.)	0	1	2	3	4	5	6	7	8	9	10
4. Sleep	0	1	2	3	4	5	6	7	8	9	10
5. Mood	0	1	2	3	4	5	6	7	8	9	10
6. Concentration	0	1	2	3	4	5	6	7	8	9	10
7. Relations with others	0	1	2	3	4	5	6	7	8	9	10
8. Sexuality	0	1	2	3	4	5	6	7	8	9	10
9. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10
10. Overall quality of life	0	1	2	3	4	5	6	7	8	9	10

18.4 Appendix 4: EQ-5D-5L

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

We would like to know how good or bad your health is TODAY.

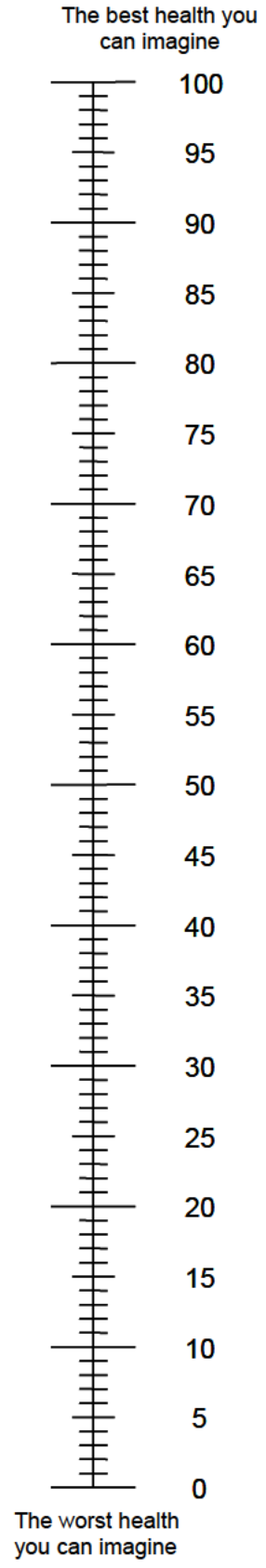
This scale is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



18.5 Appendix 5: PROMIS Fatigue Scale

PROMIS Item Bank v1.0 – Fatigue – Short Form 8a

Fatigue – Short Form 8a

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35	How much were you bothered by your fatigue on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP49	To what degree did your fatigue interfere with your physical functioning?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
FATIMP3	How often did you have to push yourself to get things done because of your fatigue?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP16	How often did you have trouble finishing things because of your fatigue?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

18.6 Appendix 6: Performance Status

ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

ECOG - Karnofsky Performance Status Conversion Table

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—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—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare 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 personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead