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STUDY TITLE: The Association between *HSD3B1* Genotype and Steroid Metabolism in Normal and Prostate Cancer Tissue of Men with Intermediate and High-risk Prostate Cancer Undergoing Radical Prostatectomy after Treatment with Apalutamide and Leuprolide.

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SUPPLIED AGENT: Apalutamide (Supplied by Janssen Scientific Affairs, LLC)

OTHER AGENT: LEUPROLIDE (Standard of Care)

SUMMARY OF CHANGES

Protocol Date	Section	Change
03/15/2016		Initial PRMC approval
11/15/2016	Front page	Version date, Remove Hamid
	Entire document	Change ARN-509 to Apalutamide, footer version date
	4.1.2	Added: 'any one of the following' and changed and to or.
	4.1.3	Removed: and at least 50% tumor involvement in one of the core biopsies is required.
	6.1	Deleted duplicate paragraph
	10.2.2	Added: 1 mL purple top tube will be used for genotyping purposes at indicated time points.
	10.4	Added: 1 10mL red top tube will be used for serum steroid studies at indicated time points.
	11 footnotes	e: Blood will be drawn for HSD3B1 genotyping and for steroid metabolites for the research laboratory, anytime during the study.
5/23/2017	Front page	Version Date
	3.1	Changed biopsies from 3 to 1
	4.1.3	Changed biopsies from 3 to 1
12/29/2017	Front Page	Version date, changed statistician
	Table of Contents & throughout	Corrected sections
	9.2.2	Adverse Events of Special Interest added
	6.6 & 11.0	Allow variability of timing for post-op visit to coordinate with surgical post-op visit. Ideally, 4-8 weeks post-surgery.
2/15/2018	Front page	Version date & Co-I removal
	5.2.3.3 & 11.0	Added labs: Direct Renin and Aldosterone/Direct Renin Ratio
3/26/18	5.1 & 14.1	Added verbiage allowing any subjects that are unable to provide tissue samples from surgery, to be replaced, in order to obtain the target number of samples per cohort.
10/30/18	Front page	Version Date, remove Andrew Stephenson MD, Allison Tyler & Kimberly Schach, add Sarah Devonshire and Pam Profusek

Protocol Date	Section	Change
10/30/18	1.2	Apalutamide now listed as FDA approved for the treatment of non-metastatic castrate resistant prostate cancer. Still investigational in this trial setting.
	5.3	Remove name of study coordinator. Already listed on pg. 2
	11	Table 2 addition of serum collection at eligibility/screening. Footnotes 'e' removed "anytime during the study" verbiage. Footnote 'l' added to allow 1-3 day window for prostatectomy lab collection.
07/30/19	Front page	Version Date and administrative changes throughout. Jorge Garcia removed as Principal Investigator and replaced with Moshe Ornstein. Removed Cristina Magi Galluzzi and Pam Profusek. Added Jesse McKenney and Susan Taylor. Remove Brian Rini.
	Study Schema	Deleted study schema graphic on pg 5. Duplicate in section 3.2
	Protocol Summary	Sample Size: Accrual increased to 80 patients to account for replacement patients and logistical restrictions. Sample size remains at 57 patients.
	1.2	Included metastatic castration sensitive prostate cancer as FDA approved. Updated clinical studies with Apalutamide.
	3.2	Replaced graphic to include the change of ARN-509 to Apalutamide and post- op visit timeline
	4.2	Systemic steroid therapy and herbal products deleted from exclusion criteria and moved to section 6.3.2.1. Hypertension permitted at provider discretion.
	5.2	Timeline clarification: Cycle 1 Day (-28) or within 28 days
	6.2.1	Dosing clarification: Subjects should take Apalutamide up to and including the day before radical prostatectomy
	6.3.2.1	Systemic steroid therapy and herbal products added
	7.1	TSH (T3 and T4) lab collection clarification
	9.2.2	Adverse events of special interest for Apalutamide removed
	9.2.5	SAE reporting timeline added and clarification on reporting to Sponsor Investigator and Janssen
	9.3	For Apalutamide, package insert link provided to determine the expectedness of an adverse event.
	9.9	SAE Fax transmission number updated
	11	Study calendar updated: timeline for laboratory tests and procedures updated and clarified

Protocol Date	Section	Change
	13.1	Updated database collection from Oncore to Forte EDC
	14.1	Language updated to include new accrual increase to 80 patients to account for replacement patients and logistical restrictions. Sample size remains at 57 patients.
	Appendix III	Medication Diary updated to include dosing instructions and side effects
	Appendix IV	Steroid therapy and herbal products added to Prohibited medication list

PROTOCOL SUMMARY

Protocol Number/Title	**CASE5815** The Association Between *HSD3B1* Genotype and Steroid Metabolism in Normal and Prostate Cancer Tissue of Men with Intermediate and High-risk Prostate Cancer Undergoing Radical Prostatectomy after a short-term treatment with Apalutamide and leuprolide acetate.
Study Phase	Phase II Study
Brief Background/Rationale	As homozygosity for *HSD3B1*(1245C) SNP can impact response and mediate resistance to androgen deprivation therapy (ADT), evaluating the effect of such genotype variation on the level of steroid metabolites and the intratumoral DHT concentration in benign and tumor tissue of men receiving a short course of Apalutamide and leuprolide acetate prior to undergo RP is of significant interest. We hypothesize that patients with homozygous *HSD3B1* (1245C) inheritance that leads to a gain of function in 3βHSD1, will have a sustained androgen synthesis from extragonadal precursor steroids and higher concentrations of DHT compared to patients with wild-type *HSD3B1* (1245A) inheritance in the context of testosterone suppression. In addition, it is expected that heterozygous *HSD3B1* (1245C) patients will have intermediate levels of DHT. We also hypothesize that treatment with Apalutamide will reverse the effects of elevated DHT on AR signaling in benign and malignant prostate tissue. For example, although DHT concentrations will be higher in the *HSD3B1* (1245C) groups, PSA expression will likely be similar among all groups. We anticipate that these studies will serve as the first step in identifying patients with localized and locally advanced prostate cancer who will benefit from upfront treatment with Apalutamide in addition to medical castration prior to undergo local definitive therapy with surgery.
Primary Objective	Primary Endpoint DHT concentration in benign prostate tissue after neo-adjuvant leuprolide and Apalutamide based on genotype status
Secondary Objective(s)	Secondary Endpoint(s) 1. Other androgens (testosterone (T), dehydroepiandrosterone (DHEA), androstenediol, 5α-androstanedione (5α-dione), androstenedione (AD),

	androsterone and 5α-androstanediol) concentration in benign prostate tissue after neo-adjuvant leuprolide and Apalutamide based on genotype status 2. Other androgens (DHT, T, DHEA, androstenediol, 5α-dione, AD, androsterone and 5α-androstanediol) concentration in malignant prostate tissue after neo-adjuvant leuprolide and Apalutamide based on genotype status. 3. PSA, FKBP5, TMPRSS2, EZH2, H3K27, and UBE2C expression (via IHC and qPCR) in benign and malignant prostate tissue after neoadjuvant leuprolide and Apalutamide based on genotype status.
Sample Size	Based on the known frequency of the genotypes in question, approximately 120 male patients will be genotyped prior to enrollment on study. The sample size required to carry-out the objectives of the study will be 57 male patients. Due to logistical restrictions, an accrual goal of 80 male patients may be needed in order to capture all objectives to support this sample size. There won't be any ethnic restrictions for study entry including during the initial genotype identification state.
Disease sites/Conditions	Prostate cancer
Interventions	Leuprolide acetate, Intramuscular injection - 7.5 mg, one time dose on day (-28) ± 3
	Apalutamide, PO, 240 mg daily, starting day (-28) ± 3 up to and including the day before radical prostatectomy. Apalutamide will be initiated the same day patients receive their leuprolide acetate injection.

ABBREVIATIONS

AA	abiraterone acetate
AA/P	abiraterone acetate plus prednisone
AR	androgen receptor
AD	androstenedione
ADT	androgen deprivation therapy
AE	adverse event
BID	bis en die (twice daily)
5α-dione	5α-androstanedione
CRF	case report form
CRPC	castration-resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
CYP17A1	cytochrome P450c17
DHEA	dehydroepiandrosterone
DHEA-S	dehydroepiandrosterone-sulfate
DHT	dihydrotestosterone
DLT	dose limiting toxicity
DMFS	distant metastasis-free survival
HPLC	high performance liquid chromatography
HSD3B1	3β-hydroxysteroid dehydrogenase-1
HSD3B2	3β-hydroxysteroid dehydrogenase-2
HSD17B3	17β-hydroxysteroid dehydrogenase type 3
HSD17B5	17β-hydroxysteroid dehydrogenase type 5
LBD	ligand-binding domain
LC-MS/MS	liquid chromatography, mass spectrometry/mass spectrometry
MFS	metastasis free survival
OS	overall survival
PD	progression of disease
PFS	progression free survival
PSA	prostate-specific antigen
RP	radical prostatectomy
SAE	serious adverse event
SRD5A1	steroid 5α-reductase-1
SRA5A2	steroid 5α-reductase-2
T	testosterone
ULN	upper limit of normal

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1 Introduction

1.1 Prostate Adenocarcinoma

Prostate cancer represents 14.0% of all new cancer cases in the U.S. It is the second most common cause of cancer death in American males and the leading cause of cancer death in males over 85. In 2015, it is estimated that there will be 220,800 new cases of prostate cancer and an estimated 27,540 people will die of this disease.[1] Androgen deprivation therapy (ADT), with either medical or surgical castration, is a critical and the most effective component of therapy for patients with metastatic or high-risk localized prostate cancer. Normally, serum testosterone (T) is irreversibly converted to DHT in the prostate by steroid 5α-reductase (SRD5A). Dihydrotestosterone (DHT) is the chief endogenous agonist for the androgen receptor (AR) and binds and activates AR with 10-fold higher potency than T. ADT lowers serum T concentrations to less than 1.7 nmol/l and generates an initial tumor response in about 90% of the patients. However, nearly all patients will eventually progress to a "castration-resistant" state.

Castration-resistant prostate cancer (CRPC) is often manifested by rising levels of prostate-specific antigen (PSA), progressive disease on imaging studies, worsening of symptoms and ultimately death.[2,3] It is well known that the AR continues to play a major role in disease progression in a large majority of cases, as demonstrated by the level of AR overexpression in castration-resistant tumor tissue and the level of expression of the AR regulated gene, PSA.[4] In vitro growth of a metastatic prostate cancer cell line, LNCaP cells, maintained physiologic levels of intracellular DHT (10 nM) and proliferated despite castrate levels of testosterone in the media.[5] Moreover, clinical studies have clearly demonstrated significantly higher levels of intra-tumoral androgens in CRPC from anorchid men compared with primary prostate tumors from untreated eugonadal men.[6] As clinically demonstrated, adding a secondary hormonal therapy to further reduce androgen synthesis or directly inhibit AR can lead to declines in PSA level and disease control in CRPC. This points to the importance of intratumoral androgens in driving tumor progression in CRPC.[7–9] Emerging evidence also demonstrates that AR can be activated in a ligand-independent fashion by growth factors or cytokines working independently or in combination.[4,10] Changes in the level of ligand(s) in tumor tissue, increased levels of the protein due to gene amplification, activating mutations in the receptor, and changes in co-regulatory molecules are some of the proposed mechanisms behind the development of castration-resistant disease that are just beginning to unfold.[11–14]

1.2 Apalutamide

Apalutamide is an orally available, non-steroidal selective antagonist of the androgen receptor (AR). Apalutamide was recently FDA approved for the treatment of metastatic castration sensitive prostate cancer and non-metastatic castration-resistant prostate cancer, however, Apalutamide is still considered investigational because of its use prior to surgery. Apalutamide directly antagonizes the binding of androgen to the ligand-binding domain of the AR, impairing nuclear translocation and DNA binding. Apalutamide binds the AR with 5-fold greater affinity than the first-generation anti-androgen bicalutamide. Apalutamide is currently being developed for the treatment of both hormone-sensitive and castration-resistant prostate cancer (CRPC).

Clinical Studies with Apalutamide

Study ARN-509-001 is an ongoing Phase 1/2 study in subjects with progressive CRPC. In the Phase 1 component of the study, 30 subjects with metastatic CRPC (mCRPC) received at least 1 dose of Apalutamide at escalating dose levels ranging from 30 to 480 mg/day. All subjects received Apalutamide orally once daily, except those in the 300-, 390-, and 480-mg cohorts who received a twice-daily dosing regimen. There was 1 dose-limiting toxicity (DLT) observed at the 300-mg dose level (Grade 3 treatment-related abdominal pain).26 The event lasted 6 days and resolved with dose interruption and subsequent dose reduction to 240 mg (120 mg twice daily). Three additional subjects were treated at the 300-mg dose level with no reported DLTs. No seizures were reported at any dose level. The maximum tolerated dose (MTD) was not determined. The pharmacokinetics (PK) profile was determined to be linear and dose-proportional[15]. The dose of 240 mg was chosen as the dose for subsequent phase III studies.

Ninety-seven subjects are being evaluated in the Phase 2 portion (Cohort 1: non-metastatic [NM]-CRPC n=51; Cohort 2: mCRPC without previous ketoconazole, abiraterone acetate/prednisone, enzalutamide or chemotherapy [for mCRPC] n=25; and Cohort 3: mCRPC post abiraterone acetate/prednisone and no previous chemotherapy [for mCRPC] n=21). Treatment-related adverse events (AEs) in the Phase 2 portion that have been reported to date in >10% of the subjects across the 3 cohorts included fatigue, diarrhea, nausea, abdominal pain, hot flush, hypothyroidism, decreased blood thyroid stimulating hormone, dysgeusia, decreased appetite (including weight loss), and skin rashes. In the Phase 2 portion, no serious adverse events (SAEs) were assessed as treatment-related. The safety profile of Apalutamide is consistent with the preclinical pharmacology and toxicology, and is as expected for an AR antagonist.

Apalutamide demonstrated prostate-specific antigen (PSA) reductions of ≥50% at 12 weeks of 89% for Cohort 1, 88% for Cohort 2, and 22% for Cohort 3. Similar data were observed after 24 weeks for Cohorts 1 and 2. The time to PSA progression was 24 months (95% confidence interval [CI]: 16.3, NE [not estimable] for Cohort 1), 18 months (95% CI: 8.3, NE) for Cohort 2, and 3.7 months (95% CI: 2.8, 5.6) for Cohort 3. These data indicate that Apalutamide demonstrates efficacy and an acceptable safety profile in both NM-CRPC and mCRPC patients.

Study Apalutamide-003 was a Phase 3 study of Apalutamide compared with placebo for the treatment of subjects with high-risk (defined as a PSA doubling time ≤10 months) NM-CRPC. Among men with nonmetastatic castration-resistant prostate cancer, metastasis-free survival and time to symptomatic progression were significantly longer with apalutamide than with placebo. Study 56021927PCR3001 was a Phase 3 study of Apalutamide plus abiraterone acetate and prednisone compared with abiraterone acetate and prednisone for the treatment of subjects with chemotherapy-naïve mCRPC. No clinical results are available for this study.

For the most comprehensive nonclinical and clinical information as well as Reference Safety Information regarding Apalutamide, refer to the latest edition of the Investigator's Brochure and Addenda for Apalutamide.

1.3 Leuprolide Acetate

Leuprolide is an agonist of gonadotropin releasing hormone (GnRH). Acting as a potent inhibitor of gonadotropin secretion; continuous administration results in suppression of ovarian and testicular steroidogenesis due to decreased levels of LH and FSH with subsequent decrease in testosterone (male) and estrogen (female) levels. In males, testosterone levels are reduced to below castrate levels. Leuprolide may also have a direct inhibitory effect on the testes, and act by a different mechanism not directly related to reduction in serum testosterone.

1.3.1 Clinical Use of Leuprolide in Prostate Cancer

The objective of ADT (with any of the available GnRH agonists- in this case Leuprolide) is to lower the serum testosterone level at least to the same extent as that achieved with surgical orchiectomy. Historically, this has correlated with a level of 1.7 nmol/L (<50 ng/dL), although contemporary laboratory testing indicates that testosterone levels decline to 0.7 nmol/L (<20 ng/dL) after orchiectomy. The potential relationship between suppression of the serum testosterone and clinical outcome is illustrated by a secondary analysis of the JPR.7 trial in which 626 evaluable men were treated with continuous ADT for a rising PSA and followed for a median of eight years [Crook J, et al. NEJM 2012; 367(10):895, Klotz L, et al. JCO 2015; 33(10):1151] The risk of dying was lowest in those with the greatest suppression of serum testosterone in the first year. Compared with a first year minimum testosterone nadir <0.7 nmol/L, those with a nadir testosterone of 0.7 to 1.7 nmol/L had an increased risk of dying (hazard ratio [HR] 2.08, 95% CI 1.28-3.38), as did those a nadir >1.7 nmol/L (HR 2.93, 95% CI 0.77-4.70). Although timing to initiation of therapy remains controversial, ADT is the standard of care for men with advanced disease. ADT in combination with radiation therapy is commonly utilized in men undergoing RT as local definitive treatment for high-risk PCa. Similarly, ADT immediately after RP in men with positive lymph node disease is considered standard practice for most centers in the U.S.

1.4 Androgen Metabolism

The major sites of chemical modification on the steroid backbone for DHT synthesis are carbons 3, 5 and 17, which are modified in 3 enzymatic steps for the conversion of DHEA to DHT (Figure 1). DHEA is a 3β-hydroxy, Δ^5 steroid (double bond between carbons 5 and 6) and is enzymatically converted in CRPC tissues to Δ^4-androstenedione (AD) by 3βHSD. 3βHSD1 and 3βHSD2 are the two human isoenzymes that possess this enzymatic activity.[16,17] 3βHSD1 is thought to be the peripherally expressed isoenzyme and 3βHSD2 the isoenzyme in steroidogenic organs.[17] However, both are detected in CRPC.[6,18] We have previously shown that 3βHSD enzymatic activity is absolutely required for the synthesis of T and/or DHT, downstream AR nuclear translocation, expression of AR-responsive genes and CRPC growth.[19] It was generally thought that AD undergoes conversion to T, which is then converted to DHT by SRD5A.[20,21] However, we have recently shown that an alternative pathway is dominant, not only in cell line models but also in freshly collected tumors from patients with CRPC. In this pathway, SRD5A converts AD to 5α-androstanedione (5α-dione), which is then converted to DHT.[22] Furthermore, we have shown that only one of two SRD5A isoenzymes, SRD5A1, is specifically required in this pathway. We have also demonstrated that a pitfall of pharmacologically blocking SRD5A with dutasteride is that AD is instead

diverted to increased synthesis of T, compensating in part for depletion of the more potent DHT[22], **resulting in modest clinical activity of SRD5A inhibition against CRPC[23].**

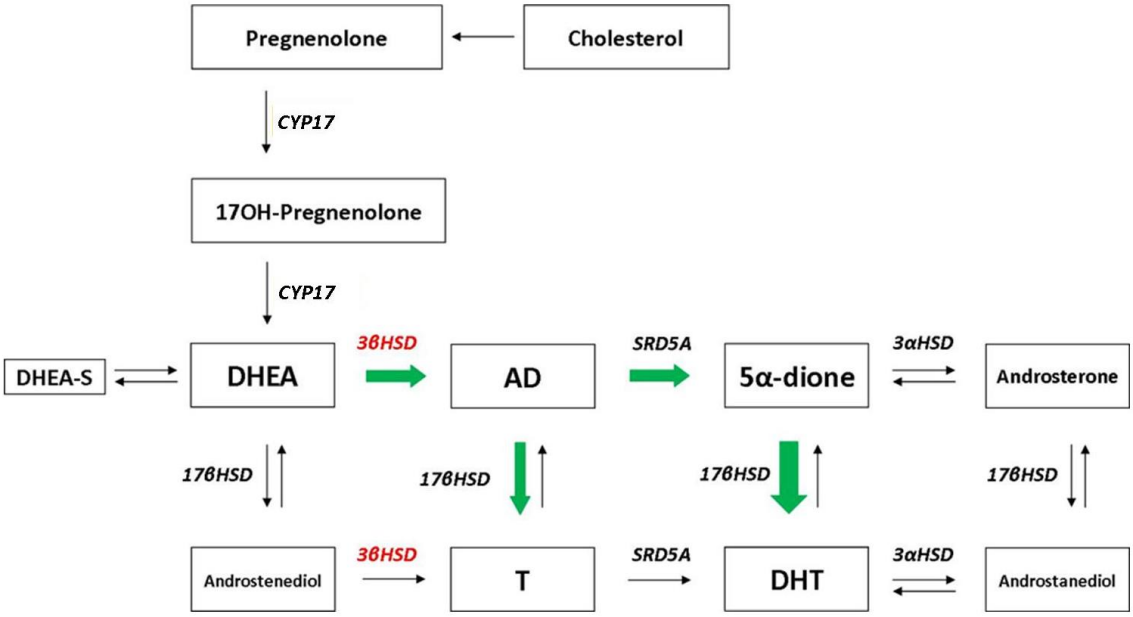


Figure 1. Synthesis of DHEA from cholesterol in the adrenal and metabolism of DHEA to intratumoral androgens in CRPC. Formation of testosterone and/or dihydrotestosterone from adrenal DHEA requires enzymatic modification of the 3-, 5-, and 17-postions of the steroid backbone by 3βHSD, SRD5A and 17βHSD isoenzymes. The dominant route of dihydrotestosterone synthesis is independent of testosterone (wide green arrows). Dihydrotestosterone is converted to the inactive metabolites androstanediol and androsterone by 3αHSD. De novo steroidogenesis through the "backdoor" pathway still requires 3β-hydroxyl-oxidation and Δ^5-isomerization of the cholesterol backbone by 3βHSD.

1.5 Preclinical Data

Recently, a gain of function single-nucleotide polymorphism (SNP) in *HSD3B1*(1245C; N367T) was identified that can also occur as a somatic mutation in CRPC tumors.[24] Germline SNP variant of *HSD3B1*(1245C, rs1047303) occurs with a reported allele frequency of 22% in general population, but appears to vary widely by ethnicity.[25] In a group of 118 prostate cancer patients at Cleveland Clinic, the frequency of the variant *HSD3B1*(1245C) allele is 36%.[26] 3β-hydroxysteroid dehydrogenase isoenzyme-1 (3βHSD1), encoded by *HSD3B1*, is one of the three enzymes involved in converting DHEA from the adrenal gland to DHT in prostate cancer tissue.[22] 3βHSD oxidizes 3β-hydroxyl to 3-keto and isomerizes Δ^5 to Δ^4 in the process of converting DHEA to AD. These reactions together make this step practically irreversible by an enzyme that is required for all possible pathways that lead to the synthesis of DHT. Chang et al have shown that CRPC sometimes expresses the 367T form of the *HSD3B1,* which increases metabolic flux from DHEA via the 5α-dione pathway to DHT by protein resistance to ubiquitination and degradation rather than increased catalytic activity. This mutation increases protein half-life from 2.1 to 27 hours which leads to a profound accumulation of 3βHSD1 with subsequent increased flux to DHT and ultimately increased AR activation and prostate cancer progression.[24] In addition, to study the possibility of *HSD3B1* (1245C) selection in human tumors, we sequenced matching germline and tumor DNA from 40 men with CRPC. Among these patients, the germline of 25, 11, and 4 individuals was homozygous wild type *HSD3B1* (1245A), heterozygous, and homozygous variant *HSD3B1* (1245C), respectively. Three of 25 (12%) CRPC tumors with homozygous *HSD3B1* (1245A) inheritance have acquired the *HSD3B1* (1245C) allele. Also, three of 11 (27%) CRPC tumors with heterozygous inheritance, have loss of heterozygosity (LOH) of the *HSD3B1* (1245A) allele, resulting in the *HSD3B1* (1245C) allele being predominantly detectable. In contrast, none of the 11 cases with heterozygous inheritance exhibited LOH of the *HSD3B1*(1245C) allele.[24] These data support the role of the *HSD3B1* (1245C) allele in the development of CRPC. Moreover, our review of the clinical outcomes in 118 men with prostate cancer who were treated with ADT for biochemical failure after prostatectomy shows that inheritance of *HSD3B1*(1245C) allele that enhances the DHT synthesis may predict resistance to ADT in prostate cancer.[26] In this group of patients allelic frequency of *HSD3B1* (1245C) was 36% with homozygous wild-type, heterozygous, and homozygous variant detected in 37%, 53%, and 10% of the patients. We demonstrated that median progression free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS) diminished as a function of the number of variant alleles inherited, showing a gene-dosage effect and stepwise decrements with 0 vs. 1 vs. 2 variant alleles in all three endpoints.[26]

1.6 Review of Relevant Prior Clinical Trials

Based on their mechanism of action and potential utility in early stages of PCa, the use of newer agents like abiraterone acetate (AA) and enzalutamide in the pre-operative phase has become an attractive therapeutic strategy. Therefore, these agents are used in multiple studies in combination with multiple other agents in the neoadjuvant setting to evaluate their potential role in this setting. The clinical activity and safety of AA/P in the neoadjuvant setting in men undergoing RP was evaluated in two separate phase II studies. The first study, a randomized phase II trial evaluated the impact of 12 weeks of AA/P + LHRH vs. LHRH alone in 50 high risk PCa patients (≥T1c GS ≥8, or ≥cT2b, GS≥ 7 and PSA >

10ng/ml).[27] The second trial evaluated 24 weeks of AA given in combination with LHRh in a similar group of patients (n=58).[28] Pathologic "tumor down-staging" and treatment effect on intra-prostatic levels of T, DHT and other markers of androgen biosynthesis were the main objectives of the studies. This clinical experience suggests that neo-adjuvant therapy with AA and LHRH is well tolerated and can lead to significant reduction of intra-tumoral androgen production that possibly results in tumor down-staging. The significance of this pathologic change remains unknown. Also, an ongoing multi-center randomized phase II trial is evaluating the neoadjuvant use of enzalutamide alone versus enzalutamide in combination with dutasteride and leuprolide in men with localized high-risk prostate cancer.[29]

1.7 **Study Rationale**

As homozygosity for *HSD3B1*(1245C) SNP can impact response and mediate resistance to ADT, evaluating the effect of such genotype variation on the level of steroid metabolites and the intratumoral DHT concentration in benign and tumor tissue of men receiving a short course of Apalutamide and leuprolide prior to undergo RP is of interest. We hypothesize that patients with homozygous *HSD3B1* (1245C) inheritance that leads to a gain of function in 3βHSD1, will have a sustained androgen synthesis from extragonadal precursor steroids and higher concentrations of DHT compared to wild-type *HSD3B1* (1245A) inheritance in the context of castration. Also, we expect intermediate levels of DHT in the heterozygous *HSD3B1* (1245C) group. We also hypothesize that Apalutamide will reverse the effects of elevated DHT on AR signaling in prostate tissue. For example, although DHT concentrations will be higher in the *HSD3B1* (1245C) groups, PSA expression will be equivalent among all groups. We anticipate that these studies will serve as the first step in identifying patients with prostate cancer who will benefit from upfront treatment with Apalutamide in addition to medical castration.

2 Objectives

2.1 Primary Objective

To evaluate the differential effect of neo-adjuvant leuprolide and Apalutamide on dihydrotestosterone (DHT) concentration in benign prostate tissue based on *HSD3B1* genotype.

2.2 Secondary Objectives

2.2.1 To evaluate the differential effect of neoadjuvant leuprolide and Apalutamide on other androgen (testosterone (T), dehydroepiandrosterone (DHEA), androstenediol, 5α-androstanedione (5α-dione), androstenedione (AD), androsterone and 5α-androstanediol) concentrations in benign and malignant prostate tissue based on *HSD3B1* genotype.

2.2.2 To compare the level of DHT, T, DHEA, androstenediol, 5α-dione, AD, androsterone and 5α-androstanediol between normal and malignant prostate tissue after neoadjuvant treatment with leuprolide and Apalutamide

2.2.3 To determine the safety of the combination of Leuprolide and Apalutamide administered prior to radical prostatectomy

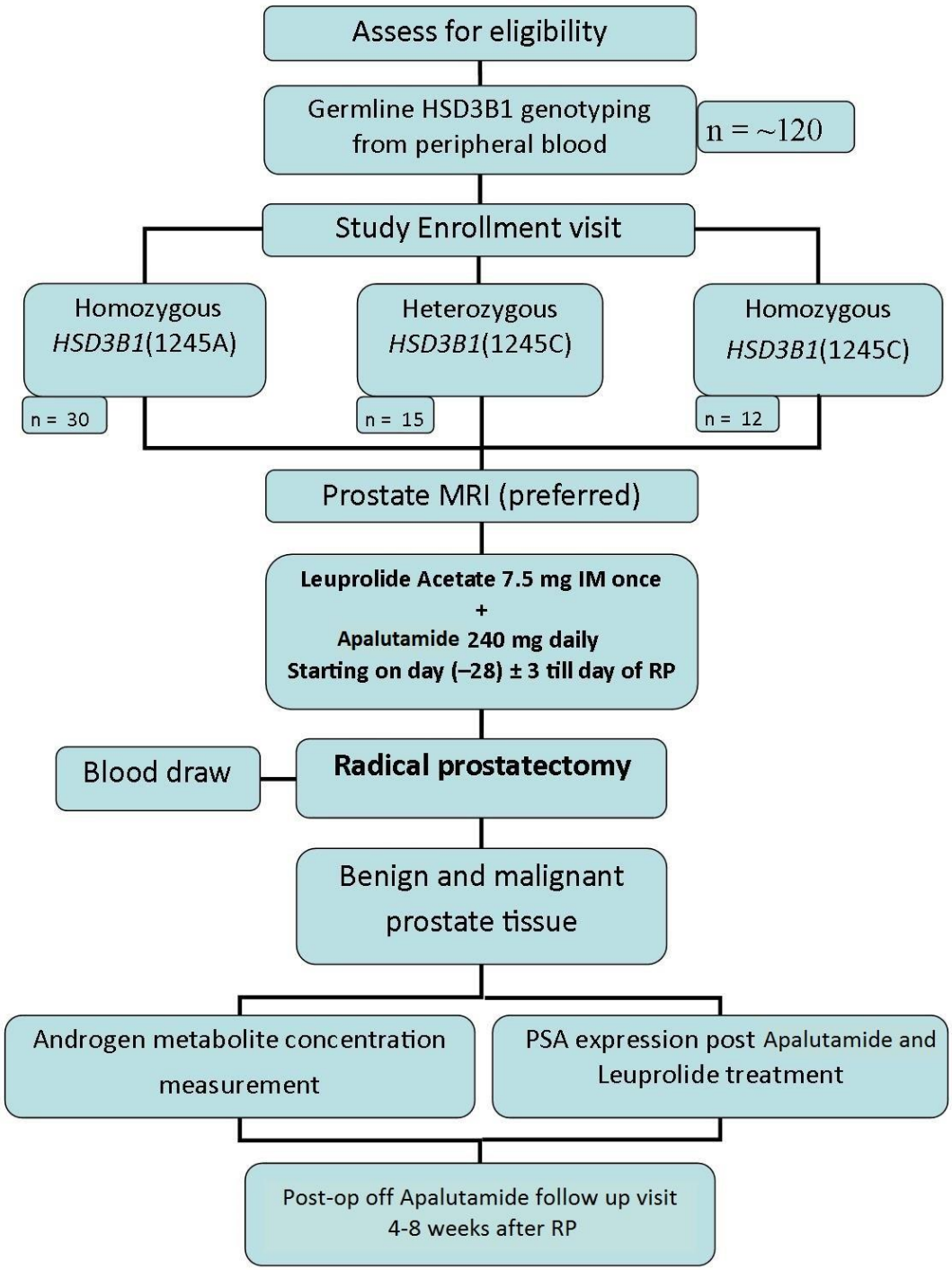
2.2.4 To evaluate PSA, FKBP5, TMPRSS2, EZH2, H3K27 and UBE2C tissue expression (via IHC and qPCR) in benign and malignant prostate tissue after treatment with Leuprolide and Apalutamide and Apalutamide.

3 Study design

3.1 Summary

The primary goal of the study is to evaluate the differential effect of neo-adjuvant Apalutamide and leuprolide on dihydrotestosterone (DHT) concentration in benign prostate tissue based on *HSD3B1* genotype. Newly diagnosed, biopsy-proven, intermediate or high-risk prostate cancer patients (G 4+3 or higher, ≥T2b, PSA ≥ 10), who are candidates for radical prostatectomy (RP) are eligible to participate in this study. In order to have enough tumor tissue to perform all of the tests, a minimum tissue requirement of ≥1 positive core biopsy. All participating patients will receive a single dose of leuprolide 7.5 mg IM in addition to Apalutamide 240 mg orally daily for four weeks prior to RP. Treatment will be started on day (-28) ± 3 from the scheduled RP date to minimize the variability of treatment duration. Apalutamide will be continued up to and including the day before radical prostatectomy. Although pre-treatment MRIs of the prostate will be ideal, this protocol does not mandate these imaging studies for study enrollment. Of note, the vast majority of patients undergoing RP at our institutions undergo MRI of prostate for further staging purposes. Thus, the vast majority of our patients will have this completed. Blood will be drawn at baseline and on the day of surgery to evaluate serum PSA and androgen metabolite levels. After RP, fresh tissue from the surgical specimen will be sampled by the GU pathologist (multiple punch biopsies to increase the chance of capturing benign and tumor tissue) with the same methodology that we have previously described.[31] All steroids will be extracted from prostate tissue (20 mg), derivatized by the Girard-T oxime methodology to increase sensitivity, and quantitated by mass spectrometry, as previously described.[32] Expression of PSA transcript and protein will be assessed as we have performed routinely and described previously.[22,24] Levels of DHT, T, DHEA, androstenediol, 5α-dione, AD, androsterone, and 5α-androstanediol will be measured in all specimens. The underlying hypothesis is that under a recessive model, homozygous *HSD3B1* (1245C) is stabilizing and leads to a gain of function in 3βHSD1 that ultimately results in sustained androgen synthesis compared to wild-type *HSD3B1* (1245A), after treatment with leuprolide. We expect to have intermediate levels of these metabolites in the heterozygous *HSD3B1* (1245C) group.

3.2 Study Schema



4 Study Population

4.1 Inclusion criteria

4.1.1 Male ≥ 18 years of age

4.1.2 Adenocarcinoma of the prostate with histological or cytological confirmation without neuroendocrine differentiation or small cell histology and with any one of the following: G 4+3 or higher or PSA ≥ 10 or ≥T2b, for whom radical prostatectomy has been recommended and who choose to undergo radical prostatectomy.

4.1.3 A minimum tissue requirement of ≥1 core biopsy with tumor involvement.

4.1.4 Have an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

4.1.5 Hemoglobin of ≥ 10 g/dL, independent of transfusion and/or growth factors within 3 months prior to randomization

4.1.6 Platelet count of ≥ 100k/mL independent of transfusion and/or growth factors within 3 months prior to randomization

4.1.7 Serum albumin ≥3.0 g/dL

4.1.8 Serum creatinine < 2.0 times the upper limit of normal (ULN) {or a calculated creatinine clearance ≥ 60 mL/min}

4.1.9 Serum potassium ≥3.5 mmol/L

4.1.10 Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 x ULN

4.1.11 Total serum bilirubin levels < 1.5 x ULN (Note: 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)

4.1.12 Be capable of swallowing study agents whole as a tablet

4.1.13 Be willing/able to adhere to the prohibitions and restrictions specified in this protocol

4.1.14 Have signed an informed consent document indicating that the subject understands the purpose of and procedures required for the study and are willing to participate in the study.

4.1.15 Medications known to lower the seizure threshold (see list under prohibited meds) must be discontinued or substituted at least 4 weeks prior to study entry.

4.1.16 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 following the last dose of study drug.

4.2 **Exclusion criteria**

Potential subjects who meet any of the following criteria will be excluded from participating in the study.

4.2.1 The use of any prior hormones including LHRH agonists, LHRH antagonists, antiandrogens such as bicalutamide, flutamide and nilutamide, and/or the use of 5-alpha reductase inhibitors, PC-SPES (or PC-x product), Megestrol Acetate, or estrogen containing nutriceuticals within 6 months of study treatment initiation.

4.2.2 Prior radiation therapy, immunotherapy, chemotherapy or other investigational therapy given for prostate cancer.

4.2.3 "Currently active" second malignancy other than non-melanoma skin cancers or non-muscle invasive transitional cell carcinoma of bladder. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are now considered (by their physician) to be at less than 30% risk for relapse.

4.2.4 History of seizure or condition that may pre-dispose to seizure (including but not limited to prior stroke, transient ischemic attack, loss of consciousness within 1 year prior to randomization, brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect)

4.2.5 Have received treatment with any form of therapy with CYP17 inhibitory activity such as ketoconazole, aminoglutethemide, or an antiandrogen such as bicalutamide within 6 months of study treatment initiation.

4.2.6 Systemic corticosteroids within 6 months of enrollment

4.2.7 Active infection (eg, human immunodeficiency virus [HIV] or viral hepatitis)

4.2.8 Have uncontrolled hypertension; subjects with a history of hypertension are permitted in the study provided their blood pressure is controlled by anti-hypertensive therapy, at the discretion of the treating physician.

4.2.9 Have a known history of pituitary or adrenal dysfunction

4.2.10 Have clinically significant heart disease as evidenced by severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic

events (e.g., pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias within 6 months prior to randomization

4.2.11 Have a history of gastric bypass surgery or severe malabsorption that may interfere with the absorption of the study agents

4.2.12 Be taking or require the use of prohibited medications as listed in Section 6.3.2.1

4.2.13 Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements

4.3 Inclusion of Minorities

Men of all races and ethnic groups, English or non-English-speaking are eligible for this trial.

5 Registration

5.1 General Guidelines

All subjects who have been consented are to be registered in the OnCore Database. Eligible patients will be entered on study centrally at the Cleveland Clinic Taussig Cancer Institute by the Study Coordinator. Following registration, patients should begin protocol treatment on day (-28) ± 3 days which is set based on the scheduled surgery date. If a patient does not receive protocol therapy as scheduled following registration, the patient's registration on the study may be canceled. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded. The Study Coordinator should be notified of cancellations as soon as possible.

A subject who either prematurely discontinues from the study before completing 28 days of the treatment, prior to surgery, or for whom we are unable to obtain a tissue sample from, may be replaced at the discretion of the PI.

5.2 **Pre-treatment Evaluation**

Clinical: required on Cycle 1 Day (-28) or within 28 days before the treatment initiation

5.2.1 History and physical examination, including height, weight, and vital signs

5.2.2 Performance status evaluation

5.2.3 Laboratory /Diagnostic: required within 28 days before the treatment initiation.

5.2.3.1 CBC, platelet count and differential

5.2.3.2 Serum chemistries: includes BUN, Creatinine, ALT, and AST, glucose, alkaline phosphatase, total bilirubin, TSH and LDH. If TSH is abnormal a T3 and T4 level will be required.

5.2.3.3 Testosterone, DHEA, DHEA-S, and AD, Direct Renin and Aldosterone/Direct Renin Ratio serum level

5.2.3.4 PSA

5.2.3.5 Study blood draw for the measurement of serum steroids concentration

5.2.3.6 Imaging/Diagnostic: will be performed at the discretion of the treating physician. Obtaining prostate MRI is preferred but not mandatory for the study enrollment.

5.3 **Registration process**

To register a patient, the following documents should be completed by the research nurse and e-mailed to the Study Coordinator:

- Registration Form
- Eligibility Worksheet
- Copy of source documentation (required laboratory tests, radiographic scans (if applicable), physician notes, nursing notes, list of medications, pathology/surgical reports, etc.)

Signed patient consent form to complete the registration process, the Coordinator will

- Verify patient eligibility worksheet is complete
- Request additional documentation if necessary
- Assign a patient study number
- Register the patient on the study using the ONCORE database

6 E-mail a letter of Confirmation of Registration, including the patient study number, to the responsible research nurse treatment plan.

6.1 Packaging, Storage, and Labeling

Apalutamide will be supplied as 60mg tablets packaged in 30-ct, 120 cc HDPE bottles with child-resistant closures and tamper proof heat induction seals. At the clinical and at the patient's home, the study drug should be stored at room temperature and protected from head; do not freeze. Each bottle of study drug will be labeled with the required regulatory agency warning statement, the protocol number, and directions for patient use and storage. The Investigator will ensure that the study drug is stored in appropriate conditions in a secure location with controlled access.

6.2 **Dosage and Administration**

6.2.1 Description of Study agents and Administration

Study agents include Apalutamide and leuprolide. Apalutamide will be provided by the study. Subjects are to receive the following:

- Leuprolide 7.5 mg IM x 1 dose on day (-28) ± 3 days
- Apalutamide 240 mg (4 x 60 mg tablets) by mouth [PO] on a continuous once-daily dosing regimen.

Sufficient study medication for an entire treatment course till the day of surgery will be distributed on the first day of treatment. Apalutamide will be self-administered on an outpatient basis during the study, once daily, with or without food. Treatment will start on Day (-28) ± 3 days from the scheduled date for radical prostatectomy. Subjects may take Apalutamide up to and including the day before radical prostatectomy, at which time the medication will be discontinued.

It is anticipated that individual patients may occasionally forget to take a dose. In those cases, missed doses should only be replaced if the patient remembers within a 12-hour window. After that, patients should just take the next dose the following day, without compensating for the missed dose.

6.3 General Concomitant Medication and Supportive Guidelines

6.3.1 Pre-study therapy

To be eligible for this study, subjects must have a new diagnosis of prostate cancer with no history of previous treatments for prostate cancer.

6.3.2 Concomitant therapy

All patients should be maintained on the same medications throughout the entire study period, as medically feasible, with minimum introduction of new chronic therapies. Standard medical treatment as applicable is allowed except for treatments noted in the exclusion criteria and/or listed in the prohibited medications section below.

6.3.2.1 Prohibited medications and treatments

As a class effect, androgen receptor antagonists have been associated with seizures due to an off-target mechanism of action (GABAA inhibition).[33,34]

To date, no patients receiving Apalutamide have experienced seizures, however, in preclinical experiments, at very high doses, dogs treated with Apalutamide had tremors and generalized seizures. Patients will be closely monitored for seizures, but as a precautionary measure, drugs known to decrease the seizure threshold and/or cause seizure will be prohibited while on study. A list of the medications which are PROHIBITED while on study:

- Aminophylline/theophylline
- Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperidine and pethidine
- Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
- Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
- Herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (e.g. saw palmetto). All herbal supplements must be discussed with the study provider and discontinued at the provider's discretion.
- Current systemic steroid or corticosteroid therapy (inhaled or topical steroids are also not allowed), unless waived at the provider's discretion.

[Please see the appendix IV for a more comprehensive list (with brand names)]

6.3.2.2 Restricted Concomitant Medications

- Apalutamide is metabolized primarily by human CYP3A4, thus co-administration with strong inhibitors or inducers of CYP3A4 should be avoided as much as possible. Apalutamide may also induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have a narrow therapeutic index. 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

- 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 Coumadin, re-assess PT/INR as clinically indicated and adjust the dose of Coumadin accordingly.
- Corticosteroids: due to possible resistance mechanisms which may be contributed by glucocorticoid receptor signaling, concurrent use of corticosteroids during the study is not recommended.
- Avoid grapefruit and pomegranate juice and/or fruits

6.3.3 Life style guidelines

Patients of childbearing potential must agree to practice some form of effective contraception, such as vasectomy, double barrier contraception, or sexual abstinence prior to entering into the study and for 6 months following the last dose of study drug.

There are no dietary restrictions with the exception of grapefruit and pomegranate fruits and/or juice while the patient is on study. Study treatment can be taken with or without food.

6.4 Duration of Therapy

All patients will be treated with one dose of leuprolide given IM on day (-28) ± 3 days followed by Apalutamide starting on day (-28) ± 3 days from the date of RP. The treatment will start on Day (-28) ± 3 days which is set based on the scheduled date of RP and will be continued till the day of surgery.

6.5 Measures of Treatment Compliance

All patients will complete a daily diary documenting the intake of Apalutamide

At post-op follow up visit, patients will be asked to return any remaining study drug as well as all used and unused study drug containers.

Treatment compliance will be defined as the number of tablets taken divided by the expected number of tablets and reported as percentage. In case of dose reductions, the expected number of tablets should reflect the new dose level.

Tablets that are not returned will be considered to have been taken, unless otherwise specified in the case report form (CRF).

6.6 Duration of Follow up

All patients will be evaluated within 4-8 weeks after RP to rule out any potential AEs after discontinuation of the treatment. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached. If patient has no AEs with regards to study agents this will be the last study related follow up.

7 Dose Delays/ Dose Modifications

7.1 Safety Monitoring

Thyroid stimulating hormone (TSH) should be evaluated throughout the study (with T3 and T4 done only if TSH is abnormal) as follows:

- Cycle 1, Day (-28) or within 28 days before treatment initiation
- Pre-Op Evaluation
- Follow Up Visit

7.2 Apalutamide Dose Modifications in the Event of Toxicity

Dose interruptions and/or reductions for each patient will be permitted provided that study discontinuation criteria have not been met (please see Section 9.16 End of Treatment).

- Patients experiencing Grade 3 treatment-related adverse events will have study drug held until the severity of the toxicity decreases to Grade 1 or returns to baseline. If improvement occurs within 7 days, dosing may be restarted at the next level dose reduction. Exception to hold includes clinically insignificant lab abnormalities and hypertension, as deemed by the treating physician. Events that can be mitigated with optimal treatment within 2 days of the occurrence do not require a dose reduction; dose may resume at previous level.
- Any patient experiencing a drug related Grade 4 toxicity of any duration will be permanently discontinued.
- Patients experiencing treatment-related seizure of any grade or grade (G) 4 neurotoxicity will have study drug permanently discontinued.
- At any given dose level, if patients experience gastrointestinal (GI) discomfort due to the number of tablets, they will be allowed to switch to a BID regimen as needed.
- A maximum of one dose level reduction will be allowed.
  Any patient requiring Apalutamide treatment interruption longer than 7 days during the treatment period will meet the criteria for end of study treatment and study discontinuation.

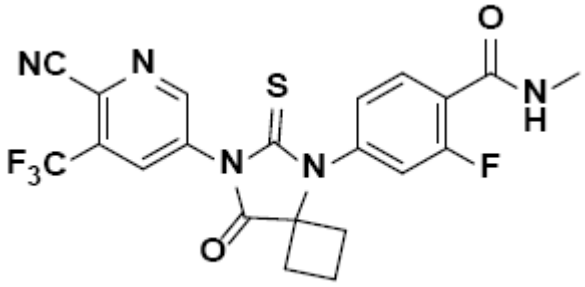
Table 1. Apalutamide Dose Levels

Toxicity	Dose of Apalutamide (assuming 240 mg/day dosing)
Grade 1 or 2	No change
≥Grade 3 or higher	Hold until Grade 1 or baseline, resume at full dose
First Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)
First occurrence of seizure of any grade or Grade 4 neurotoxicity	Discontinue
More than 7 days off treatment due to treatment related toxicity	Discontinue

8 Pharmaceutical Information

8.1 Apalutamide

Molecular Formula and Chemical Class
Apalutamide drug substance is a white to off-white crystalline solid.
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)
Chemical structure:



Molecular Formula: C21H15F4N5O2S Molecular Weight: 477.44

Physical Description of Study Drug(s)
The Case 5815 tablet supplied for this study contains 60 mg of Apalutamide. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Packaging
Apalutamide tablets (60-mg) will be packaged in 120-count, 160 cc high-density polyethylene (HDPE) bottles with child-resistant closures.

Labeling
Study drug labels will contain information to meet the applicable regulatory requirements.

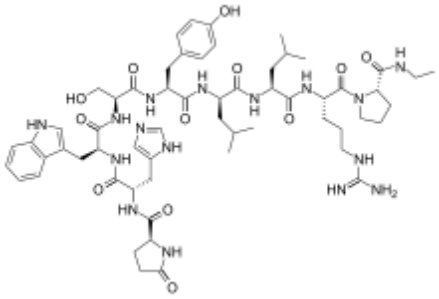
Preparation, Handling, and Storage
The study drugs must be stored in a secure area and administered only to subjects enrolled in the clinical study in accordance with the conditions specified in this protocol. Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

Drug Accountability
The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers. Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

8.2 **Leuprolide**

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula



Leuprolide acts as an agonist at pituitary GnRH receptors. By interrupting the normal pulsatile stimulation of, and thus desensitizing, the GnRH receptors, it indirectly downregulates the secretion of gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to hypogonadism and thus a dramatic reduction in estradiol and testosterone levels in both sexes.

LUPRON INJECTION is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 mL multiple-dose vial containing leuprolide acetate (5 mg/mL), sodium chloride, USP (6.3 mg/mL) for tonicity adjustment, benzyl alcohol, NF as a preservative (9 mg/mL), and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF.

As Lupron is a standard treatment for the management of prostate cancer. All patients will receive this agent according to institutional guidelines.

Pharmacodynamics and Pharmacokinetics

Onset of action: Following transient increase, testosterone suppression occurs in ~2-4 weeks of continued therapy.
Distribution: Males: Vd: 27 L
Protein binding: 43% to 49%
Metabolism: Major metabolite, pentapeptide (M-1)
Bioavailability: SubQ: 94%
Excretion: Urine (<5% as parent and major metabolite)

9 Adverse Events and Potential Risks

9.1 Management of Safety Data

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

For the purposes of this study, the Janssen medicinal product is Apalutamide.

9.2 Definitions

9.2.1 Adverse Event (AE)

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

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

Surgical AEs such as urinary incontinence, erectile dysfunction and wound complications will be assessed per institutional guidelines. These will not be captured as part of treatment related AEs.

9.2.2 Adverse Events of Special Interest

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

There are no adverse events of special interest identified for apalutamide.

9.2.3 Identified Individual Case Safety Report (ICSR)

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

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

The minimum information required is:

- Suspected Janssen medicinal product (doses, indication)
- Date of therapy (start and end date, if available)
- Batch or lot number, if available
- Subject details (subject ID and country)
- Gender
- Age at AE onset
- Reporter ID
- Adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

9.2.4 Product Quality Complaint (PQC)

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

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/tablets
- Suspected Contamination
- Suspected Counterfeit

9.2.5 Serious Adverse Event (SAE)

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

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It

does not refer to an adverse event which hypothetically might have caused death if it were more severe.

- Requires **inpatient hospitalization or prolongation of existing hospitalization for AEs related to study drug and not for the scheduled radical prostatectomy**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.
    - However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT WITHIN 30-DAYS OF THE LAST DOSE OF APALUTAMIDE AS STATED IN SECTION 9.2.5.2.

SAE reports and any other relevant safety information are to be emailed to Dr. Garcia at garciaj4@ccf.org and to the Cleveland Clinic SAE inbox at cancersaeinbox@ccf.org.

SAE reports and any other relevant safety information are also to be sent to the COMPANY (Janssen Research & Development, LLC) within 24 hours via secure email at IIS-BIO-VIRO-GCO@its.jnj.com as described in sections 9.7.1 and 9.9.

9.2.5.1 **Hospitalization**

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

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

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

9.2.5.2 **Life-Threatening Conditions**

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

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.

9.3 **Unlisted (Unexpected) Adverse Event/Reference Safety Information**

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

For Apalutamide, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

For Apalutamide, the link to the package insert is:

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

9.4 **Special Reporting Situations**

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

- Drug exposure during pregnancy (maternal and paternal)

- Overdose of a Janssen medicinal product
  Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- 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

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

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

9.5 Pregnancy

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

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

9.6 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The INSTITUTION and PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs' request.

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

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

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

9.7.1 SAEs and Special Reporting Situations

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

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

- The INSTITUTION and the PRINCIPAL INVESTIGATOR will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by the COMPANY **within 24-hours of becoming aware of the event(s).**

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

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

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

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

9.7.2 Non-Serious AEs

All non-serious adverse events should be reported to COMPANY according to the timeframe

outlined in the Research Funding Agreement section entitled Reporting of Data.
SAE Report Form SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

9.7.3 PQC Reporting

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

All initial PQCs involving a Janssen medicinal product under study must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR within 24 hours after being made aware of the 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 PRINCIPAL INVESTIGATOR must report the PQC to the COMPANY according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the COMPANY.

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

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

9.9 Transmission Methods

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

- Electronically via Janssen SECURE Email service at IIS-BIO-VIRO-GCO@its.jnj.com (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax) to 1-866-451-0371, receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

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

9.10 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur after taking the first dose of Apalutamide through 30 days after the final dose of study drug. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness (es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

9.11 Institutional Review Board Reporting Requirements:

Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

9.12 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into OnCore

9.13 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to Janssen Scientific Affairs, LLC and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

9.14 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.15 Criteria for Defining the Severity of an Adverse Event

9.15.1 Severity of adverse events will be graded according to the Cancer Therapy and Evaluation Program (CTCAE) Common Terminology Criteria for Adverse Events v. 4.0 available at http://ctep.cancer.gov. For terms not specified within NCI-CTCAE, the following guideline should be used to determine grade:

Table 2. Criteria for Severity of Adverse Event Terms Not Specified Within NCICTCAE

Toxicity Grade	Description

Grade 1	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

9.16 End of Treatment

A patient may be discontinued from study treatment at any time if the patient, the Investigator and his (her) team, feels that it is not in the patient's best interest to continue on study. The following is a list of possible reasons for early discontinuation of study treatment:

- Disease progression
- Any episode of seizure
- Any other adverse event that cannot be adequately managed with dose modifications, including dose interruption for up to 7 days
- Protocol violation requiring discontinuation of study treatment
- Patient is not compliant with study procedures
- Lost to follow-up
- Patient withdrawal of consent
- Sponsor request for early termination of study

Patients will be followed for at least 28 +/-7 calendar days after the last dose of study drug. If a patient is withdrawn from treatment due to an adverse event, the patient will be followed until the adverse event has resolved or stabilized as per Section 7.6.

9.16.1 Data to be collected for the end of treatment visit:

- Record any adverse events (optional if performed within 1 week)
- Record changes to concomitant medications (optional if performed within 1 week)
- Assess study drug compliance
- Perform abbreviated physical examination (optional if performed within 1 week)

- Perform and record vital signs and ECOG performance status (optional if performed within 1 week)
- Collect blood and urine for clinical laboratory assessments (optional if performed within 1 week)

9.16.2 Safety Follow-Up (4-8 weeks following the Last Dose of Study Drug)

- Record any adverse events
- Record changes to concomitant medications

10 Tissue Studies

10.1 Tissue Procurement

Radical prostatectomy tissue will be processed in a standardized fashion according to institutional protocols established by the Specimen Core. Immediately after removal, prostatectomy specimens will be transferred into sterile ice-cold slurry of normal saline. Specimens will be accessioned and assigned a research number by the Tumor Procurement Service and tissue for study will be harvested according to standard protocols established and described in the Specimen Core and processed for pathological analysis as per established standards. Once harvested, the tissue to be used for this study will be snap frozen in liquid nitrogen and stored at -80 degrees until required for the planned analysis. All study related tissue (after official pathology review) will be stored within the GU core pathology department following standard institutional procedures and policies. Access to study tissue will be granted to appropriate personnel listed in the study protocol.

10.2 *HSD3B1* genotyping

10.2.1 *HSD3B1* Genotyping By Sequencing

Genomic DNA will be prepared from peripheral blood using DNeasy Blood and Tissue Kit (QIAGEN, Germantown, MD). *HSD3B1* genotyping will be determined through a melting curve analysis on an ABI 7500 Real Time PCR System (Applied Biosystem, Carlsbad, CA). To determine genotype of *HSD3B1*, primer set (Forward: 5'-GTCAAATAGCGTATTCACCTTCTCTTAT-3' and Reverse 5'-GAGGGTGGAGCTTGATGACATCT-3') and probe (GGAGA+ACCTGAAGTCCAAGACTCAGTGATTAAGG) will be used. The assay will consist of an initial denaturing set at 95°C for 2m, followed by amplification for 60 cycles of 95°C for 30s, 66°C for 30s and 75°C for 30s. A melting curve will follow amplification (95°C for 30s, 25°C for 60s, 50°C for 15s and final ramp rate (0.3%-1%) to 95°C for 15s. Each reaction will be done with 40 ng DNA, 50nM forward primer, 500nM reverse primer, and Light scanner HRM LC green Master Mix (Biofire Diagnostics, Salt Lake City, Utah).

10.2.2 *HSD3B1* Genotyping by Melting Curve Assay

Genomic DNA will be prepared from peripheral blood using DNeasy Blood and Tissue Kit (QIAGEN, Germantown, MD). PCR products of the promoter region, all exons, exon-intron junctions and the

30-UTR will be sequenced to identify mutations in *HSD3B1*. To sequence the 30 flanking region of *HSD3B1*, primer set (Forward: 50-ATGTGGAGGGAGGTGTGAGT-30 and Reverse: 50-ACGGAGATGGGTCTCTTCCA-30) will be used with an annealing temperature of 62_C. Genotyping PCR reaction (50 ml) will be done with 30-100 ng genomic DNA, 1 x PCR buffer with 0.2 mM dNTP, 0.2 mM of each primer, and 0.5 ml Phusion High-Fidelity DNA Polymerase (New England BioLabs Inc, Ipswich, MA). 1 mL purple top tube will be used for genotyping purposes at indicated time points.

10.3 Immunohistochemical Staining Of Cellular And Molecular Markers In Prostate Tumor Tissue

IHC for PSA will be performed as routinely done by Dr. Cristina Magi-Galluzzi in the pathology department at the Cleveland Clinic.

10.4 Steroid Extraction and Measurements

Prostate tissue (20mg) will be homogenized using a Minilyse bead homogenizer (Bergin Corp, Rockville, MD). Steroids and internal standard will be extracted using methyl tart Butyl-ether (Sigma-Aldrich, St. Louis, MO). Steroids will be derivative using a Girard T reagent (Sigma-Aldrich, St. Louis, MO) as previously described (22). Steroid concentrations will be assessed through stable isotope ratios and quantitated using developed methodology on a liquid chromatography mass spectrometer. 1 10mL red top tube will be used for serum steroid studies at indicated time points.

10.5 mRNA Expression

Prostate tissue (<20 mg) will be homogenized and RNA will be extracted using a Gene lute Mammalian Total RNA Miniprep Kit (Sigma Aldrich, St. Louis, MO). Extracted RNA will be synthesized into cDNA using an iScript cDNA Synthesis Kit (Bio-Rad, Hercules, CA). Expression for PSA, TMPRSS2, FKBP5, EZH2, H3K27, and UBE2C will be assessed by quantitative real time PCR on an ABI 7500 Real Time PCR System (Applied Biosystem, Carlsbad, CA). Each reaction (20µL) will consist of 100-500 ng of synthesized cDNA, 500 nM each forward and reverse primer set, and 10 µL of iTaq Universal SYBR Green Supermix (Bio-Rad, Hercules, CA). The qPCR protocol consists of an initial denaturation at 95̊C for 2m followed by 40 cycles of 95̊C for 3s and 60̊C for 35s, with a final hold at 4̊C. AR-Responsive gene expression will be normalized to housekeeping gene *RPLPO.* The rationale behind these exploratory analyses derives from existing data demonstrating that alterations of the androgen-regulated TMPRSS2 and ETS transcription factor genes in prostate cancer tissue leads to worse outcome. Similarly, FKBP5, EZH2, H3K27, and UBE2C are considered potential prognostic putative cancer stem cell markers that have been associated with tumor aggressiveness and might be altered by the use of Apalutamide and leuprolide therapy

11 Study Calendar

Table 2. Study Calendar

	Eligibility screening	Cycle 1, Day (-28)[g]	Pre-op evaluation (1 to 3 days before surgery)		off Apalutamide follow-up visit in 4 -8 weeks after RP[h]
Leuprolide IM injection + Apalutamide distribution		X[a]			
Tissue Core Biopsy from Initial Diagnosis		X			
MRI Prostate [b]					
Informed consent		X			
Demographics		X			
Medical History		X	X		X
Prior and concomitant medication review [c]		X	X		X
Vital Signs		X	X		X
Height/Weight/BSA		X	X		X
Physical Exam		X	X		X
Performance Status		X	X		X
CBC/diff, platelets		X	X[J]		X
Serum chemistries[d]		X	X[J]		X
TSH[L]		X	X		X
PT/PTT		X	X[J]		
Genotyping Analysis	X[e]				
Evaluation of AE's		X	X		X
PSA		X	X[I]		
Testosterone, DHEA, DHEA-S, Androstenedione, Direct Renin and Aldosterone/Direct Renin Ratio		X	X[I]		
Blood for Correlative Studies[f]	X			X	

Prostatectomy (Day of surgery)[K]

a: Study agents include Apalutamide. Patients will receive these medications for the entire treatment course at Day (-28) ± 3 days up to and including the day before prostatectomy (day of surgery).

b: MRI of the prostate will be completed at the discretion of the treating Physician. Although this imaging technique is routinely done at the Cleveland clinic prior to patients undergoing RP, it will desired but not be mandatory for study entry.

c: Refer to Section 7.3 for further details on reporting prior and concomitant medications.

d: Sodium, potassium, chloride, CO2, BUN, Creatinine, Glucose, LFT's (AST/ALT/Alkaline Phosphatase, Albumin, LDH, total bilirubin), and Calcium. Testosterone, PSA, DHEA, DHEA-S and

AD levels will be measured within 28 days of treatment initiation and at the end of C1 of therapy as above.

e: Blood will be drawn for *HSD3B1* genotyping for the research laboratory.

f: Blood draw for steroid concentration in the serum and to understand how tumors use and make hormones. This sample will be sent to Dr Sharifi's lab.

g: Laboratory tests and procedures must be completed on Cycle 1 Day (-28) or within 28 days prior to the start of study agents Leuprolide IM injection and Apalutamide distribution.

h: Post-operative follow up visit will ideally occur between 4 and 8 weeks after surgery. Time line may vary in order to coordinate with Urology follow up visit.

I: Allowable window for lab collection is 1-3 days prior to, or on, the day of prostatectomy.

J: Allowable window for lab collection is 1-7 days prior to prostatectomy.

K: Must be completed within 28 days ±3 from the start of Leuprolide IM injection and Apalutamide distribution.

L: Thyroid stimulating hormone (TSH) should be evaluated throughout the study (with T3 and T4 done only if TSH is abnormal) as follows: On Cycle 1 or within 28 days before treatment initiation, at the end of Cycle 1 (approximately day 28 Pre-op evaluation), and 4-8 weeks after RP (Follow Up evaluation).

12 Measurement of Effect

12.1 Benign and malignant tissue concentration of DHT and other androgen (testosterone (T), dehydroepiandrosterone (DHEA), androstenediol, 5α-androstanedione (5α-dione), androstenedione (AD), androsterone and 5α-androstanediol), Direct renin and Aldosterone/Direct Renin Ratio will be measured by IHC as stated in section 10 of the protocol.

12.2 PSA, FKBP5, TMPRSS2, EZH2, H3K27, and UBE2C expression in benign and malignant prostate tissue after neoadjuvant leuprolide and Apalutamide will be also analyzed by IHC and qPCR as noted in section 10 of the protocol.

12.3 Toxicity will be evaluated using standard CTC guidelines as per section 9 of the protocol. All patients enrolled on study will be evaluable for toxicity from the time of their first treatment with leuprolide and Apalutamide. Surgical safety data will be captured following standardized surgical templates routinely used in the GU clinic.

12.4 Although clinical endpoints are not the aim of this biologic study, results of the surgical pathology and PSA changes pre-treatment, during treatment and after surgery will be collected.

13 Records to Be Kept/ Regulatory Considerations

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 9. Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The Forte EDC™ and OnCore™ databases will be utilized, as required by the Case Comprehensive Cancer Center and Cleveland Clinic, to provide data collection for both accrual entry and trial data management. Forte EDC and OnCore™ are Clinical Trials Management Systems housed on secure servers. Access to data through Forte EDC and OnCore™ is restricted by user accounts and assigned roles. Once logged into the Forte EDC or OnCore™ system with a user ID and password, Forte EDC™ and OnCore™ define roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu for OnCore™ access, and taussigoncore@ccf.org for Forte EDC™ access.

Forte EDC™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. When properly utilized, Forte EDC™ is 21 CFR 11 compliant. This study will utilize electronic Case Report Form completion in the Forte EDC™ database. A calendar of events and required forms are available in Forte EDC™.

13.2 **Regulatory Considerations**

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.
The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

13.2.2 Subject data protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, case report forms, source documents, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations and the institution in which the study will be conducted, or for the period specified by the sponsor, whichever is longer. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the Cleveland Clinic's clinical trials office, a regulatory authority, an Independent Ethics Committee (IEC), a designee from the Cleveland Clinic's Institutional Review Board (IRB), or a Janssen Scientific Affairs, LLC representative may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

13.2.5 Data safety and monitoring plans

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

13.2.6 Patient's financial responsibilities during the study

13.2.6.1 There will be no cost for the Apalutamide or any of the correlative histologic and/or molecular studies. Leuprolide is considered standard of care in men with prostate cancer thus it will be billed to patient's insurance.

13.2.6.2 Charges incurred to pre-surgical evaluation, such as monitoring complete blood counts, comprehensive metabolic panel, and other necessary tests per surgical protocols will be charged to the patient's insurance company in standard fashion.

13.2.6.3 Charges incurred to monitor the safety and efficacy of this treatment, such as monitoring complete blood counts, comprehensive metabolic panel, baseline testosterone level and PSA, which are not indicated per patient's standard treatment plan, will be paid by the study grant.

14 Biostatistical Considerations

All subjects will be receiving Apalutamide starting day (-28) ± 3 days from the scheduled RP date and will be genotyped for *HSD3B1* before enrollment in the study as a part of the screening. We expect a higher concentration of DHT in patients with homozygous *HSD3B1*(1245C) genotype as a result of flux to DHT due to 3βHSD1 abundance.

14.1 Sample Size and Accrual

In a recent report by Chang et al[24] the prevalence of the homozygous *HSD3B1*(1245C) genotype was 10% in 40 CRPC patients. The prevalence however is to some extent race-dependent.[25]

The prevalence of the wild type and heterozygous genotypes were approximately 2:1, and therefore the homozygous variant genotype is "rate-limiting" for accrual. The target enrollment is 12 patients who have the homozygous *HSD3B1*(1245C) genotype, 15 patients who are heterozygous, and 30 wild-type patients. Because of the low prevalence of homozygous *HSD3B1* (1245C), enrollment in each cohort will proceed until its target is reached. A subject who either prematurely discontinues from the study before completing 28 days of the treatment, prior to surgery, or for whom we are unable to obtain a tissue sample from, may be replaced in order to achieve target enrollment in each cohort. All safety and efficacy data from all accrued patients independent of the availability of post-treatment tumor material will be collected and analyzed.

Overall, based on the prevalence of the homozygous variant genotype, we predict that we may need to screen up to 120 patients to reach our accrual objective. Due to logistical restrictions, an accrual goal of 80 male patients may be needed in order to capture all objectives for a sample size of 57 patients. Accrual is expected to be approximately 2 years in the three cohorts.
With 57 patients there will be statistical power >80% to detect a 4-fold trend in the primary endpoint, DHT concentrations in the resected prostate tissue, as well as similar trends in other androgens and molecular markers. The calculation is based on a 2-sided test with 5% type I error; a codominance model where there is a 4-fold difference in hormone concentration between the wild-type and homozygous variant genotypes and a concentration approximately mid-way between the two for the heterozygous genotype; and that variability in this concentration could be as much as 125% of the mean hormone tissue concentration for each genotype. Note that 125% of the mean is a conservative estimate of variability. If it turns out in fact to be lower – e.g. similar to the 75% seen in a recent study in which patients were treated with 6 months leuprolide prior to RP[35] , there will be >95% power to detect a 4-fold range, >90% to detect a 3-fold range, and 75% to detect a 2-fold range.

14.2 Data Analysis

Hormone concentrations and tissue PSA, TMPRSS2, FKBP5, EZH2, H3K27, and UBE2C measured by qPCR will be summarized as means and standard errors, possibly after data transformation. Differences between genotypes within and between tissue types will be analyzed using linear or non-linear models.

Pearson or Spearman rank correlations will be used to assess associations between the concentrations of the different hormones and molecular markers. All tests of statistical significance will be two-sided.

15 References

1. SEER Stat Fact Sheets: Prostate Cancer. at <http://seer.cancer.gov/statfacts/html/prost.html>
2. OH, W. K. & Kantoff, P. Management of Hormone Refractory Prostate Cancer: Current Standard and Future Prospects. *J. Urol.* **160,** 1220–1229 (1998).
3. Chi, K. N. *et al.* Castration-resistant Prostate Cancer: From New Pathophysiology to New Treatment Targets. *Eur. Urol.* **56,** 594–605 (2009).
4. Taplin, M.-E. & Balk, S. P. Androgen receptor: A key molecule in the progression of prostate cancer to hormone independence. *J. Cell. Biochem.* **91,** 483–190 (2004).
5. Sedelaar, J. P. M. & Isaacs, J. T. Tissue culture media supplemented with 10% fetal calf serum contains a castrate level of testosterone. *The Prostate* **69,** 1724–1729 (2009).
6. Montgomery, R. B. *et al.* Maintenance of Intratumoral Androgens in Metastatic Prostate Cancer: A Mechanism for Castration-Resistant Tumor Growth. *Cancer Res.* **68,** 4447–4454 (2008).
7. Sharifi, N., Dahut, W. L. & Figg, W. D. Secondary hormonal therapy for prostate cancer: what lies on the horizon? *BJU Int.* **101,** 271–274 (2008).
8. Attard, G. *et al.* Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **27,** 3742–3748 (2009).
9. Ryan, C. J. *et al.* Phase I Clinical Trial of the CYP17 Inhibitor Abiraterone Acetate Demonstrating Clinical Activity in Patients With Castration-Resistant Prostate Cancer Who Received Prior Ketoconazole Therapy. *J. Clin. Oncol.* **28,** 1481–1488 (2010).
10. Navarro, D., Luzardo, O. P., Fernández, L., Chesa, N. & Díaz-Chico, B. N. Transition to androgen-independence in prostate cancer. *J. Steroid Biochem. Mol. Biol.* **81,** 191–201 (2002).
11. Mostaghel, E. A. *et al.* Resistance to CYP17A1 inhibition with abiraterone in castration resistant prostate cancer: Induction of steroidogenesis and androgen receptor splice variants. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **17,** 5913–5925 (2011).
12. Feldman, B. J. & Feldman, D. The development of androgen-independent prostate cancer. *Nat. Rev. Cancer* **1,** 34–45 (2001).
13. Grossmann, M. E., Huang, H. & Tindall, D. J. Androgen Receptor Signaling in Androgen-Refractory Prostate Cancer. *J. Natl. Cancer Inst.* **93,** 1687–1697 (2001).
14. Scher, H. I., Buchanan, G., Gerald, W., Butler, L. M. & Tilley, W. D. Targeting the androgen receptor: improving outcomes for castration-resistant prostate cancer. *Endocr. Relat. Cancer* **11,** 459–476 (2004).
15. Rathkopf, D. E. *et al.* Phase I Study of Apalutamide, a Novel Antiandrogen, in the Treatment of Castration-Resistant Prostate Cancer. *J. Clin. Oncol.* **31,** 3525–3530 (2013).
16. Lorence, M. C., Murry, B. A., Trant, J. M. & Mason, J. I. Human 3 beta-hydroxysteroid dehydrogenase/delta 5----4isomerase from placenta: expression in nonsteroidogenic cells of a protein that catalyzes the dehydrogenation/isomerization of C21 and C19 steroids. *Endocrinology* **126,** 2493–2498 (1990).
17. Simard, J. *et al.* Molecular biology of the 3beta-hydroxysteroid dehydrogenase/delta5-delta4 isomerase gene family. *Endocr. Rev.* **26,** 525–582 (2005).

18. Cai, C., Wang, H., Xu, Y., Chen, S. & Balk, S. P. Reactivation of Androgen Receptor Regulated TMPRSS2:ERG Gene Expression in Castration Resistant Prostate Cancer. *Cancer Res.* **69,** 6027–6032 (2009).
19. Evaul, K., Li, R., Papari-Zareei, M., Auchus, R. J. & Sharifi, N. 3beta-hydroxysteroid dehydrogenase is a possible pharmacological target in the treatment of castration-resistant prostate cancer. *Endocrinology* **151,** 3514–3520 (2010).
20. Scher, H. I. & Sawyers, C. L. Biology of Progressive, Castration-Resistant Prostate Cancer: Directed Therapies Targeting the Androgen-Receptor Signaling Axis. *J. Clin. Oncol.* **23,** 8253–8261 (2005).
21. Ryan, C. J. & Tindall, D. J. Androgen Receptor Rediscovered: The New Biology and Targeting the Androgen Receptor Therapeutically. *J. Clin. Oncol.* **29,** 3651–3658 (2011).
22. Chang, K.-H. *et al.* Dihydrotestosterone synthesis bypasses testosterone to drive castration-resistant prostate cancer. *Proc. Natl. Acad. Sci. U. S. A.* **108,** 13728–13733 (2011).
23. Shah, S. K. *et al.* Phase II Study of Dutasteride for Recurrent Prostate Cancer During Androgen Deprivation Therapy. *J. Urol.* **181,** 621–626 (2009).
24. Chang, K.-H. *et al.* A Gain-of-Function Mutation in DHT Synthesis in Castration-Resistant Prostate Cancer. *Cell* **154,** 1074–1084 (2013).
25. http://genome.ucsc.edu/.
26. Hearn, J. W. D. *et al.* HSD3B1 and resistance to androgen deprivation therapy in prostate cancer. *J. Clin. Oncol.* **33,** (2015).
27. Efstathiou, E. *et al.* Cytoreduction and androgen signaling modulation by abiraterone acetate (AA) plus leuprolide acetate (LHRHa) versus LHRHa in localized high-risk prostate cancer (PCa): Preliminary results of a randomized preoperative study. *J. Clin. Oncol.* **30,** (2012).
28. Taplin, M.-E. *et al.* Effect of neoadjuvant abiraterone acetate (AA) plus leuprolide acetate (LHRHa) on PSA, pathological complete response (pCR), and near pCR in localized high-risk prostate cancer (LHRPC): Results of a randomized phase II study. *J. Clin. Oncol.* **30,** (2012).
29. Medivation, Inc. Study of MDV3100 as a Neoadjuvant Therapy for Patients Undergoing Prostatectomy for Localized Prostate Cancer [ClinicalTrials.gov identifier NCT01547299] US National Institutes of Health; (2012). at <https://clinicaltrials.gov/ct2/show/study/NCT01547299>
30. Attard, G. *et al.* Phase I Clinical Trial of a Selective Inhibitor of CYP17, Abiraterone Acetate, Confirms That Castration-Resistant Prostate Cancer Commonly Remains Hormone Driven. *J. Clin. Oncol.* **26,** 4563–4571 (2008).
31. Ercole, C. E. *et al.* Dehydroepiandrosterone metabolism in fresh human prostate: A feasibility study. *J. Clin. Oncol.* **32,** (2014).
32. Tamae, D. *et al.* Development, validation and application of a stable isotope dilution liquid chromatography electrospray ionization/selected reaction monitoring/mass spectrometry (SID-LC/ESI/SRM/MS) method for quantification of keto-androgens in human serum. *J. Steroid Biochem. Mol. Biol.* **138,** 281–289 (2013).
33. Foster, W. R. *et al.* Drug safety is a barrier to the discovery and development of new androgen receptor antagonists. *The Prostate* **71,** 480–488 (2011).

34. Rathkopf, D. *et al.* Phase I dose-escalation study of the novel antiandrogen BMS-641988 in patients with castration-resistant prostate cancer. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **17,** 880–887 (2011).
35. Taplin, M.-E. *et al.* Intense Androgen-Deprivation Therapy With Abiraterone Acetate Plus Leuprolide Acetate in Patients With Localized High-Risk Prostate Cancer: Results of a Randomized Phase II Neoadjuvant Study. *J. Clin. Oncol.* **32,** 3705–3715 (2014).

APPENDIX I

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

APPENDIX II

Subject Registration Form

Protocol CASE5815	Title: The Association between *HSD3B1* Genotype and Steroid Metabolism in Normal and Prostate Cancer Tissue of Men with Intermediate and High-risk Prostate Cancer Undergoing Radical Prostatectomy after Treatment with Apalutamide and Leuprolide.	Date: ___/___/_____

Subject Demographics

Study Site: Cleveland Clinic			
MRN:	Last Name:	First Name	MI:
Gender: X Male	Ethnicity: □ Hispanic □ Non-Hispanic □ Unknown	Race: □ American Indian or Alaska Native □ Asian □ Black or African American □ Native Hawaiian or Other Pacific Islander □ Unknown □ White	
Date of Birth: ___/___/_____	On Study Date: ___/___/_____	Study Patient No:	
Disease Site: PROSTATE			
Histology: PROSTATE			
Registrar's Name		Registrar's Signature	

APPENDIX III **IRB CASE 5815 Study Medication Diary**

Subject Initials_____ Subject Number_____ Cycle _____

Take 4 tablets at the same time once a day with or without food.
Take at approximately the same time each day.
Last does of Apalutamide will be taken the day before surgery.
Please record the time and number of tablets you take each day on the table below:

Cycle Day	Date	Time of Daily Dose	Number of Tabs taken	Side Effects
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Signature of patient:

Signature_____ Date _____

APPENDIX IV

Medications Prohibited while on active treatment with Apalutamide

Generic Name	Brand Name*
aminophylline	Aminocont; Aminomal; Diaphyllin; Filotempo; Neophyllin; Norphyl; Phyllocontin; Syntophyllin; Tefamin; Truphylline; Xing You Shan;
aminophylline in combination	Asmeton; Cha Xin Na Min; Emergent-Ez; Fufang Dan An Pian; Ke Zhi
amitriptyline	Amirol; Amitrip; Amixide; Deprelio; Diapatol; Elatrol; cElatrolet; Elavil; Endep; Enovil; Emitrip; Klotriptyl; Laroxyl; Levate; Limbitrol; Limbitryl; Mutabase; Mutabon; Nobritol; Novo-Triptyn; Pertriptyl; Redomex; Saroten; Sarotex; Sedans; Syneudon; Teperin; Triptizol; Triptyl; Tryptizol
amitriptyline in combination	PMS-Levazine
bupropion	Aplenzin; Buproban; Contrave; Elontril; Forfivo; Fortivo XL; Le Fu Ting; Prexaton; Quomem; Voxra; Wellbutrin; Wellbutrin XL; Wellbutrin SR; Yue Ting; Zyban
chlorpromazine	Aminazin; Chlorazin; Hibernal; Klorproman; Largactil; Megaphen; Ormazine; Plegomazin; Solidon; Taroctyl;Thorazine; Vegetamin; Wintermin; Zuledin Note: in Ireland also called “Clonazine” – very easy to confuse with clozapine.
clozapine	Azaleptin; Clopine; Closastene; Clozaril; CloZAPine; Denzapine; Elcrit; Fazacio ODT; Klozapol; Lanolept; Leponex; Lozapine; Nemea; Ozapim; Synthon, Versacloz; Zaponex
desipramine	Deprexan; Norpramin; Nortimil; Pertofrane
doxepin	Adapin; Anten; Aponal; Deptran; Gilex; Li Ke Ning; Quitaxon; Silenor; Sinepin; Sinequan; Zonalon
imipramine	Impril; Melipramin; Mipralin; Norfranil,; Novo-Pramine; Persamine; Pertofram; Pryleugan; Talendep; Tofranil; Tolerade
lithium	Arthriselect; Camcolit; Carbolith; Carbolithium; Eskolith; Hypnorex; Li-Liquid; Licarbium; Limas; Liskonum; Litarex; Lithane; Lithicarb; Lithioderm; Lithionit; Lithobid; Liticarb; Litiomal; Lito; Maniprex; Neurolepsin; Plenur; Priadel; Quilonorm; Quilonum; Saniquiet; Sedalit; Teralithe
lithium in combination	Boripharm No 23; Emser Salz; Girheulit HOM; Helidonium-Plus; Heweurat N; rheuma-loges; Rhus Toxicodendron Compose; Rhus-Plus; Ricinus Compose
maprotiline	Cronmolin; Deprilept; Ludiomil; Mapromil; Melodil; Neuomil; Psymion

meperidine/pethidine	Alodan ; Atropine and Demerol; Centralgine ; Demerol ; Dolantin ; Dolantina,; Dolantine ; Dolargan,; Dolcontral,; Dolestine ; Dolosal ; Dolsin; Fada; Hospira; Liba; Mepergan ; Meprozine,; Mialgin,; Opystan; Pethidine ; Petigan Miro ; Psyquil compositum
meperidine/pethidine in combination	Pamergan P100
mesoridazine	Serentil, Mesorin
mirtazapine	Arintapin; Avanza; Axit; Combar; Esprital; Mi Er Ning; Miro; Mirta TAD; Mirtabene; Mirtachem; Mirtadepi; Mirtagamma; Mirtalan; MirtaLich; Mirtamylan; Mirtaron; Mirtaz; Mirtazelon; Mirtazon; Mirtazonal; Mirtel; Mirtin; Mirtor; Mirzaten; Norset; Noxibel; Paidisheng; Psidep; Remergil; Remergon; Remeron; Remirta; Rexer; Yarocen; Zispin
olanzapine	Anzorin, Arenbil; Arkolamyl; Atyzyo; Bloonis; Clingozan; Egolanza; Lansyn; Lanzek; Lazapix; Nolian; Nykob; Olafid; Olanzaran; Olanzep; Olanzin; Olanzine; Olapin; Olasyn; Olazax; Olpinat; Olzapin; Olzin; Ou Lan Ning; Ozilormar; Parnassan; Ranofren; Sanza; Stygapon; Synza; Ximin; Zalasta; Zamil; Zappa; Zapris; Zerpi; Zolafren; Zolaxa; Zonapir; Zopridoxin; Zylap; Zypadhera; Zypine; Zyprexa; Zyprexa Relprew; Zydis
olanzapine in combination	Symbyax
risperidone	Aleptan; Apo-Risperid; Arketin; Calmapride; Diaforin; Doresol; Hunperdal; Jing Ping; Ke Tong; Leptinorm; Lergitec; Orizon; Ozidal; Perdox; Ranperidon; Resdone; Ridal; Ridonex; Rileptid; Ripedon; Risepro; Rispa; Rispaksole; Rispefar; Rispemylan; Rispen; Rispera; Risperanne; Risperdal; Risperdalconsta; Risperdaloro; Risperigamma; Risperon; Rispolept; Rispolux; Rispond; Rispons; Risset; Rixadone; Rorendo; Ryspolit; Si Li Shu; Sizodon; Speridan; Suo Le; Torendo; Zhuo Fei; Zhuo Fu; Ziperid; Zoridal
theophylline	Aerolate; Afonilum; Aminomal; An Fei Lin; Apnecut; Apo-Theo; Asmalix; Asmalon; Bi Chuan; Bronchoparat; Bronchoretard; Cylmin; Diffumal; Elixifilin; Elixophyllin; Etipramid; Euphyllin; Euphyllina; Euphylline; Euphylong; Frivent; Gan Fei Lin; Nuelin; Protheo; Pulmophylline; Quelesu; ratio-Theo-Bronc; Respicur; Retafyllin; Shi Er Ping; Slo-Bid; Slo-Phyllin; Telbans; Teotard; Terdan; Teromol; Theo-24; Theo-Dur; Theo; Theochron; Theodur; Theofol; Theolair; Theoplus; Theospirex; Theostat ; Theotard; Theotrim; Theovent; Tromphyllin; Unicon; Unicontin; Unifyl; Uniphyl; Uniphyllin Continus; Uniphyllin; UniXan; Xanthium; Xi Fu Li; Yan Er
theophylline in combination	Antong; Baladex; Bi Chuan; Binfolipase; Broncho-Euphyllin; Broncomar; Do-Do ChestEze; Elixophyllin-GG; Elixophyllin-KI; Insanovin; Marax ; Neoasma; Theofol Comp; Theophedrinum-N; Xu Hong; Yi Xi Qing
thioridazine	Detril; Elperil; Melleril; Ridazin; Ridazine; Thiodazine; Thioril; Sonapa
ziprasidone	Geodon; Li Fu Jun An; Pramaxima; Si Bei Ge; Ypsila; Zeldox; Zipwell; Zypsila; Zypsilan

herbal products	All herbal products must be discontinued if applicable, per provider discretion
steroid therapy	Systemic steroid therapy (inhaled or topical steroids); Corticosteroids; unless waived at the provider's discretion.

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