MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2016-0527
Protocol Title	**A Pre-Operative Study to Assess the Effects of Apalutamide plus LHRH Agonist or Apalutamide plus Abiraterone Acetate plus LHRH Agonist for Six Months for Prostate Cancer Patients at High Risk for Recurrence**
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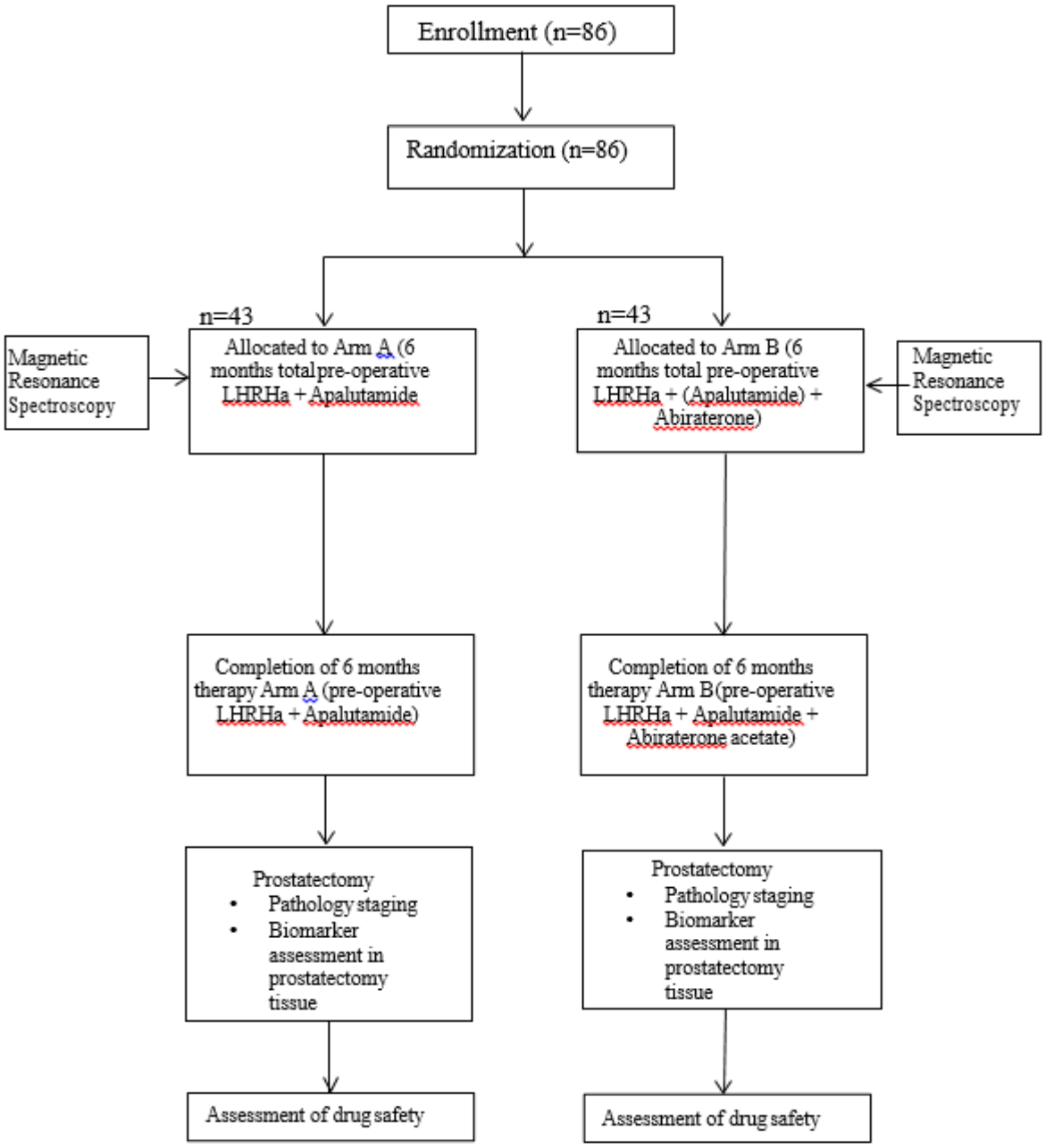
Version 08	01/04/2019	IRB Resubmission
Version 09	04/23/2019	IRB Resubmission
Version 10	01/11/2021	IRB Resubmission

SCHEMA


Enrollment (n=86)
Randomization (n=86)
n=43
n=43
Magnetic Resonance Spectroscopy
Allocated to Arm A (6 months total pre-operative LHRHa + Apalutamide
Allocated to Arm B (6 months total pre-operative LHRHa + (Apalutamide) + Abiraterone)
Magnetic Resonance Spectroscopy
Completion of 6 months therapy Arm A (pre-operative LHRHa + Apalutamide)
Completion of 6 months therapy Arm B (pre-operative LHRHa + Apalutamide + Abiraterone acetate)
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1.0 OBJECTIVES

1.1. Primary Objectives

To assess the rate of pathologic stage ≤ pT2N0 at prostatectomy for Group A (LHRHa plus apalutamide 240 mg PO daily for 6 months as preoperative therapy) and Group B (LHRHa plus apalutamide 240 mg PO daily plus abiraterone acetate 1000 mg PO daily and prednisone 5 mg PO QD for 6 months as preoperative therapy)

1.2. Secondary Objectives

- To assess the tumor epithelium volume following treatment in groups A and B
- To assess the rate of positive surgical margins in Group A and Group B.
- To assess the time to PSA recurrence (TTR_{PSA})
- To assess the safety profile of the two treatment arms (apalutamide with and without abiraterone acetate and low dose prednisone) for six months in a preoperative setting.

1.3 Exploratory Objectives

- Assessment of the steroid hormone metabolome in blood plasma and tissue by liquid chromatography tandem mass spectrometry
- Assessment of androgen signaling (canonical and non-canonical) and candidate pathways of resistance to androgen signaling inhibition by protein and RNA analysis
- Assessment of citrate intracellular TCA cycle metabolite concentrations with LCMS/MS
- Proportion of patients who achieve pathological CR
- Hyperpolarized 1-13C-pyruvate imaging at study entry and at 3 months in Arm A and Arm B.

2.0 BACKGROUND

2.1 Introduction

Many patients diagnosed with localized prostate cancer are curable with local therapy, however approximately 20% of patients in modern series initially present with locally advanced or high-grade prostate cancer not amenable to a single therapeutic approach i.e. surgery or radiation therapy alone. The prostate cancer experience with preoperative therapy over the past 15 years has differed significantly from other solid tumors; pathologic complete response is rarely achieved with first generation anti-

androgens including flutamide and cyproterone or LHRH analogues alone. The addition of pre-operative chemotherapy has provided similarly disappointing results. While pCR remains elusive, several studies of pre-operative androgen ablations have reported reduction in the rate of positive surgical margins, rates of lymph node involvement, and increased rates of organ confined disease. Importantly, such trials have failed to impact outcomes to date for a variety of reasons. Ensuing knowledge challenges the potential association of pCR with improved outcomes and underscores the importance of minimal residual tumor volume. Moreover high risk locally advanced prostatic carcinoma is characteristic for biologic heterogeneity that invariably will govern responsiveness to therapeutic choices suggesting the need for predictive markers of outcome.

In recent years, three pre-operative trials incorporating a new generation of androgen-targeting agents including abiraterone and enzalutamide have been reported. These have documented rates of conversion to pathologic stage ≤pT2N0 ranging from 40-55%;[1,2,3] reinforcing the anticipated association with underlying biologic heterogeneity within this disease stage . Correlative biomarkers have been evaluated, and while these remain investigational at this time, with further validation these may ultimately be used to provide a predictive framework to identify patients with high risk localized disease who will benefit from intensive pre-operative androgen deprivation.

Combination anti-androgen therapy with abiraterone and enzalutamide has demonstrated safety and profound depletion of intraprostatic androgens in metastatic CRPC [3,4.] Localized prostate cancer is dependent on androgens for proliferation, providing the rationale for moving a combination approach with LHRHa, apalutamide and abiraterone acetate to the hormone-naïve but high-risk prostate cancer setting. We hypothesize that intensification of pre-operative androgen deprivation will further decrease intraprostatic androgens, leading to decreased cell proliferation and less advanced pathologic stage at prostatectomy.

Apalutamide is an investigational agent not yet approved by the FDA, and is an androgen receptor antagonist similar in structure to enzalutamide, an FDA-approved agent for the treatment of metastatic CRPC. Both agents prevent AR translocation to the nucleus and binding to androgen response elements. A proposed advantage of Apalutamide over enzalutamide may include an improved therapeutic index including limited CNS toxicity.[5] Phase I/II trials have demonstrated safety and tolerance in humans.[6]

2.2 Agents

i. **Apalutamide** is an androgen-receptor antagonist that prevents AR translocation to the nucleus and binding to androgen response elements. In preclinical models, Apalutamide produced responses in both castration-sensitive and castration-resistant human prostate cancer xenograft models and showed maximal antitumor efficacy in these models at a three-fold lower dose and approximately nine-fold lower plasma level than enzalutamide, suggestive of a higher therapeutic index.[5]

The first in-human phase I study of Apalutamide was published in 2013, and a recommended phase II dose of 240mg PO daily was established. This study reported ≥50% decline in PSA at 12 weeks in 46.7% of patients, with grade 1/2 fatigue the most frequently reported adverse effect.[6]

ii. LHRH Agonists (ie, Leuprolide Acetate, Goserelin, Triptorelin)

At the time of diagnosis localized prostate cancers are categorized as low, intermediate or high risk based on clinical stage, prostate specific antigen (PSA) level/velocity and tumor Gleason score. Patients who fall into intermediate and high risk categories have unacceptably high relapse rates (30-80%) after primary local therapy or salvage local approaches. The standard systemic treatment for prostate cancer is androgen deprivation therapy (ADT) most commonly administered with an LHRHa with/without an antiandrogen. Treatment of systemic prostate cancer with ADT is not curative as patients develop castration resistant prostate cancer (CRPC).

To date, ADT in high risk localized prostate cancer patients using LHRHa alone has reduced prostate volume by roughly 30% and decreased the rate of positive surgical margins, but has not been shown to improve the biochemical relapse rate for patients who undergo radical prostatectomy. However, because the addition of novel androgen targeting agents like abiraterone and Apalutamide to LHRHa further lowers androgen levels compared to LHRHa alone in CRPC, there is a strong scientific rationale to test whether this more potent combination therapy can improve surgical outcomes.

iii. Abiraterone Acetate

Abiraterone acetate (ZYTIGA) is converted in vivo to abiraterone, an androgen biosynthesis inhibitor that inhibits 17 α hydroxylase/C17, 20-lyase (CYP17). This enzyme is expressed in testicular, adrenal and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals.

Abiraterone acetate has received marketing approval in more than 100 countries for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) after docetaxel treatment. It is also approved for the treatment of mCRPC in men who have not previously received chemotherapy. The pre-operative combination proposed in this protocol is not FDA approved.

2.3 Rationale

Abiraterone has demonstrated activity in patients with mCRPC who have progressed on hormonal and currently available chemotherapeutic options. Apalutamide is a novel, potent inhibitor of the androgen receptor that has demonstrated safety in patients with CRPC. Both alterations in the steroid metabolism and the androgen receptor are implicated in the clinically observed resistance to castration. Importantly as we have first reported in the more advanced disease setting each agent alone induces physiologic feedbacks that may contribute to treatment resistance. Taken together, these observations provide compelling rationale to combine optimum medical castration, inhibition of the androgen receptor, and altered androgen biosynthesis in patients at high risk for recurrence.

The proposed study will examine this combination in the pre-operative, hormone-naïve but high risk setting. A prior phase II study has examined pre-operative LHRHa plus abiraterone compared with LHRHa alone in patients with localized high risk prostate cancer (LHRPC). At the time of prostatectomy, pathology staging ≤ pT2N0 occurred in 24/44 (54.5%) for Abiraterone plus LHRHa versus 8/21 (33.1%) for LHRHa alone, P = 0.21. Tumor Epithelial density for Abiraterone plus LHRHa was lower compared to LHRHa alone (P < 0.0001). Post-treatment prostate-specific antigen (PSA) nadir was ≤ 0.2 ng/ml in 41/44 (93.2%) for Abiraterone + LHRHa versus 3/21 (14.3%) for LHRHa alone (P < 0.0001). For the cohort of patients receiving abiraterone and LHRHa, higher ARV7, GR, both by protein and RNA assays were associated with increased residual tumor. These findings suggest resistance emerges within 3 months of androgen signaling inhibition despite universal serum PSA declines, which have clinical implications on designing combinational treatment strategies for LHRPC.

Another phase II study has examined pre-operative LHRHa plus abiraterone plus enzalutamide compared with LHRHa plus abiraterone. Complete molecular characterization of these results are still pending, but suggestions of early resistance and responsiveness were identified, with tumors with favorable pathology stage (≤ pT2N0) demonstrating higher canonical androgen signaling

The studies summarized above have outline proposed biomarker profiles of resistance and responsiveness to LHRHa alone, LHRHa plus abiraterone, and LHRHA plus abiraterone plus enzalutamide. The proposed study will add to these results by characterizing the biomarker profiles of responsiveness and resistance to apalutamide plus LHRHa and apalutamide plus LHRHa plus abiraterone. These profiles may ultimately provide the framework for personalized pre-operative treatment for LHRPC.

This knowledge will build on our understanding of the effect of optimum androgen inhibition in the setting of newly diagnosed, high-risk prostate cancer. The findings will lead to a framework that will allow us to personalize androgen signaling targeted therapy, by stage of progression, within individual patients and assure the safe use of the drug and the development of a rational combination therapy. Exploratory biomarker studies will be used to explore the subset of patients who benefit most from two-agent

or three-agent pre-operative androgen ablation, and a subset with early resistance. Ultimately, biomarker patterns of pre-operative androgen resistance may be used to guide intensification of alternative therapies for patients who demonstrate resistance despite maximal androgen ablation.

2.4 Correlative Studies Background

The diagnosis of prostate cancer is dependent on core needle biopsy, as will be our assessments of correlative biomarkers (discussed below) in the proposed study. Core needle biopsy is associated with morbidity, and is by definition susceptible to overlooking areas of interest due to sampling. The ramifications of our current reliance on prostate biopsies are demonstrated by the significant number of patients who are up-staged at the time of prostatectomy.

2.4.1 Magnetic resonance spectroscopy

Hyperpolarized magnetic resonance spectroscopy (MRS) is a functional imaging technique that allows for acquisition of detailed metabolic information during non-invasive MR imaging, eliminating both the sampling error and the morbidity associated with core needle biopsy. Incorporating MRS into our assessment of high-risk localized prostate cancer will validate its use in this setting and allow for comprehensive assessment of metabolism in all foci of prostate cancer. We hypothesize that pre-operative intensive androgen depletion will also have differential effects on citrate flux in responders and non-responders. Normal prostate cells have the unique characteristic of accumulating and secreting high concentrations of citrate, usually employed by eukaryotic cells in the oxidative metabolism of carbohydrates via the tricarboxylic acid (TCA) cycle. Loss of this high citrate concentration is an early hallmark of malignant transformation, and is consistently observed in prostate cancers. In prostate cancer cells, citrate is diverted to anabolic pathways including fatty acid (FA) synthesis and de novo testosterone synthesis via acetyl-CoA; therefore citrate serves as the central link between intermediary metabolism and androgen signaling in the prostate cancer cell. Citrate flux profiles after pre-operative androgen deprivation will enable non-invasive monitoring of efficacy, that when paired with cell density and molecular characterization will enable early identification resistance to androgen deprivation in the localized setting.

2.4.2 Laboratory Biomarkers

Efstathiou and Titus have presented and published extensively on molecular characterization of CRPC treated with Abiraterone, enzalutamide and the combination in the metastatic setting. Responders to both Abiraterone and enzalutamide have increased nuclear N-terminal AR staining and ≥10% CYP17 tumor expression. These studies serve as proof of principle that molecular characterization can yield predictive information.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

a) Patients must have histologically or cytologically confirmed adenocarcinoma of the prostate with no histological variants (such as small cell, sarcomatoid, pure ductal cancer, transitional cell carcinoma).

b) Patients may have received one prior depot injection of LHRH agonist or LHRH antagonist (degarelix) within 30 days prior to study entry. Patients who have received any other prior hormonal therapy or any chemotherapy for prostate cancer will be excluded.

(Patients who have discontinued finasteride or dutasteride or testosterone supplementation for at least 2 weeks will be allowed to enroll)

3.1.1 Each patient must meet the following criteria to be enrolled in this study:

1) Be willing/able to adhere to the prohibitions and restrictions specified in this protocol.
2) Have signed an informed consent document indicating that the subject understands the purpose of and procedures required for the study and is willing to participate in the study.
3) Written Authorization for Use and Release of Health and Research Study Information has been obtained.
4) Age ≥18 years. Because no dosing or adverse event data are currently available on the use of Abiraterone in combination with apalutamide (in patients <18 years of age, children are excluded from this study.
5) Pathology review at MD Anderson (Note: if patient's prostate biopsy was not read at MD Anderson, it must be reviewed at the study site to confirm eligibility).
6) Prostate Biopsy. If previous biopsy has been performed within 3 months of screening, second biopsy procedure will not be required, if archival biopsies and at least one formalin fixed paraffin embedded biopsy tissue block containing tumor is available. (Refer to section 4.2.5)
7) The following tumor stage and Gleason scores:
   - Clinical ≥stage T1c/T2 tumor with Gleason score ≥8
   - Clinical stage ≥T2b tumor with Gleason score ≥7 and PSA >10 ng/ml
8) Serum testosterone >150 ng/dL. For patients treated up to 1 month of LHRH agonist, a testosterone measurement prior to the LHRH treatment will be used

to determine eligibility, and must have been > 150 ng/dL. If no testosterone level is available from before LHRHa injection up to 30 days prior to study entry, the patient will be ineligible.

9) Patient is suitable for prostatectomy.
10) No evidence of metastatic disease as determined by imaging procedures.
11) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
12) Hemoglobin ≥9.0 g/dL independent of transfusion.
13) Platelet count ≥100,000/μL.
14) Patients should have adequate bone marrow function defined as an absolute peripheral neutrophil count (ANC) >1,000.
15) Creatinine clearance ≥50 mL/min
16) Serum potassium ≥3.5 mmol/L.
17) Serum bilirubin ≤ 1.5x ULN or ALT and AST ≤ 2.5x ULN
18) Serum Albumin ≥ 3.0 g/dl
19) Able to swallow the study drug whole as a tablet.
20) Patients must have normal coagulation profile and no history of substantial non-iatrogenic bleeding diathesis.
21) Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.
22) Willing to take abiraterone acetate on an empty stomach; no food should be consumed at least two hours before and for at least one hour after the dose of abiraterone acetate is taken.
23) Life expectancy of greater than 12 months.

3.2 Exclusion Criteria

1) Patients who have had any prior chemotherapy or radiotherapy for prostate cancer.
2) Patients who have had >1 LHRH agonist or antagonist depot injection or received depot injection >30 days before study entry.
3) Patients may not be receiving any other investigational agents.
4) Patients may not be receiving the concomitant administration of any systemic therapy, biologic therapy, or other agents with anti-tumor activity against prostate cancer while the are on study.

5) Patients with known metastatic prostate cancer.
6) History of allergic reactions attributed to compounds of similar chemical or biologic composition to Leuprolide acetate, abiraterone acetate, prednisone or apalutamide or other agents used in the study.
7) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
8) HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with apalutamide and abiraterone. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.
9) Avoid concomitant strong CYP3A4 inducers during abiraterone acetate treatment. If a strong CYP3A4 inducer must be co-administered, increase the abiraterone acetate dosing frequency.
10) Avoid co-administration of abiraterone acetate with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

11. patients receiving medications known to lower the seizure threshold are ineligible unless discontinued or substituted at least 4 weeks prior to study entry.

These include:

- Aminophylline/theophylline;
- Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone);
- Bupropion;
- Lithium;
- Pethidine;
- Phenothiazine antipsychotics (e.g., prochlorperazine (compazine), chlorpromazine, mesoridazine, thioridazine);
- Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine).

12. Chronically uncontrolled hypertension, defined conventionally as consistent systolic pressures above 170 or diastolic pressures above 110 despite anti-hypertensive therapy. Note that this is NOT a criterion related to particular BP results at the time of assessment for eligibility, nor does it apply to acute BP excursions that are related to iatrogenic causes, acute pain or other transient, reversible causes. (For example doctor's visit related stress i.e. "white coat syndrome".

13. Requirement for corticosteroids greater than the equivalent of 10 mg of prednisone daily for more than 2 weeks.

14. Poorly controlled diabetes defined by Hemoglobin A1C > 9.0 at screening

15. Active or symptomatic viral hepatitis or chronic liver disease.

16. Known history of pituitary or adrenal dysfunction.

17. Other malignancy, except non-melanoma skin cancer, that is active or has a ≥ 30% probability of recurrence within 12 months.

18. History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug.

19. Prior hormone therapy for prostate cancer including orchiectomy, antiandrogens, ketoconazole, or estrogens (5-α reductase inhibitors allowed), or LHRH agonists/antagonists (*Note: LHRH allowed if begun within 1 month of Day 1).

20. Prior systemic treatment with an azole drug within four weeks of Cycle 1 Day1.

21. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of Cycle 1 Day 1.

22. Allergies, hypersensitivity, or intolerance to prednisone, LHRH analog or excipients of prednisone LHRH analog, abiraterone acetate and apalutamide.

23. Previous use of abiraterone acetate or other investigational CYP17 inhibitor (e.g., TAK-700).

24. Previous investigational antiandrogens (e.g., apalutamide, enzalutamide, BMS-641988).

25Condition or situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's participation in the study.

26. Patients unable to tolerate transrectal ultrasound.

27. Anti-androgens (steroidal or non-steroidal) such as cyproterone acetate, flutamide, nilutamide, bicalutamide, etc. other than assigned study drug unless given for <=4 weeks.

28. Estrogens, progestational agents such as megestrol, medroxyprogesterone, DES, cyproterone, spironolactone > 50 mg/kg, etc. unless discontinued at least two weeks prior to randomization

29. Androgens such as testosterone, dehydroepiandrosterone [DHEA], etc. unless discontinued at least two weeks prior to randomization.

30. Herbal products that may decrease PSA levels (e.g., saw palmetto) unless discontinued two weeks prior to randomization

31. Active infection or other medical condition that would make prednisone/ prednisolone (corticosteroid) use contraindicated.

32. Severe hepatic impairment (Child-Pugh Class C).
33. History of significant bleeding disorder unrelated to cancer, including:
    - Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease)
    - Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies) of screening visit.
    - History of GI bleeding within 3 months of screening visit requiring ≥2 units packed red blood cells.

3.2.1 Clinically significant cardiovascular disease including:

- Myocardial infarction within 6 months of Screening visit;
- Uncontrolled angina within 3 months of Screening visit;
- Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past, or history of anthracycline or anthracenedione (mitoxantrone) treatment, unless a screening echocardiogram or multi-gated acquisition scan (MUGA) performed within three months of the Screening visit results in a left ventricular ejection fraction that is ≥50%.
- History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsade de pointes).
- Prolonged corrected QT interval by the Fridericia correction formula (QTcF) on the screening Electrocardiogram (ECG) > 470 msec.
- History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
- Hypotension (systolic blood pressure < 86 mmHg or bradycardia with a heart rate of <50 beats per minute on the Screening ECG., unless pharmaceutically induced and thus reversible (i.e. beta blockers).

3.3 Inclusion of Minorities

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

4.0 TREATMENT PLAN

4.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for apalutamide, leuprolide, and abiraterone acetate are described in Section 6. Appropriate dose modifications for apalutamide and abiraterone acetate are described in Section 5.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

REGIMEN DESCRIPTION					
Agent	**Premedications/ Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Leuprolide*		22.5 mg	IM	IM every 3 months	4 weeks (28 days)
Abiraterone Acetate	Take on an empty stomach	1000 mg	PO	Daily, days 1-28	
Prednisone		5 mg	PO	QD, days 1-28	
Apalutamide		240 mg	PO	Daily, days 1-28	

* Any analogue or antagonist of equivalent dosing and schema as long as the total dosing does not exceed 6 months.

4.1.1 Apalutamide

No specific prophylactic or supportive care regimen is required.

4.1.2 Abiraterone Acetate

Co-administration with prednisone 5mg PO QD is indicated for the prevention of mineralocorticoid excess.

4.1.3 LHRH Agonist/ Antagonist

No specific prophylactic or supportive care regimen is required.

4.1.4 Medication Compliance

Compliance (individual drugs) **within 80%** of instructed dose and schedule is expected of participants each cycle. Variations in dosing within expected compliance will not constitute a protocol deviation or violation. Missed dosed may be documented in the electronic case report form.

4.2 Surgical Procedures

4.2.1 Radical Prostatectomy

Tissue from the prostatectomy and baseline pretreatment prostate biopsies will be collected for correlative studies.

4.2.2 Extent of Operation

All patients will have a planned radical prostatectomy.

4.2.3 Timing of Prostatectomy

The surgery will be planned at the end of Cycle 6. Patients must be off apalutamide and, if applicable, abiraterone acetate no less than 48 hours prior to surgery. Prednisone discontinuation will be up to provider's determination. To permit flexibility in surgical scheduling a study window of a maximum of four weeks will be allowed. In the event the surgery is delayed, the patient will be required to return to the clinic for safety assessment.

Surgery will be performed only after recovery from any side effects from abiraterone acetate or apalutamide to a level considered safe for surgery. In the event of delayed recovery, the patient will be maintained on LHRHa until the clinical condition permits surgery.

4.2.4 Assessment of Surgical Complication

It will be the responsibility of the attending surgeon to accurately tabulate complications and the progress of the surgical procedure. Specifically tabulated will be the duration of anesthesia, blood product requirement blood loss, fluid requirement, and gross description of the operative field (presence or absence of desmoplasia).

4.2.5 Prostate Tissue Handling

An archival tumor tissue block (or at least 20 unstained slides from the tumor tissue block; archived or recent) or fresh frozen tissue in liquid nitrogen will be required from the patient's initial prostate biopsy. These will be reviewed by the pathologist for confirmation of cancer and Gleason scoring. The patient will not be required to undergo a second biopsy procedure prior to starting study therapy (screening) if archival biopsies and unstained slides are available.

In order to preserve androgen levels in tissues, open intraoperative cores biopsies will be obtained prior to prostatectomy. The biopsies must be obtained prior to ligation of the vascular supply to the prostate. A minimum of 6 biopsies will be obtained attempting to focus on known regions of cancer. Each biopsy core should be placed in a separate 2 ml screwtop cryotube and immediately snap frozen in liquid nitrogen or dry ice/ethanol bath and stored at -80°C. If there is palpable tumor, it is recommended that at least 3 cores be obtained from the area of suspected tumor.

To process the radical prostatectomy specimen post-operatively, the following procedures must be followed:

- The prostate will be inked in four colors depicting left, right, superior and inferior sections and serially sectioned.
  Alternate coronal sections will be numbered sequentially from apex to base, divided into 4 quadrants (also labeled clockwise from the superoposterior quadrant as A, B, C, D) and immediately frozen in OCT (liquid nitrogen or dry ice/ethanol bath) for subsequent evaluation. The alternate sections will be placed in formalin, then processed and imbedded in paraffin using the tissue-tek®vip® 6 system (for histology analysis) and stored in the Prostate Tissue Bank at MDACC for future analysis. The coronal sections embedded in OCT will be stored, in the GU biorepository located at MDACC, for future analysis.
  Any future additional analyses not specified in this protocol will be agreed upon by prior approval from Janssen Scientific Affairs, LLC.
- Tissue samples collected on this study for future analysis are optional and not a requirement to be enrolled on this protocol.

4.2.7 Correlative Biomarkers

For all patients who provide informed consent, prostate tumor and normal prostate tissue will be obtained by macrodissection when possible. Testosterone and DHT and steroid metabolites of interest will be analyzed by a research laboratory at MD Anderson.

Standard methods such as IHC and whole exome sequencing will be used to assess prostate tumor for canonical and non-canonical androgen signaling proliferation cell cycle neuroendocrine markers, angiogenesis (CD31, VEGF, VEGFR,) and other relevant biomarkers likely associated with steroid metabolism and prostate cancer will be analyzed by the Stanford Alexander laboratory at MD Anderson.

Transcriptomic characterization of the tumor will be conducted in the Laboratory of Dr. Mark Titus at MD Anderson. Where available, analysis will be carried out on the pre-prostatectomy specimens, and prostatectomy specimens using fresh frozen tissue for primary tumor. RNA Analysis will include long non coding RNA (lnRNA) examples as per www.lncrnadb.org; oncomir RNA; and micro RNA (miRNA) such as #205, 146, 1256 and let7. DNA analysis will also be performed.[8,9] DNA analysis will also be performed.

Upon completion of research any remained tissue or other sample will be returned to institutional tissue bank after publication of research. Patient Identity will be safeguarded in accordance with HIPAA and MDACC guidelines.

4.3 General Concomitant Medication and Supportive Care Guidelines

4.3.1 Effects of Apalutamide on Drug Metabolizing Enzymes

Because there is a potential for interaction of apalutamide with other concomitantly administered drugs through the cytochrome P450 system, the concurrent use of all other drugs, over-the-counter medications, or alternative therapies will be recorded in the patient's medical records. **The Principal Investigator should be alerted by the research nurse or study coordinator performing current medication review at each study visit if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.**

In vitro, CYP3A4 and CYP2C8 are the enzymes primarily responsible for the metabolism of apalutamide.

Coadministration of a strong CYP3A4 inhibitor (itraconazole) had no clinically meaningful effect on the PK of apalutamide and its metabolite JNJ-56142060 (M3). Coadministration of a strong CYP2C8 inhibitor (gemfibrozil) increased the AUC of apalutamide by 68% but decreased the AUC of JNJ-56142060 (M3) by 15%. Use

caution if strong CYP2C8 inhibitors (eg, gemfibrozil) are coadministered with apalutamide.

The effects of CYP3A4 inducers or CYP2C8 inducers on the PK of apalutamide have not been evaluated in vivo. Coadministration of apalutamide with the following drugs that can induce CYP3A4 or CYP2C8 should be avoided as coadministration with any of these agents may decrease apalutamide plasma concentrations. Alternative therapies should be used when available.

- Strong CYP3A4 inducers: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, efavirenz, tipranivir, St. John's wort
- CYP2C8 inducers: rifampin

4.3.2 Effects of Abiraterone on Drug Metabolizing Enzymes

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10%, when pioglitazone was given together with a single dose of 1000 mg abiraterone acetate. Although these results indicate that no clinically meaningful increases in exposure are expected when abiraterone acetate is combined with drugs that are predominantly eliminated by CYP2C8, patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone acetate.

4.3.3 Drugs that Inhibit or Induce CYP3A4 Enzymes

1) Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during abiraterone acetate treatment.Avoid concomitant strong CYP3A4 inducers during abiraterone acetate treatment. If a strong CYP3A4 inducer must be co-administered, increase the abiraterone acetate dosing frequency.

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

4.3.4 Previous Medication (Drugs and Therapies)

Medication taken within four weeks prior to registration must be captured in the medical record. At each visit, all concomitant treatments, including blood and blood products, must be reported on the source documentation. Concomitant medications must also be documented at the time of discontinuation and at the 30 day follow-up visit.

The dosage and regimen of the following medications and any chronic permitted concomitant medications should be stabilized for 4 weeks prior to Day 1 and held constant throughout the study:

- Bisphosphonates
- Denosumab (or other RANK-ligand inhibitor)
- GnRH agonist/antagonist

No other new systemic therapy or new radiotherapy for treatment of prostate cancer is permitted while subject is on study.

The following medications are prohibited while the subject is on study drug:

- Chemotherapeutic, biologic, or other agents with anti-tumor activity against prostate cancer other than assigned study drug.
- Anti-androgens (steroidal or non-steroidal) such as cyproterone acetate, flutamide, nilutamide, bicalutamide, etc. other than assigned study drug.
- Estrogens, progestational agents such as megestrol, medroxyprogesterone, DES, cyproterone, etc.
- Androgens such as testosterone, dehydroepiandrosterone [DHEA], etc.Ketoconazole.
- Herbal products that may decrease PSA levels (e.g., saw palmetto).

Medications that inhibit platelet function and anticoagulants should be used with caution while the subject is on study drug, including:

- Aspirin or aspirin-containing combinations.
- Clopidogrel, dipyridamole, tirofiban, dipyridamole, epoprostenol, eptifibatide, and cilostazol.
- Abciximab, ticlopidine, cilostazol, warfarin.
- Heparin/low molecular weight heparin [eg, danaparoid, dalteparin, tinzaparin, enoxaparin].
- Use of heparin for flushes of intravenous lines is allowed.

4.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 6 cycles or until one of the following criteria applies:

X Disease progression,

X Intercurrent illness that prevents further administration of treatment,

X Unacceptable adverse events(s),

X Patient decides to withdraw from the study, or

X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.5 Duration of Follow Up

Patients will be followed for 4 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.6 Criteria for removal from Study

To discontinue Study Treatment, any of the criteria below must be met:

- The patient completed 6 cycles of study treatment.
- Sustained side effects: patients who have sustained toxicities, such as hyperglycemia or hypertension that do not return to NCI CTCAE (version 4.03) grade 1 or less with appropriate medical management, should be discontinued from the study treatment phase. All end-of-study treatment procedures should be conducted. The patient will be followed to 4 weeks after the EOS visit.
- Dosing noncompliance: study treatment administration and dosing compliance will be assessed on Day 1 of all cycles and at Pre-surgery/End of Study Visit. A count of study treatment will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not >75% in the absence of toxicity, patient should be re-instructed regarding proper dosing procedures and continue in the protocol. Subsequent dosing compliance procedure will be conducted at each study visit. If a patient misses 14 or more doses within 4 weeks, the patient should be discontinued from the study treatment phase. All end-of-study treatment procedures should be followed. The patient will be followed to 4 weeks after the EOS visit.

- Initiation of new anticancer treatment: patients will be discontinued from the study treatment when investigator, in his or her judgment, determines new treatment for prostate cancer is warranted. All end-of-study treatment procedures should be conducted and the patient will be followed to 4 weeks after the EOS Visit.

Administration of prohibited medications: the patient will be discontinued from the protocol treatment when prohibited drug is administered. All end-of-study treatment procedures should be conducted and the patient will be followed to 4 weeks after the EOS visit. Supportive care medications are permitted with their use following institutional guidelines. The concurrent administration of other anticancer therapy, including cytotoxic, hormonal, or immunotherapy is prohibited during study treatment phase. Use of other investigational drug therapy for any reason is prohibited.

Patient met Grade 4 criteria for elevated Liver Function Tests or the criteria for dose discontinuation of non-mineralocorticoid based side-effects.

Subjects experiencing toxicity considered to be related to the use of prednisone for which a dose reduction is needed, which that would require discontinuation of study drugs.

5.1 DOSING DELAYS/DOSE MODIFICATIONS

In subjects who experience toxicity who cannot be ameliorated by the use of adequate medical intervention, dose reductions can be performed. In these cases dose reductions of abiraterone acetate should be performed first, followed by reduction in apalutamide doses (if needed).

For abiraterone acetate, 2 dose reductions are allowed, though dosing may be interrupted without a dose reduction. Patients who experience a Grade 3 or greater toxicity considered to be related to abiraterone acetate will be dose reduced per the following schema. At each dose reduction, one tablet of abiraterone acetate will be removed, e.g., 4→3 tablets, and 3→2 tablets. Any return to protocol dose level after dose reduction or after treatment interruption must follow documentation of adverse event resolution and a discussion with the Principal Investigator. Dosing with abiraterone may be held for up to 28 days without discontinuation from therapy.

Patients who experience a Grade 3 or greater toxicity considered to be related to apalutamide that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a Grade 2 or lower severity. Patients may subsequently be re-started on study drug at a reduced dose as per the discretion of the Principal Investigator. Dosing with apalutamide may be held for up to 28 days without discontinuation from therapy. Subjects will remain on abiraterone acetate and prednisone during apalutamide dose interruption.

No dose reductions for leuprolide or prednisone are allowed. Subjects experiencing toxicity considered to be related to the use of prednisone for which a dose reduction is needed will require discontinuation of study drugs.

Subjects should be able to take all four study drugs (abiraterone acetate, apalutamide,

leuprolide, and prednisone) to participate in the study. An interruption of one of these drugs is allowed as per instruction above.
Discontinuation of one of these drugs, while continuing the two other drugs, is permitted per investigator's discretion.

Study treatment will be stopped in all patients experiencing grade 4 toxicity which is clinically significant per PI discretion. Patients will be recommended to proceed to planned surgery upon recovery.

5.2 Dose Modification Tables

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

Table 5.1.1 Dose Modifications for Toxicity Attributed to Apalutamide

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

5.1.2 Dose Modifications for Rash

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

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

Severity	Intervention
Grade 1	• Continue apalutamide at current dose • Initiate dermatological treatment[a] o Topical steroid cream AND o Oral Antihistamines • Monitor for change in severity[a]
Grade 2 (or symptomatic Grade 1)[b]	• Hold apalutamide for up to 28 days • Initiate dermatological treatment[a] o Topical steroid cream AND o Oral Antihistamines • Monitor for change in severity[a] o If rash or related symptoms improve, reinitiate apalutamide when rash is Grade≤1. Consider dose reduction at a 1 dose level reduction[c].
Grade ≥3[d]	• Hold apalutamide for up to 28 days • Initiate dermatological treatment[a] o Topical steroid cream AND o Oral Antihistamines AND o Consider short course of oral steroids • Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the subject to a dermatologist o Reinitiate apalutamide at a 1 dose level reduction[c] when rash is Grade≤1. o If the dose reduction will lead to a dose less than 120mg, the study drug must be stopped (discontinued) • If after 28 days, rash has not resolved to Grade≤1, contact study PI.

Note: Rash may be graded differently according to the type of rash and associated symptoms. For example, maculo-papular rash is graded by body surface area covered and not severity of the rash. Please consult NCI-CTCAE Version 4.03 for specific grading criteria for other types of rash.

a Obtain bacterial/viral cultures if infection is suspected
b Subject presents with other rash related symptoms such as pruritus, stinging, or burning
c 1 dose level reduction = 60mg (1 apalutamide tablet)
d If there is blistering or mucosal involvement, stop apalutamide dosing immediately and contact PI
e If a subject previously started oral corticosteroids, continue for at least 1 week after resumption of reduced dose of apalutamide. If the proposed total oral steroid use will exceed 28 days, contact PI.

Table 5.1.3 Dose Modifications for LFT Abnormalities Attributed to Abiraterone Acetate

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

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	No change	No change	No change
Grade 3	Hold until return to baseline or to AST or ALT ≤2.5 x ULN and total bilirubin ≤1.5 x ULN, resume at 750 mg (3 tablets)	Hold until return to baseline	No change
Recurrence Grade 3	Hold until return to baseline or to AST or ALT ≤2.5 x ULN and total bilirubin ≤1.5 x ULN, resume at 500 mg (2 tablets)	Hold until return to baseline	No change
Grade 4	Discontinue AA treatment	Hold until return to baseline	No change or consider tapering if AA discontinued
Concurrent elevation of AST/ALT > 3x ULN with bilirubin >2x ULN (unless the concurrent elevation is related to biliary obstruction or other causes unrelated to study treatment)	Discontinue AA treatment		No change or consider tapering if AA discontinued

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

Table 5.1.4 Dose Modifications for Hypokalemia Attributed to Abiraterone Acetate

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

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	Initiate oral potassium supplementation, titrate to ≥3.5 to ≤5.0 mmol/L, maintenance at ≥4.0 mmol/L recommended	No change	No change
≥Grade 3	Hold and initiate IV potassium and cardiac monitoring	No change	No change or consider tapering if AA is discontinued

Table 5.1.5 Dose Modifications for Hypertension and Edema/Fluid Retention Attributed to Abiraterone Acetate

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

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

6.1 ADVERSE EVENTS

6.2 Adverse Event Monitoring

Adverse events will be evaluated according to the NCI CTCAE Version 4.03 on a continuous basis starting from when the patient takes the first dose of abiraterone acetate or apalutamide to follow up visits. Events, such as abnormal laboratory values, considered by the principal investigator to be not clinically significant (related to the study or study drug) will not be documented. **The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.** If abnormal lab values, which were not pre-existing or which worsened after the first dose of study drug, meet Common Terminology Criteria (CTC) for reporting as adverse events (AE), they will be documented in the AE source document and captured in an institutionally approved database. For the lab results that do not meet the CTC for reporting as an AE, they will be considered not clinically significant (NCS). No additional documentation will be required to neither specify NCS lab results nor require physician investigator signature

6.3 Adverse Events for Apalutamide

In a phase I dose-finding trial of apalutamide, treatment-emergent AEs were reported in 97% of subjects. Related treatment-emergent AEs were reported in 93% of subjects. Serious adverse events (SAEs) were reported in 23% of subjects. 7% of subjects experienced SAEs assessed as treatment-related. Grade 3 AEs were reported in 17% of subjects; no Grade 4 AEs were reported. Adverse events leading to permanent discontinuation of study drug were reported in 10% of subjects. No deaths were reported. Treatment-related AEs observed in >10% of subjects were fatigue (53%), nausea (30%), abdominal pain (20%), diarrhea (17%), arthralgia (13%), dyspnea (13%), hot flush (13%), and peripheral sensory neuropathy (13%).

In Phase II studies, all subjects experienced at least 1 treatment-emergent AEs. Related treatment-emergent AEs were reported in 87% of subjects. Serious adverse events were reported in 27% of subjects; no subject experienced an SAE assessed as retreatment-related. Grade 3 AEs were reported in 34% of subjects; Grade 4 AEs were reported in 3% of subjects. Adverse events leading to permanent discontinuation of study drug were reported in 10% of subjects. Two deaths were reported.

6.4 Adverse Event List(s) for Abiraterone Acetate

- Joint swelling or discomfort
- Muscle aches and fatigue

- Fluid retention
- Hot flashes
- Hypertension
- Diarrhea
- GERD
- Hypokalemia
- Hepatotoxicity
- Acute liver failure/hepatitis which might be fatal
- Allergic alveolitis

Refer to the package insert for a comprehensive list of adverse events.

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

Abiraterone acetate may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. The safety of abiraterone acetate in patients with left ventricular ejection fraction <50% or NYHA Class III or IV heart failure has not been established because these patients were excluded from the randomized clinical trial. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with abiraterone acetate.

Adrenocortical Insufficiency

Adrenocortical insufficiency has been reported in clinical trials in patients receiving abiraterone acetate in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual physiologic stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after physiologically stressful situations.

Hepatotoxicity

Marked increases in liver enzymes leading to drug discontinuation or dosage modification have occurred. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with abiraterone acetate, every two weeks for the first three months of treatment, and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced abiraterone acetate dose, measure

ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5 × upper limit of normal (ULN) or total bilirubin greater than 3.0 × ULN occur in patients with baseline moderate hepatic impairment, discontinue abiraterone acetate and do not re-treat patients with abiraterone acetate.

The safety of abiraterone acetate re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Refer to the package insert for a comprehensive list of adverse events associated with abiraterone acetate.

6.5 *A*dverse Event List(s) for LHRH Agonist/ Antagonist

- Hot flashes, characterized by sudden intense feelings of heat over the face and body, often with sweating.
- Decrease in sexual desire
- Osteopenia and osteoporosis with chronic use
- Headaches
- Pain or local skin reaction at the injection site
- Fluid retention
- Potentially life-threatening blood clots are rare but serious potential AE's
- Allergic reaction

Refer to the package insert for a comprehensive list of adverse events.

6.6 *A*dverse Event List(s) for Prednisone

- Mood changes, rarely severe
- GERD
- Glucose intolerance
- Increased intra-ocular pressure
- Cushing syndrome, immunosuppression, and adrenocortical and pituitary unresponsiveness in times of stress (with prolonged use)

Refer to the package insert for a comprehensive list of adverse events.

6.7 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version

4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov). We will collect data in accordance with phase II trials from the table below.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

6.7 Serious Adverse Event Reporting (SAE) for MD Anderson-Sponsored IND Trials

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or 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 dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy**.**

6.8 Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

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

6.9 Investigator Communications with Janssen Scientific Affairs, LLC

6.9.1 Possible Reports That Janssen Scientific Affairs, LLC May Receive

- Serious Adverse Events Exceptions (See Appendix 2)
- Adverse Events of Special Interest (See Appendix 3)
- Safety data includes adverse events (AE)s
- Product quality complaints (PQC's)
- Special situations including pregnancies
- SAEs
- Non-serious AEs

6.9.2 Transmission Methods

The following methods are acceptable for transmission of safety information to the Janssen Scientific Affairs, LLC:

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

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

7.1 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found starting in Section 6.0.

7.2 Apalutamide

Apalutamide is an immediate-release oral tablet containing 60 mg of Form B drug substance, with a non-functional green film coat.

7.3 Abiraterone

- Abiraterone acetate 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. Abiraterone acetate 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.
- **Food effect:** Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken.

Abiraterone C_{max} and AUC0-∞ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures has not been assessed.

7.4 Handling abiraterone acetate and apalutamide tablets

- These medicines may cause harm to the unborn child if taken by women who are pregnant. They should not be taken by women who are breast-feeding. Women who are pregnant or who may be pregnant should wear gloves if they need to touch abiraterone acetate or apalutamide tablets**.** Study staff and caregivers will be notified of this information, to ensure the appropriate precautions are taken.

7.5 Pharmacy Storage Requirements

- The study treatment must be stored in a secure area and administered only to patients entered into the clinical study in accordance with the conditions specified in this protocol. Bottles of study treatment should be stored at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F) in the original container/closure with the cap on tightly; it should never be refrigerated. Additional information is provided in the abiraterone acetate and apalutamide respective Investigator's Brochure.

7.6 Leuprolide acetate

- Leuprolide acetate 22.5 mg is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as an intramuscular injection to be given once every 3 months

7.7 Prednisone

- Prednisone 5 mg tablets are white to off-white, round tablets debossed with MP51 on one side.

8.0 STUDY CALENDAR

All events have a window of +/- 7 days	**Screening**	**C1D1[c]**	**Day 15 of Cycle 1, 2 & 3**	**Day 1 of Cycles 2,3,5, & 6**	**C4D1**	**Pre-Surgery Visit/End of Treatment**	**Surgery[e]**	**4 Weeks Post-Surgery[j]**
Physical Exam at MD Anderson	X[a]	X		X		X		X
Vital Signs	X[a]	X		X		X		X
Weight	X[a]	X		X				
Height	X[a]							
ECOG PS	X[a]	X		X		X		X
CBC/diff and pit	X[a]	X				X		X
Serum Chemistry	X[a,b]	X[b]		X[b]		X[b]		X[b]
Liver Function Tests (AST, ALT, LDH, ALK-P, total Bilirubin)	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]		X[d]
PT/PTT	X[a]					X		
PSA	X[a]	X		X		X		X
HGB A1C, ACTH	X[a]	X			X	X		X
Serum Testosterone	[a]	X						X
TSH Monitoring	X[a,f]	X[f]		X[f]	X[f]			
Urinalysis	X[a]	X				X		
CT Scan Abd/ CT Scan or MRI Pelvis	X[a]							
Magnetic Resonance Spectroscopy/ MRI of Prostate[K]	X					X		
Prostate Biopsy	X[h]							
Chest X-Ray or CT Chest	X[a]					X		X
MUGA or ECHO	X[a]							

All events have a window of +/- 7 days	**Screening**	**C1D1[c]**	**Day 15 of Cycle 1, 2 & 3**	**Day 1 of Cycles 2, 3, 5, & 6**	**C4D1**	**Pre-Surgery Visit/End of Treatment**	**Surgery[e]**	**4 Weeks Post-Surgery**
Monitor Adverse Events	←	—	—	—	—	—	—	→
Concomitant Medications	←	—	—	—	—	—	—	→
Bone Scan	X[a]							
Blood for Correlative Studies	X[a,i]	X[i]		X[g,i]		X[i]		X[i]
Tissue for Correlative Studies							X[i]	
Archived Tissue for Correlative Studies	X[h]							

a) Within 30 days of registration
b) Serum Chemistry with electrolytes: albumin, calcium, lactate dehydrogenase (LDH), sodium, potassium, chloride, magnesium, carbon dioxide, creatinine, BUN, total protein, Vitamin D 25OH and glucose. At screening and the pre-surgery visit, C4D1 the following will also be done: total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol and triglycerides.
c) If visit occurs within 7 days of screening visit, C1D1 procedures will not be repeated.
d) Liver Function Tests ONLY: AST, ALT, LDH, ALKP and Total Bilirubin. These LFTs may be done at a local physician's office. Results should be faxed to MDACC.
e) Study medication will be continued up to 48 hours prior to surgery
f) Thyroid stimulating hormone (TSH) should be evaluated throughout the study (with T3 and T4 done only if TSH is abnormal).
g) Occurs at cycles 2,3, and 6
h) If previous biopsy has been perform with 3 months of screening, second biopsy procedure will not be required, if archival biopsies and unstained slides are available.
i) Optional Procedure
j) Patients who are free of PSA recurrence at the 4 week post-surgery follow-up will continue to be followed until PSA recurrence, death, or until 6 months after the last patient is enrolled, whichever comes first.

[k]Optional procedure.

Correlative studies will include:

1. Assessment of the steroid hormone metabolome in blood plasma (pretreatment, C3 and C6) and tissue by liquid chromatography tandem mass spectrometry. Measured components will be testosterone, dihydrotestosterone, androstenedione, and pregnenolone.
2. Assessment of steroid signaling components including:
    - Protein and DNA/RNA assessment of canonical and noncanonical androgen signaling including glucocorticoid receptor. Markers of cell cycle angiogenesis and neuroendocrine markers
    - AR copy number by PC pre, during, and post-treatment in the primary tumor microenvironment
3. Assessment of intracellular TCA cycle metabolite concentrations with LCMS/MS assessment of pyruvate and lactate, and assessment of citrate concentration
4. Proportion of patients who achieve pathological CR
5. Cell density in Group A and Group B on prostatectomy
6. Hyperpolarized 1-13C-pyruvate imaging at study entry and at 3 months and 6 months in Arm A and Arm B. MRS data obtained at baseline and at three months will be compared with pyruvate, lactate and citrate concentrations as determined by LCMS/MS in #3 above.

9.0 MEASUREMENT OF EFFECT

Assessment of effect will be assessed by reporting pathologic T and N stage at the time of prostatectomy.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Considerations

The goal of this trial is to estimate clinical efficacy of both treatment arms while also having sufficient patients to achieve secondary and exploratory objectives. At the completion of the original 66 patients, no patients had been able to be measured hyperpolarized 1-13C-pyruvate imaging results due to a delay in approval of the FDA IND for this procedure. In order to accomplish this goal, an additional 20 patients are planned for the revised protocol in March 2019. This is reasonable based on the observed safety and efficacy to date. Among the 34 patients receiving surgery, 15 have achieved the primary endpoint, which is very close to the target improvement. There are no alternative effective treatments for these patients. No patients have died prior to going to surgery.

10.2 Study Design/Endpoints

10.2.1 Primary Endpoint

The primary endpoint is the rate of pathologic stage ≤ pT2N0 at prostatectomy. Patients who do not undergo prostatectomy will be included in this evaluation as not achieving pathologic stage ≤ pT2N0.

10.2.2 Secondary/Exploratory Endpoints

- Tumor epithelium volume in the surgical specimen
- Presence of positive surgical margins in the surgical specimen

- Time to PSA recurrence (TTR_{PSA}) will be measured from the date of randomization until PSA recurrence, death, or date of last follow-up without recurrence.
- Adverse events according to CTCAE (version 4.03) and attribution to study treatment
- Steroid hormone metabolome in blood plasma and tissue by liquid chromatography tandem mass spectrometry
- Protein and RNA analysis results of canonical and non-canonical androgen signaling candidate pathways of resistance to androgen signaling inhibition
- Citrate intracellular TCA cycle metabolite concentrations
- Pathological response
- Hyperpolarized 1-13C-pyruvate imaging results

10.2 Sample Size/Accrual Rate

A previous study of neoadjuvant LHRHa alone in high risk localized prostate cancer as defined in this study demonstrated a rate of pathologic ≤ pT20N0 of 33.3%. Taking this as P_0, we propose a P_1 of 55% for each arm. The original sample size of 33 patients per arm would provide 82% power to detect a documented ≤ pT20N0 of 33% vs. 55% based on a one- sided binomial test with a targeted 5% significance level. The actual significance level for this test is 0.047. Calculations were performed in PASS 2005. We propose the same P_1 in both arms, as there is insufficient data to support the hypothesis that one arm will be superior to the other among these patients. With the increased sample size of 43 patient per arm, we would have nearly 90% power to detect the same difference and 80% power to detect a difference of 33% vs. 52%.

With the March 2019 protocol ammendment eighty-six patients will be enrolled and randomized equally over a 12-18 month period. Our group has extensive experience conducting neoadjuvant trials for prostate cancer with both androgen deprivation therapy and chemotherapy. Furthermore, we have recent experience with conducting trials on intensive androgen deprivation such as the one proposed; a recent pre-operative androgen deprivation trial comparing LHRH agonist plus abiraterone vs LHRH agonist plus abiraterone plus enzalutamide opened in October 2013, accrued 62 patients over the following 14 months, and first results were reported as an abstract at ASCO 2015. A similar timeline is expected with the proposed protocol. The original 66 patients were enrolled between Nov 2017 and January 2019 in just over 14 months. The next 20 are expected to accrue at a similar rate, allowing completion within 4-5 months after re-initiation enrollment.

10.3 Randomization

This is a randomized, parallel, single-stage phase II trial. A total of 86 patients will be randomized via permuted block randomization of random block sizes to Group A (LHRHa + apalutamide) or Group B (LHRHa + apalutamide + abiraterone acetate) in a 1:1 ratio. Randomization will be performed in CORe in collaboration with the trial biostatistician.

- If an arm is stopped for safety reasons as described below, then randomization will stop and the other arm will continue to accrue as a single arm trial.

As all patients will be newly diagnosed with high risk localized prostate cancer, no stratification is proposed.

10.4 Interim Analysis

Monitoring for safety will be implemented separately for each arm based on the method of Thall et al. (1995) using an initial cohort of 6 patients and then continuously thereafter. The first assessment will occur once the first 6 patients have been treated for the first cycle, with continuous monitoring implemented monthly. Calculations were performed in MultcLean 2.1. We will continue enrollment during assessment of each arm so the average number of patients treated will be slightly larger than the calculated operating characteristics, but the overrun expected is only 1-1.5 patients per arm per month.

For trial monitoring and decisions about future trials, extreme toxicities (TOX) will be defined as any adverse event preventing surgery or death from any cause before surgery. A patient who voluntarily leaves the trial for any reason, including toxicity, but is still able to have surgery off protocol will not count as having a TOX. Denote the probability of TOX by θ_T. Our stopping rule is given by the following probability statement: Pr ($\theta_T > 0.20$ | data) >0.95. That is, we will stop the relevant arm of the trial if, at any time during the study, we determine that there is more than an 95% chance that the TOX rate is more than 20% in that arm. TOX rate is estimated with a prior $\theta_T \sim$ beta (1, 1) for the current study. The stopping boundaries for this toxicity rule are to terminate the arm if the number of patients with TOX compared to the number of patients having received treatment exceeds the limits in the table below. Each arm will stop at 33 patients, but if there are 11 or more TOX events by the end, then that combination will be unsafe for future trials at these doses in this patient population. Accrual will not be held during TOX review. Patients who started treatment early enough to complete the first cycle will be included. However, a TOX event may occur later and will be counted at the next monthly monitoring. The operating characteristics are described below.

Stopping Criteria for Excessive TOX for Each Arm

If there are this many (or more) patients with TOX:	3	4	5	6	7	8	9	10	11	12	13
Stop the arm if there are this many (or fewer) evaluable patients:	6	9	13	16	20	24	28	31	35	39	43*

*Always stop with 43 patients, but if 13 or more have TOX, then this combination is

not safe for further investigation in these patients.

The operating characteristics are described in Table 4. Note, that with 0 patients missing surgery due to toxicity or death out of the 66 enrolled (34 with surgery so far) prior to the revision, these operating characteristics are not accounting for the good toxicity profile so far. The probability of stopping early is overestimated and numbers of patients treated may be underestimated.

Table 4. The Operating Characteristics under Varying Toxicity Rates

True Overall Toxicity Rate	Probability of Stopping Early	Average number of patients Treated*	Median (25^{th} %ile, 75^{th} %ile)
0.05	0.003	42.9	43 (43, 43)
0.10	0.02	42.2	43 (43, 43)
0.20	**0.24**	**35.9**	**43 (43, 43)**
0.30	0.70	23.2	20 (6, 43)
0.40	0.96	13.1	8 (6, 16)
0.50	>0.99	8.6	6 (6, 9)

*The average number of patients treated may be slightly higher due to allowing accrual to continue during assessment.

The Investigator is responsible for completing a safety/Efficacy summary report and submitting it to the IND office Medical Affairs and Safety Group for review. This should be submitted after the first 6 evaluable patients per cohort reach 6 months after starting study treatment, and every 10 evaluable patients per arm, thereafter

10.5 Analysis Plan

Patient characteristics will be summarized using descriptive statistics for each arm. For the primary endpoint, we will provide a point estimate and 95% confidence interval of the proportion of patients with pathologic stage ≤ pT2N0 at prostatectomy for each arm.

Secondary and exploratory continuous endpoints will be summarized descriptively and graphically. Comparisons between two the arms or patient subgroups will use a t-test or non-parametric alternative as indicated. Secondary and exploratory categorical endpoints will be summarized using proportions with 95% confidence intervals. Comparisons between the two arms will use a chi-square test or Fisher's exact if indicated. TTR_{PSA} will be summarized by Kaplan-Meier estimates and confidence intervals. Treatment-related adverse events will be summarized according to CTCAE v4.03, and the incidence of SAE and 95% confidence interval will be provided overall as well as for each major affected organ category. We will explore whether subsets of patients will benefit more from one arm than then other with logistic regression for pathologic stage ≤ pT2N0 or Cox regression for TTR_{PSA}.

10.6 Analysis Populations

10.6.1 Toxicity Evaluable

All patients will be evaluable for toxicity from the time of their first treatment with apalutamide, abiraterone or leuprolide.

10.6.2 Response Evaluable

All randomized patients will be included in the primary analysis as part of an intention to treat analysis.

Exploratory analyses will be performed on all patients with available information depending on tissue procurement, especially at diagnostic and 3 month biopsy. The number of patients included in each exploratory analysis will be reported with the results of that analysis.

11.1 ETHICAL ASPECTS

11.2 Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

This data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

Data will be entered into MD Anderson institutionally approved and compliant database(s). The database(s) have secure portal that requires users to login with validated credentials, uses approved encryption protocols as defined by institutional information security standards. Systems have granular data access controls to ensure that the minimal amount of information required to complete a task is presented, can handle de-linking and de-identification of patient information to maintain patient confidentiality if necessary. The system(s) are 21 CFR 11 compliant. Standard data collection, storage procedures, and quality assurance procedures will be followed, to ensure integrity and auditability of all information entered.
All patients will be registered in the University of Texas M. D. Anderson Cancer Center Office of Research Administration database. Registration will occur following informed consent process and prior to initiation of investigational intervention(s). All eligibility criteria must be satisfied.

11.3 Long-Term Retention of Samples for Additional Future Research

Samples will only be used to understand apalutamide or abiraterone acetate, to understand prostate cancer, to understand differential drug responders, and to develop tests/assays related to apalutamide or abiraterone acetate. The research may begin at any time during the study or the post study period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research.

APPENDIX 1

Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death

	hours.		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 2

Serious Adverse Events Exceptions

- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. Hospitalization for a complication of therapy administration will be reported as a serious adverse event.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, sampling for laboratory tests, or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Surgery or procedure planned before entry into the study. Note: Hospitalizations that were planned before the signing of the ICF, 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.
- 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.

APPENDIX 3

Adverse Events of Special Interest

Adverse events of special interest are events that the Janssen Scientific Affairs, LLC 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 or abiraterone acetate.

APPENDIX 4:

PROHIBITED OR RESTRICTED MEDICATIONS OR SUPPLEMENTS WHILE ON STUDY

Medications that are PROHIBITED while on study:

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

Supplements that are RESTRICTED while on study:

- Pomegranate

Medications that are RESTRICTED while on study:

Investigators should refer to the apalutamide Investigator's Brochure and associated addenda for complete details on the drug interaction potential of apalutamide. Highlights of drug interaction are summarized below.

- .
- Medications that inhibit CYP2C8 or CYP3A4: Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl apalutamide). No initial dose adjustment is necessary however, consider reducing the apalutamide dose based on individual tolerability (see Section 6.2). Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.
- Effect of apalutamide on drug metabolizing enzymes: Apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of apalutamide with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of efficacy if medication is continued. Concomitant administration of apalutamide with medications that are substrates of UGT can result in decreased exposure. Use caution if substrates of UGT must be co-administered with apalutamide and evaluate for loss of efficacy.
- Effect of apalutamide on drug transporters: Apalutamide was clinically shown to be a weak inducer of P-gp, BCRP, and OATP1B1. Concomitant use of apalutamide with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure

of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with apalutamide and evaluate for loss of efficacy if medication is continued.

- Abiraterone is a moderate inhibitor of CYP2D6 in humans. Caution is advised when AA is administered with medicinal products activated by or metabolized by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolized by CYP2D6 should be considered.
- Abiraterone is a weak inhibitor of CYP2C8 in humans. When AA is combined with drugs that are predominantly eliminated by CYP2C8, subjects should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with AA.

- Corticosteroids (Oral, IV, or IM): due to possible resistance mechanisms, which may be contributed by glucocorticoid receptor signaling, concurrent use of corticosteroids during the study is not recommended; short term use (≤ 4 weeks) will be allowed if clinically indicated, however, its use must be tapered off as soon as possible.

Additional Information on CYP450 Drug Interactions
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

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