PROTOCOL TRACKING SHEET

VERSION NUMBER	VERSION DATE	REASON FOR CHANGE (high-level)
V6.4	*July 6, 2022*	*Updated statistical plan and sample size.* *Addition of GWU as an accruing site.* *Updated to most recent DCP template.*
V6.5	*September 13, 2022*	*Updated section 15.4 per CIRB review – clarification of statistical plan*
V6.6	*October 5, 2022*	*Updated version number and date due to CIRB required changes.*
V6.7	*February 21, 2023*	*Extended the study follow-up to capture late onset adverse events and added the option of remote consent; updated to DCP protocol template version 12.*
V6.8	*April 4, 2023*	*Updates per DCP consensus review dated 3/9/23.*

COVER PAGE

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Clinical Study of Bioactivity of Low Dose Apalutamide in Prostate Cancer Patients Scheduled for Prostatectomy

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SCHEMA

Clinical Study of Bioactivity of Low Dose Apalutamide in Prostate Cancer Patients Scheduled for Prostatectomy

Men with histologically confirmed organ-confined adenocarcinoma of the prostate scheduled for prostatectomy; Gleason score ≤ (4+4=8) and current serum PSA ≤ 20 ng/ml.

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Visit 1 - Screening/Baseline Visit

Informed consent; medical records release form to obtain the biopsy/prostatectomy tissues, pathology reports and prior PSA test results; medical history; concomitant medications; baseline signs and symptoms; Karnofsky performance status; height; weight; vital signs; blood for clinical labs, PSA, TSH, testosterone, and plasma apalutamide assay (the blood draw for testosterone should occur between 7-10 AM for men < 45 years of age and prior to 2 PM for men ≥ 45 years of age. If the schedule is not feasible, the blood draw may be scheduled for another day); baseline tobacco/alcohol questionnaires, the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) questionnaire, and COVID-19 assessment.

↓

Agent Initiation

The study is expected to have 2 dose groups. Participants in the first dose group will receive apalutamide 60 mg MWF for 4-8 weeks prior to prostatectomy. Based on the PSA response, an additional group of participants will receive de-escalated dose at 60 mg once per week, or escalated dose at 60 mg daily for 4-8 weeks prior to prostatectomy. **For each dosing regimen, the participant will take a loading dose (3 x 60 mg) the first day of agent intervention to reach the steady-state drug levels sooner.** Participants may receive the agent intervention up to 12 weeks if the surgery is delayed.

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Participant Contact

Participants will be contacted during the first week of agent intervention to assess compliance and safety and then every 7-10 days for the duration of the study. Participants will be contacted prior to Visit 2 to remind them of the upcoming appointment and to hold that day's dose of study agent until after their blood draw.

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Visit 2 – End-of-Intervention Visit

(within 3 days prior to surgery)

Blood draw for clinical labs, PSA, TSH, and testosterone, and plasma apalutamide assay (the blood draw for testosterone should occur between 7-10 AM for men < 45 years of age and prior to 2 PM for men ≥ 45 years of age); concomitant medications (conmeds) and adverse events (AEs) evaluation; agent compliance assessment; follow-up tobacco/alcohol questionnaires; EPIC-CP questionnaire; COVID-19 assessment; collect study agent, AE diary, and agent intake calendar if this visit occurs the day before surgery. Collection of new AEs and concomitant medications ends with the operative day.

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Visit 3 - Post-intervention Follow-up Visit

(7-14 days post-prostatectomy and may be combined with the postoperative appointment for catheter removal)

Blood draw to assess testosterone levels (should occur between 7-10 AM for men < 45 years of age and prior to 2 PM for men ≥ 45 years of age); collect study agent, AE diary, and agent intake calendar if not done at the End-of-Intervention visit. Request paraffin-embedded pre-intervention biopsy and prostatectomy tissue blocks or slides from respective pathology labs.

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Extended Post-intervention Follow-up

(60 (± 5) days post-prostatectomy)

Participants will be contacted by their preferred method(s) to capture late onset adverse events.

Endpoints

Primary endpoint: effects of low dose apalutamide on circulating PSA levels.
Secondary endpoints: reversibility of testosterone levels 7-14 days post-intervention (post-operative), post-intervention plasma trough apalutamide concentrations, health-related quality of life (HRQOL).
Exploratory endpoints: intra-prostatic immune cell infiltration, change in Gleason score, tobacco/alcohol use on study endpoints.

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1. OBJECTIVES

1.1 Primary Objectives

The primary objective is to determine the effects of low dose apalutamide on circulating levels of Prostate Specific Antigen (PSA).

1.2 Secondary Objectives

The secondary objectives, in the order of priority, are to determine the effect of low dose apalutamide on

- Reversibility of testosterone levels 7-14 days post intervention
- Post-intervention plasma trough apalutamide concentration
- Health-related quality of life.

1.3 Exploratory Objectives

The exploratory objectives are to determine the effects of apalutamide on intra-prostatic immune cell infiltration and Gleason score and the effects of tobacco/alcohol use on the study endpoints.

2. BACKGROUND

2.1 Prostate Cancer

Clinically localized prostate cancer is managed primarily through surgery or radiation therapy. Population studies suggest that a substantial proportion of men diagnosed with localized prostate cancer in the US are over-treated [1-3]. This public health problem—unnecessarily aggressive treatment of tens of thousands of men each year who subsequently suffer chronic side effects—challenges us to develop innovative therapeutic models to refine treatment paradigms within this patient population. In recent years, active surveillance has increasingly garnered attention as an alternative, and less morbid, approach to surgery or radiation in men with clinically localized, low-risk prostate cancer. Follow-up assessments in patients on active surveillance include serial PSA measures, repeat prostate biopsy and, increasingly, prostate MRI. Most men on active surveillance followed for up to 15 years will not require treatment. However, up to one-third of active surveillance patients will undergo treatment within 2 to 5 years of initiating surveillance [4].

Development of intervention strategies to prevent disease progression in patients on active surveillance thus represents an important area of prostate cancer chemoprevention.

2.2 Apalutamide

The androgen receptor (AR) signaling axis plays a critical role in the development, function and homeostasis of the prostate [5]. The classical action of AR is to regulate gene transcriptional processes via AR nuclear translocation, binding to androgen response elements on target genes and recruitment of, or crosstalk with, transcription factors. Prostate cancer initiation and progression is also uniquely dependent on AR.

Due to the critical role of AR signaling in the pathophysiology of prostate cancer, treating patients on active surveillance with an AR inhibitor may be a potential approach to prevent disease progression. However, the first-generation of AR antagonists such as flutamide, bicalutamide, and nilutamide and the next generation AR inhibitors such as enzalutamide have various adverse effects that preclude extended use in prevention settings.

Apalutamide is a second-generation AR inhibitor approved for non-metastatic castrate-resistant prostate

cancer (nmCRPC) and for metastatic castration-sensitive prostate cancer in 2018 and 2019, respectively. Apalutamide binds AR in the same ligand-binding domain as bicalutamide but with greater affinity [6]. Unlike bicalutamide, it retains full antagonist activity in the setting of AR overexpression. Furthermore, apalutamide was shown to be selective for AR versus other nuclear hormone receptors [6]. In mouse xenograft tumor models of LNCaP/AR(cs) cells that overexpressed AR, apalutamide was more efficacious than bicalutamide and enzalutamide [7]. When assessed in mice, the tumor/plasma ratios of apalutamide were significantly higher than tumor/plasma ratios of enzalutamide, possibly due to lower plasma protein binding of apalutamide, allowing for more tissue distribution [6]. Both apalutamide and enzalutamide are weak antagonists of γ-aminobutyric acid receptors in the brain, which is thought to contribute to enzalutamide-associated seizure. However, the penetration through the blood-brain barrier appears to be different between the two agents as the brain concentrations of apalutamide was lower than that of enzalutamide [6].

A Phase I study of apalutamide was conducted in 30 patients with progressive mCRPC over the dose range of 30 to 480 mg daily [8]. Apalutamide was found to be well tolerated and displayed linear pharmacokinetics. No seizures were reported at any dose level. Reduction of uptake of fluoro-5α dihydrotestosterone (FDHT) on positron emitted tomography (PET) consistent with saturation of AR binding was observed at doses ≥ 120 mg. Across all dose cohorts, ≥ 50% deduction in PSA at 12 weeks was observed in 14 of 30 patients, suggesting substantial clinical activity. A maximum efficacious dose of 240 mg daily was selected for Phase II trials based on integration of preclinical and clinical data.

Phase II trials of apalutamide have been conducted in three expansion cohorts: patients with nmCRPC, patients with mCRPC who were abiraterone-naïve and patients with mCRPC following treatment with abiraterone. In the nmCRPC cohort, apalutamide was well tolerated with fatigue as the most common AE. The median treatment duration was 26.9 months, with 89% of patients experiencing a ≥ 50% deduction in PSA at 12 weeks. The median time to PSA progression was 24 months [9]. The two cohorts of men with mCRPC, the 12-week PSA response rate (at least 50% decline from baseline) was 88% for abiraterone naïve patients and 22% for post-abiraterone patients. The median time to PSA progression was 18.2 months for abiraterone-naïve patients and only 3.7 months for post-abiraterone patients. The median duration of apalutamide treatment was 21 months for abiraterone naïve and 4.9 months in the post-abiraterone cohort. The safety profile in these two cohorts was consistent with previously reported data [10].

A Phase III trial of apalutamide in patients with nmCRPC showed that apalutamide significantly improved metastasis-free survival compared to placebo (40.5 months versus 16.2 months). Secondary endpoint of time to symptomatic progression was also significantly longer with apalutamide than with placebo. There was a PSA response for 89.7% of subjects on apalutamide vs. only 2.2% of subjects in placebo. The frequency of Aes grade 3 or above was 45.1% in the apalutamide group and 34.2% in the placebo group. Only 0.2% (two patients total) treated with apalutamide had a documented seizure, both in patients with predisposing conditions [11]. In a Phase III trial involving patients with metastatic, castration-sensitive prostate cancer, the addition of apalutamide to androgen deprivation therapy (ADT) significantly improved overall survival and radiographic progression-free survival than with placebo plus ADT. The frequency of Aes grade 3 or above was 42% in the apalutamide group and 40.8% in placebo, with rash more common with apalutamide treatment [12].

Due to the promising clinical efficacy and improved therapeutic index of apalutamide, NCI, Division of Cancer Prevention conducted preclinical studies to assess its prostate cancer preventive activity. The preclinical studies were conducted in the Bosland tumor model with tumors induced in male rats by sequential administration of antiandrogen (flutamide), androgen (testosterone propionate), and the chemical carcinogen N-methyl-N-nitrosourea (MNU), followed by chronic androgen stimulation [13].

Beginning 1 week after MNU administration, animals received apalutamide or vehicle via oral gavage at different dosing regimens. Results showed that apalutamide is a highly potent inhibitor of prostate cancer. In the vehicle control, the incidence of invasive cancers in the dorsolateral/anterior prostate and all accessory sex cancers combined was 47% and 53%, respectively. Cancer incidence in the accessory sex glands was 0% in rats receiving either apalutamide at 30 mg/kg/day or 15 mg/kg/day. Intermittent (1 week on/1 week off) apalutamide at 30 mg/kg/day was also effective in preventing accessory sex gland cancers (10% incidence) and cancers confined to the dorsolateral/anterior prostate (3% incidence) but not as effective as the continuous daily exposure. Apalutamide was well tolerated at all dose levels (1-30 mg/kg/day). No mortality was seen in any group. Optimal pharmacodynamic activity evidenced by a dose-dependent down-regulation of androgen-dependent genes in the dorsolateral prostate was observed at the doses of 15 and 30 mg/kg/day (unpublished results from agent solicitation summary).

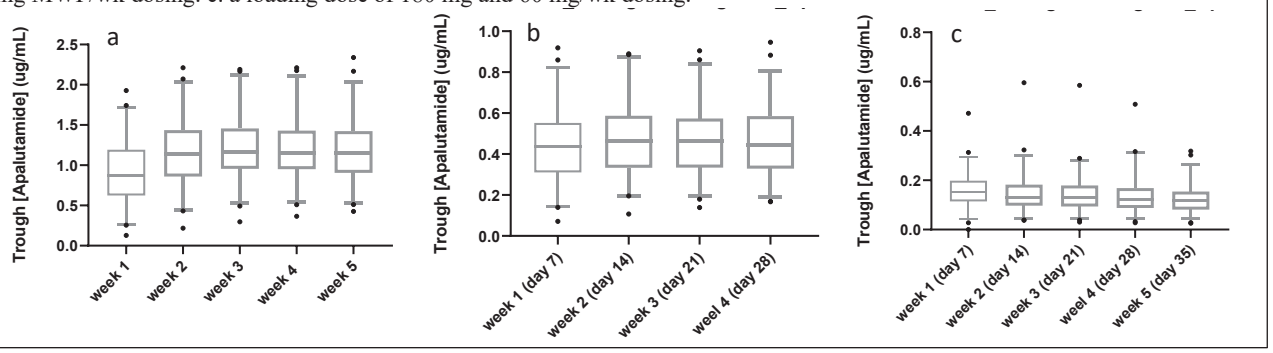
The clinical pharmacokinetics of apalutamide have been studied over the dose range of 30 to 480 mg/day (0.125 – 2 times the recommended dose) in the Phase I study [8]. Apalutamide was rapidly absorbed with peak plasma concentrations occurred 2 to 3 hours after administration. Maximum plasma concentration and area under the plasma concentration-time curve (AUC) increased proportionally over the dose range studied. Plasma concentrations declined slowly following dosing with a mean half-life of 3 to 4 days. Drug half-life and time to steady-state were independent of dose. Plasma trough concentration increased steadily with time and in proportion to dose. Most patients reached steady-state exposure after 3 weeks of continuous administration with the mean accumulation ratio of 5-fold.

2.3 Rationale

The promising biological and clinical activity of apalutamide and its improved safety profile established a rationale to test this agent for prevention of progression in the active surveillance setting. In addition, the long half-life of this drug offers the potential of utilizing an intermittent dosing schedule to further minimize its associated side effects. We propose to conduct an open label trial of low dose apalutamide in the pre-surgical setting to determine an optimal dosing regimen for further study in men on active surveillance. We hypothesize that low dose apalutamide will be tolerable and lead to favorable pharmacodynamic changes in men with localized, low/intermediate risk prostate cancer.

The primary objective of this study is to determine the effects of low dose apalutamide on circulating PSA levels. In prior Phase II-III trials in patients with nmCRPC and mCRCP, apalutamide administered at 240 mg daily was effective in suppressing circulating PSA levels with greater than 89% of patients experiencing a 12-week PSA response (at least 50% decline from baseline) [10, 11]. This study will determine whether low dose apalutamide will lead to lowered PSA levels in patients with low and intermediate risk prostate cancer.

Figure 1. Plasma trough levels over time. a. a loading dose of 180 mg and 60 mg QD dosing. b. a loading dose of 180 mg and 60 mg MWF/wk dosing. c. a loading dose of 180 mg and 60 mg/wk dosing.



Patients with Gleason score 8 are included because we expect the PSA response (and the response of other study endpoints) to low dose apalutamide to be similar to patients with Gleason score 6 and 7. However, any Gleason pattern 5 is an exclusion. The prior Phase I study in patients with castration-resistant prostate cancer showed that apalutamide taken at 60 mg per day resulted in steady-state plasma trough apalutamide concentrations similar to plasma concentrations observed at a dose level that led to tumor growth inhibition in the murine model of castration-resistant prostate cancer [8]. We have, therefore, selected to study the 60 mg dose at different dosing schedules up to 60 mg per day. Due to the anticipated short intervention period (4-8 weeks, depending on the surgery schedule), pharmacokinetic simulations were performed to select optimal loading dose to reach steady-state drug levels sooner to increase the likelihood of observing the drug effects. Figure 1 illustrates the plasma trough levels over time with a loading dose of 180 mg for three maintenance dosing schedules (data generated by Dr. Cody Peer, NCI Clinical Pharmacology Program). A loading dose of 180 mg for the 60 mg once a day dosing schedule will reach steady-state levels at the end of 2 weeks. Similar time to steady-state is achieved with a loading dose of 180 mg for the 60 mg q M-W-F dosing schedule. A loading dose of 180 mg for the 60 mg once a week dosing schedule will allow the target level to be achieved and maintained after the first dose.

A recently completed trial of enzalutamide in prostate cancer patients with biochemical recurrence showed that elevated testosterone levels with enzalutamide treatment decline rapidly following discontinuation of enzalutamide (personal communication provided by NCI, DCP). This study will assess the reversibility of circulating testosterone levels after low dose apalutamide. We also plan to assess the plasma trough apalutamide levels and to determine whether the systemic drug levels correlate with the PSA response.

Suppression of androgen signaling has been reported to lead to immune-stimulatory effects (reviewed in [14]). Clinical studies have shown that androgen deprivation therapy (ADT) induces expansion of naïve T cells and increases T-cell responses in peripheral blood mononuclear cells [15]. ADT is also associated with infiltration of T-cells, macrophages, and nature killer cells into the prostate [16-18]. Prior preclinical studies demonstrated that ADT enhances susceptibility of AR-overexpressing prostate cancer cells to immune-mediated T-cell killing through improved immune recognition [19, 20]. Emerging clinical data also reveals that ADT could enhance the efficacy of various immunotherapies [21-23]. A number of ongoing trials are evaluating the combination of ADT and/or inhibitors of androgen receptor or androgen synthesis with different immunotherapies. This study offers the opportunities to determine whether low dose apalutamide will lead to changes in intra-prostatic immune cell infiltration.

Furthermore, this study will determine the effects of low dose apalutamide on health-related quality of life. This information will help inform the feasibility of implementing low dose apalutamide in patients undergoing active surveillance.

In addition, the study will explore the effects of apalutamide on Gleason score of pre- and post-intervention tumor(s) with matched location. It is expected that such materials will only be available in a subgroup of participants where pathology review can be performed on *ex vivo* prostate tissue sample collected at prostatectomy from the tumor(s) that MRI directed biopsies were collected prior to enrollment.

Increasing evidence suggests that tobacco and alcohol use are risk factors in the development of intraepithelial neoplasia and cancer. In addition, tobacco and alcohol use may adversely affect agent intervention, for example by altering the safety profile or metabolism of a drug. Standardized assessments of tobacco and alcohol use during clinical trials will aid in understanding the potential relationship between the use of these products and clinical endpoints or cancer prevention biomarkers. Therefore,

NCI, DCP is including assessment of tobacco and alcohol use at baseline and post-intervention, to determine the potential impact of tobacco and alcohol use on 1) treatment toxicity and symptom burden, and 2) the efficacy of treatment intervention.

The NCI, DCP Assessment of COVID-19 exposure and vaccine status at baseline and end of study will be used to determine the potential impact on 1) treatment toxicity and symptom burden, and 2) the efficacy of treatment intervention.

3. SUMMARY OF STUDY PLAN

We propose a Phase IIa open label dose-finding trial of low dose apalutamide in prostate cancer patients scheduled to undergo radical prostatectomy. The study is expected to include 2 dose groups. Up to twenty eligible participants will be accrued into each dose group to initiate agent intervention. We anticipate accruing 1 participant every two months until all sites are activated. Once all sites are activated, we anticipate accruing 1-2 participants every month, we expect to complete the accrual of each dose cohort in 20 months. We plan to recruit men over the age of 18 with good performance status and normal renal, hepatic, marrow, and thyroid function. Eligibility disease characteristics include histologically confirmed organ-confined adenocarcinoma of the prostate (Pca), Gleason score ≤ (4+4) and current serum PSA ≤ 20 ng/ml.

The exclusion criteria include prior or ongoing hormonal treatment for prostate; prostate cancer with distant metastases; presence of neuroendocrine differentiation; serum testosterone < 200 ng/dL; a history of prior malignancies other than prostate cancer within the past 2 years, excluding non-melanoma skin cancer; 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 registration; history of seizure or known condition that may pre-dispose to seizure; use of drugs known to lower the seizure threshold; receiving any other investigational agents; history of allergic reactions attributed to compounds of similar chemical composition of apalutamide; and uncontrolled intermittent illnesses or medical conditions which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

Accrued participants in the first dose group will receive apalutamide 60 mg MWF/week for 4-8 weeks prior to prostatectomy. Participants may receive the agent intervention up to 12 weeks if the surgery is delayed. Based on the PSA response, an additional cohort of participants will receive a de-escalated dosing regimen at 60 mg once per week, or an escalated dosing regimen at 60 mg daily for 4-8 weeks prior to prostatectomy. To improve the efficiency of trial conduct, a continuous monitoring plan will be used for efficacy/futility evaluation after 12 participants have completed the dosing regimen and the dose cohort will be stopped early for efficacy or futility. For each dosing regimen, the participant will take a loading dose (3 x 60 mg) on the first day of agent intervention to reach the steady-state drug levels sooner.

The agent intervention is not meant to delay the curative surgery. Only patients whose surgery is planned to allow for a minimum of 4 weeks and up to 12 weeks of agent intervention will be enrolled. The intervention duration will be adjusted depending on the planned surgery schedule.

At the screening/baseline visit, the informed consent form and medical records release form will be signed in order to obtain the biopsy/prostatectomy tissues, pathology reports and prior PSA test results. Participants will be evaluated for height, weight and vital signs (temperature, pulse, and blood pressure), concomitant medications, medical history and baseline symptoms and signs. Baseline blood samples will

be collected for CBC-diff, CMP, PSA, TSH, testosterone, and plasma apalutamide assay. The blood draw for testosterone should occur between 7-10 AM for men < 45 years of age and prior to 2 PM for men ≥ 45 years of age because of circadian variation in testosterone levels [33]. If the schedule is not feasible, the blood draw may be scheduled for another day. Aliquots of plasma will be stored for plasma apalutamide assay. Participants will also complete baseline tobacco/alcohol questionnaires and the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) questionnaire, and COVID-19 assessment. Subjects will be instructed in how to complete the Intake Calendar and Adverse Event Diary.

When eligibility is confirmed from lab results, participants will be provided with the study drug in amount sufficient for the entire study duration based on the surgery schedule and the assigned dosing regimen plus an extra week of agent supply.

Participants will return to the clinic within 3 days prior to surgery for a post-intervention blood draw for CBC-diff, CMP, PSA, TSH, testosterone, and research endpoints. Similarly, the blood draw for testosterone should occur between 7-10 AM for men < 45 years of age and prior to 2 PM for men ≥ 45 years of age. Adverse events, concomitant medications and agent compliance will be assessed. Participants will complete the follow-up tobacco/alcohol questionnaires and EPIC-CP questionnaire, and COVID-19 assessment. In order to assess the plasma trough apalutamide levels, participants will be asked to hold the apalutamide dose on the day of the visit until after the blood draw.

A blood sample will be collected 7-14 days post-prostatectomy to assess reversibility of circulating testosterone levels and plasma apalutamide levels. Blood draw for testosterone should occur between 7-10 AM for men < 45 years of age and prior to 2 PM for men ≥ 45 years. This visit may be combined with the postoperative appointment for catheter removal.

Participants will be contacted 60 days (± 5 days) post-prostatectomy by their preferred method of contact to capture any late onset adverse events, excluding adverse events that are related to prostatectomy.

At the discretion of the treating urologist, a testosterone test may be repeated at the 3-month post-surgery standard-of-care visit if the testosterone levels remained elevated at Visit 3. The testosterone results will be captured through a chart review if this was repeated at the 3-month post-op visit.

Paraffin-embedded pre-intervention biopsy and prostatectomy tissue blocks or slides will be requested from respective pathology labs for measurement of secondary tissue biomarkers.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Histologically confirmed organ-confined adenocarcinoma of the prostate (Pca) suitable for prostatectomy.

4.1.2 Gleason score ≤ (4+4), however no Gleason pattern 5.

4.1.3 Current serum PSA ≤ 20 ng/ml.

4.1.4 Age >18 years.

4.1.5 Karnofsky ≥70%; see Appendix A

4.1.6 Participants must meet the following laboratory measures:

- Leukocytes ≥3,000/μL
- Absolute neutrophil count ≥1,500/μL
- Platelets ≥100,000/μL
- Total bilirubin ≤1.5 x institutional upper limit of normal (ULN) ((note: in subjects with Gilbert's syndrome, if total bilirubin is > 1.5 x ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤ 1.5 x ULN, subject may be eligible)
- AST (SGOT)/ALT (SGPT) <2.5 x institutional ULN
- Creatinine <2 x institutional ULN

4.1.7 TSH within the institutional normal range.

4.1.8 Willing to use adequate contraception (barrier method; abstinence; subject has had a vasectomy; or partner is using effective birth control or is postmenopausal) for the duration of study participation.

4.1.9 Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

4.2.1 Prior or ongoing hormonal treatment for prostate cancer including, but not limited to orchiectomy, antiandrogens, abiraterone, ketoconazole, or estrogens, or luteinizing hormone-releasing hormone (LHRH) agonists/antagonists. Men on stable doses of 5-alpha reductase inhibitors (e.g., finasteride, dutasteride) are eligible as long as there is no planned dose change while on study.

4.2.2 Patients who have prostate cancer with distant metastases.

4.2.3 Presence of neuroendocrine differentiation in the prostate biopsies.

4.2.4 Serum testosterone (blood collected between 7-10 AM for men < 45 years of age and prior to 2 PM for men ≥ 45 years of age) < 200 ng/dL.

4.2.5 Have a history of prior malignancies other than prostate cancer within the past 2 years, excluding non-melanoma skin cancer.

4.2.6 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 registration.

4.2.7 History of seizure or known 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 registration, brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect).

4.2.8 Use of drugs known to lower the seizure threshold, including: atypical antipsychotics (e.g. clozapine, olanzapine, risperidone, ziprasidone), bupropion, lithium, meperidine, pethidine, phenothiazine antipsychotics (e.g. chlorpromazine, mesoridazine, thioridazine), and tricyclic antidepressants (e.g. amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine).

4.2.9 Concurrent use of drugs in category X drug interactions with apalutamide (see list in Appendix E).

4.2.10 Participants may not be receiving any other investigational agents.

4.2.11 History of allergic reactions attributed to compounds of similar chemical composition of apalutamide.

4.2.12 Uncontrolled intermittent illnesses or medical conditions which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient. Such illnesses/conditions may include, but are not limited to, hypertension, ongoing or active infection, or psychiatric illness/social situations.

4.3 Inclusion of Women and Minorities

Men of all races and ethnic groups are eligible for this trial. Since women and children are not subject to prostate cancer, they will be excluded from this study.

4.4 Recruitment

Study participants will be recruited from patients seen in the urology clinics at Johns Hopkins University, University of Southern California, George Washington University, NCI Clinical Center for Cancer Research, and University of Arizona (Banner/University Medicine).

Depending on the clinic workflow, one or all of the following recruitment strategies will be implemented:
1. Study investigators (urologic surgeons) and/or their clinic staff will have access to identifiable health information of patients seen in the urology clinics. They will screen patients for their potential eligibility. The investigators and/or their clinic staff will present the study to potentially eligible patients to assess interests in study participation.
2. Urologic surgeons and/or their clinic staff will make the initial contact (oral or written communication) with patients seen in the urologic clinics to assess their interests in being contacted by the research staff for a research study. The names of those who are willing to be contacted will be forwarded to the research staff. The research staff will contact these patients to further describe the study and to assess interests and potential eligibility in study participation.
3. A study information letter will be developed along with the option of allowing the research staff to review their identifiable health information to assess their potential eligibility for the study and to contact them if they were found potentially eligible. The research staff will contact patients who opt in for contact and chart review and are potentially eligible to further describe the study and to assess interests in study participation.

Although this intervention is relatively brief, study personnel will be sensitive to the stress participants will likely experience in preparing for a major surgical procedure. The study team is committed to providing a friendly and comfortable study setting for participants from initial contact through the completion of their study activities. Demands upon the subjects will be minimized to foster comfort while preserving the research goals. Wherever possible, flexibility will be built into the study schedule to promote compliance and acknowledge the dependence upon surgical and hospitalization schedules.

4.5 Planned Accrual

Racial Categories	Not Hispanic or Latino: Female	Not Hispanic or Latino: Male	Hispanic or Latino: Female	Hispanic or Latino: Male	Total
American Indian/Alaska Native	-	1	-	0	1
Asian	-	3	-	0	3
Native Hawaiian or Other Pacific Islander	-	1	-	0	1
Black or African American	-	5	-	1	6
White	-	22	-	4	26
More Than One Race	-	2	-	1	3
Total	-	34	-	6	40

1. REGISTRATION PROCEDURES

5.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually which is done via the Registration and Credential Repository (RCR).

To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Rave or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR (Investigator)	NPIVR (Non-physician Investigator)	AP (Associate Plus)	A (Associate)	AB (Associate Basic)
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to participate in all CP-CTNet clinical trials.

All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be registered in the RCR.

Personnel associated with the five registration types include, but is not limited to, the following:

- **Investigator (IVR)** — MD, DO, or international equivalent
- **Non-Physician Investigator (NPIVR)** — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD)
- **Associate Plus (AP)** — clinical site staff (e.g., RN or CRA) with data entry access to RAVE. Also includes site administrator, data administrator, and consenting person. Individuals with an auditing role should register as an AP.
- **Associate (A)** — other clinical site staff involved in the conduct of NCI-sponsored trials.
- **Associate Basic (AB)** — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems

In addition, the site-protocol Principal Investigator (PI) must meet the following criterion:
- Active registration status
- The IRB number of the CIRB (IRB of record) listed on their Form FDA 1572

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

6. NCI CENTRAL INSTITUTIONAL REVIEW BOARD

The NIH policy on the Use of a Single Institutional Review Board for Multi-Site Research https://grants.nih.gov/grants/guide/notice-files/not-od-16-094.html became effective on January 25, 2018. In compliance with this policy, NCI Central IRB (NCI CIRB) is the sole IRB of record for all accruing sites conducting clinical trials through the CP-CTNet, all CP-CTNet U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB), and utilize the Cancer Prevention and Control CIRB as their IRB of record. International sites should submit Research Ethics Board (REB) approval to the DCP Regulatory contractor following country-specific regulations.

Signatory Institutions must submit a Study Specific Worksheet (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the Principal Investigators at the Signatory Institution and the Regulatory Contractor. In order for the SSW approval to be processed, the Signatory Institution must inform which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the CIRB prior to implementation.

7. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 8.2.

7.1 Dose Regimen and Dose Groups

The study is expected to have 2 dose groups. For each dosing regimen, participants will take three 60 mg tablets (the loading dose) on the first day of agent intervention. Participants in the first dose group will receive apalutamide 60 mg MWF/wk for 4-8 weeks prior to prostatectomy. Based on the PSA response, an additional group of participants will receive de-escalated dose at 60 mg once per week, or escalated dose at 60 mg daily for 4-8 weeks prior to prostatectomy. Participants may receive the agent intervention up to 12 weeks if the surgery is delayed. The agent intervention is not meant to delay the curative surgery. Only patients whose surgery is planned to allow for a minimum of 4 weeks and up to 12 weeks of agent intervention will be enrolled. The intervention duration will be adjusted depending on the planned surgery schedule.

7.2 Apalutamide Administration

- Participant will self-administer the study agent.
- Depending on the dose group, participants will take one 60 mg tablet once a day, one 60 mg tablet three times a week (Monday, Wednesday, Friday), or one 60 mg tablet once a week.
- **For each dosing regimen, participants will take three 60 mg tablets (the loading dose) on the first day of agent intervention.**
- Participants will be instructed to take the dose in the morning with or without food.

7.3 Run-in Procedures

Not applicable.

7.4 Contraindications

None.

7.5 Concomitant Medications

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of apalutamide and its active metabolite, N-desmethyl-apalutamide) No initial dose adjustment is necessary, however, reduce the dose based on tolerability.

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 activity if medication is continued. Concomitant administration of apalutamide with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with apalutamide and evaluate for loss of activity.

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate). 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 activity if medication is continued.

Participants will be excluded if they are using drugs known to lower the seizure threshold, including: atypical antipsychotics (e.g. clozapine, olanzapine, risperidone, ziprasidone), bupropion, lithium, meperidine, pethidine, phenothiazine antipsychotics (e.g. chlorpromazine, mesoridazine, thioridazine), and tricyclic antidepressants (e.g. amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine).

Participants will also be excluded if they are using drugs in category X drug interactions with apalutamide (see list in Appendix E).

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include: 1) start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g.*, biopsy) should also be included.

7.6 Dose Modification

No dose modification will be made for Grade 1 adverse events.

For Grade 2 adverse events definitely, probably, or possibly related to study agent persisting for more than 3 days, the agent dose will be held until toxicity is resolved to Grade 1 or less.

Participants with Grade 3 or 4 events that are definitely, probably, or possibly related to the study agent will receive no further doses and be followed for resolution of adverse events. If appropriate, they should remain on-study and undergo the prostatectomy.

For adverse events not considered related to study agent, the agent intervention may be continued or omitted at the discretion of the study physician.

7.7 Adherence/Compliance

7.7.1 Participants will be considered compliant for secondary "per protocol" statistical analysis if they have taken ≥ 80% of their assigned study doses based on pill count.

7.7.2 The primary measure of medication compliance is based on pill count and supplemented with the Intake Calendar. The secondary measure of compliance will be determination of plasma apalutamide levels.

8. PHARMACEUTICAL INFORMATION

8.1 Apalutamide (IND # [redacted] IND Sponsor NCI, Division of Cancer Prevention)

Apalutamide, also known as ARN-509, is a second-generation androgen receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR to inhibit nuclear translocation, DNA binding, and transcription [6]. The drug retains full antagonist activity in the setting of AR overexpression and is selective for AR vs. other nuclear hormone receptors [24]. In mouse xenograft models of prostate cancer, apalutamide administration decreased tumor cell proliferation and increased apoptosis, leading to decreased tumor volume [6]. Apalutamide, marketed under the brand name Erleada®, was approved by FDA for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) and metastatic castration-sensitive prostate cancer (mCSPC) [12, 25].

- The drug product, Erleada®, is supplied as film-coated tablets for oral administration containing 60 mg of apalutamide drug substance. Inactive ingredients of the core tablet are colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl methylcellulose-acetate succinate, magnesium stearate, microcrystalline cellulose, and silicified microcrystalline cellulose. The tablets are finished with a commercially available film coating comprising the following excipients: iron oxide black, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The recommended dose of apalutamide for the treatment of prostate cancer is 240 mg (four 60 mg tablets) administered orally once daily [26].

8.2 Reported Adverse Events and Potential Risks

The safety and efficacy of apalutamide have been established in phase 3 clinical trials enrolling patients with mCSPC (*Targeted Investigational Treatment Analysis of Novel Anti-androgen* [TITAN] study NCT02489318) and nmCRPC (*Selective Prostate Androgen Receptor Targeting with ARN-509* [SPARTAN] study NCT01946204).

The adverse events observed in each of the two trials are summarized below. Please refer to the package insert for more details [34].

TITAN study: This is a randomized, double-blind, placebo-controlled, multi-center clinical study, enrolling patients with mCSPC. Patients received either Erleada® at a dose of 240 mg daily or placebo. All study participants received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. The median duration of exposure was 20 months (range: 0–34 months) in patients who received Erleada® and 18 months (range: 0.1–34 months) in patients who received placebo. Ten patients (2%) who were treated with Erleada® died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). Erleada® was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of Erleada® occurred in 23% of patients; the most frequent (>1%) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of Erleada®-treated patients and in 20% of patients receiving placebo.

Additional adverse reactions of interest occurring in 2% but less than 10% of patients treated with Erleada® included diarrhea (9% vs. 6% on placebo), muscle spasm (3% vs. 2% on placebo), dysgeusia (3% vs. 1% on placebo), and hypothyroidism (4% vs. 1% on placebo).

SPARTAN study: This is a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolling patients with nmCRPC. Patients received either Erleada® at a dose of 240 mg daily or placebo. All patients received a concomitant GnRH analog or had a bilateral orchiectomy. The median duration of exposure was 16.9 months (range: 0.1–42 months) in patients who received Erleada® and 11.2 months (range: 0.1–37 months) in patients who received placebo. Eight patients (1%) who were treated with Erleada® died from adverse reactions. The reasons for death were infection (n=4), myocardial infarction (n=3), and cerebral hemorrhage (n=1). One patient (0.3%) treated with placebo died from an adverse reaction of cardiopulmonary arrest (n=1). Erleada® was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of Erleada® occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of Erleada®-treated patients and in 23% of patients receiving placebo. The most frequent serious adverse reactions (>2%) were fracture (3%) in the Erleada® arm and urinary retention (4%) in the placebo arm. Additional clinically significant adverse reactions occurring in 2% or more of patients treated with

Erleada® included hypothyroidism (8.1% vs. 2% on placebo), pruritus (6.2% vs. 2% on placebo), and heart failure (2.2% vs. 1% on placebo).

There were reversible breast changes in a small minority of participants in this study on the three time a week regimen. These participants reported enlargement of one or both breasts 1-2 months after stopping the study drug. The breast swelling resolved after 3-4 months of follow-up without any treatment.

8.3 Availability

Apalutamide is manufactured by the Janssen Pharmaceutical Companies of Johnson & Johnson, and will be purchased by the research pharmacy at each study institution.

8.4 Agent Distribution

The institutional research pharmacy will repackage the pills into light protected bottles with amount sufficient for the entire study duration based on the surgery schedule and the assigned dosing regimen plus an extra week of agent supply. The bottles will be dispensed to the research staff for distribution to the study participants or directly from research pharmacy to the study participants. Participants will be provided with the study drug in amount sufficient for the entire study duration based on the surgery schedule and the assigned dosing regimen plus an extra week of agent supply. The study drug may be delivered to the subject by study staff or contracted courier. Participant may also pick up the study agent from the clinic. If surgery is delayed, additional study drug may be delivered to the subject by study staff or contracted courier or picked up from the clinic by the participant.

The study staff will review the participant's concomitant medications to exclude those who are using the medications listed in Appendix E. Participants who initiate the study agent will be provided with a clinical trial wallet card (Appendix D) to show to their healthcare providers. Participants will be instructed to inform study staff prior to taking any new medications during the study. During the weekly contact with the participant, the coordinator will inquire if any new medications have been started and will remind the participant to call the study staff prior to initiating any new medications.

8.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP. The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. This responsibility has been delegated to the study site PI and the Institutional Research Pharmacy. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

8.6 Packaging and Labeling

Apalutamide will be purchased from the Janssen Pharmaceutical Companies of Johnson & Johnson. The institutional research pharmacy will repackage the pills into light protected bottles with amount sufficient for the entire study duration based on the surgery schedule and the assigned dosing regimen plus an extra week of agent supply. The number of pills needed for each participant will be indicated on the prescription order. The following table summarizes how to calculate the number of pills needed for each dosing regimen.

Dosing regimen	Number of pills for agent intervention (A)	Number of pills for an extra week of agent supply €	Total number of pills to be filled
60 mg QD	3 x 60 mg tablet for day 1 + 1 x 60 mg tablet x remaining projected number of agent intervention days	7 x 60 mg tablet	A + E
60 mg MWF/wk	5 x 60 mg tablets for week 1 + 3 x 60 mg tablet x projected remaining number of agent intervention weeks	3 x 60 mg tablet	A + E
60 mg once/wk	3 x 60 mg tablet for week 1 + 1 x 60 mg tablet x projected remaining number of agent intervention weeks	1 x 60 mg tablet	A + E

The label will contain, but not be limited to, the following information:

- Protocol number
- Participant study ID number
- Dosing information (taking one tablet every day, taking one tablet on Monday, Wednesday, Friday, or taking one tablet once a week).
- Expiration date
- Number of tablets per container.

8.7 Storage

Apalutamide tablets are supplied from the Janssen Pharmaceutical Companies of Johnson & Johnson in bottles of 120 tablets. Each bottle contains silica gel desiccant. The manufacturer recommends storage at 20–25°C (68–77°F); temperature excursions are permitted to 15–30°C (59–86°F). The pharmaceutical partner, CP-CTNet Lead Academic Organization, the DCP agent repository contractor, DCP Medical Monitor, and Nurse Consultant should be notified in the event of a Temperature Excursion.

8.8 Registration/Randomization

This trial will use a web-based Registration/Randomization System, developed and maintained by the CP-CTNet Data Management, Auditing, and Coordinating Center (DMACC). The Help Desk includes technical personnel and administrators of the registration programs at the Data Management Center in Amherst, NY, USA. The Help Desk is available round the clock 7 days per week, except for New Year's Eve, Memorial Day, Independence Day, Thanksgiving Day, and Christmas Day.

Frontier Science Randomization Help Desk
4033 Maple Rd, Amherst, NY 14226 USA
Phone: +1 716 834 0900 Extension 7301
Email: UserSupport_CP-CTNet@frontierscience.org

Participants will be considered registered on the date they sign the approved informed consent document with a member of the study staff. Participants will be assigned to a dose cohort based on the sequence of registration. The study doesn't involve randomization.

Note: The Registration and Randomization process is documented in the "Stars User Guide".

8.9 Blinding and Unblinding Methods

Not applicable, this is an open-label study.

8.10 Agent Destruction/Disposal

All unused study agents and returned study bottles will be disposed according to the institutional standards.

9. CLINICAL EVALUATIONS AND PROCEDURES

9.1 Schedule of Events

Evaluation/ Procedure	Registration/Baseline (Visit 1)[1]	Agent Initiation	Agent Intervention[2]	End-of-Intervention[1,3] (Visit 2)	Follow-Up Visit[1,4] (Visit 3)	Extended Follow-Up[10]
Informed Consent	X					
Assess Eligibility	X					
Medical History	X					
Vital Signs/ Height and Weight	X			X[5]		
Baseline Signs/Symptoms	X					
Karnofsky Performance Status	X					
Clinical Labs (CBC/Diff, CMP, PSA, TSH, testosterone)	X			X	X[6]	
Blood for Plasma Apalutamide	X			X	X	
Request FFPE Tissue Slides/blocks					X	
Tobacco and Alcohol Use Assessment	X			X		
Quality of Life Questionnaire (EPIC-CP)	X			X		
COVID-19 Assessment	X			X		
Concomitant Medications	X			X[7]	X[7]	
Dispense Study Agent[8]		X				
Collect Study Agent				X[7]	X[7]	
Review Agent Intake Calendar				X[7]	X[7]	
Adverse Event (AE) Review			X[9]	X[7]	X[7]	X[10]
Telephone Contact			X[9]			X[10]

[1] For all visits, blood draw for testosterone should occur between 7-10 AM for men < 45 years of age and prior to 2 PM for men ≥ 45 years of age. If the schedule is not feasible at Visit 1, the blood draw may be scheduled for another day.

[2] 4-8 weeks. Participants may receive the agent intervention up to 12 weeks if the surgery is delayed. Participants who are taken off agent may remain on study for endpoint evaluation.

[3] Within 3 days prior to scheduled prostatectomy. In order to assess the plasma trough apalutamide levels, participants will be asked to hold the apalutamide dose on the day of the visit until after the blood draw.
[4] 7-14 days post-prostatectomy unless encountering scheduling difficulties. This visit may be combined with the postoperative appointment for catheter removal.
[5] Height required at Baseline visit only.
[6] Testosterone and plasma apalutamide levels only. If testosterone remained elevated at Visit 3, a follow-up chart review will be conducted to capture testosterone test results if the test was repeated at the 3-month post-op standard-of-care visit.
[7] Study agent return, AE diary return, and agent intake calendar return will occur during Visit 2 if this visit occurs the day before surgery. Otherwise, these will be done during post-op follow up. Collection of new Adverse Events and conmeds ends with the operative day.
[8] The study drug may be delivered to the subject by study staff or contracted courier. Participant may also pick up the study agent from the clinic.
[9] Phone contact may be substituted by text or email contact if the subject prefers. Contact will be made during the first week of agent intervention and then every 7-10 days for the duration of the study. Participants will be contacted prior to Visit 2 to remind them of the upcoming appointment and to hold that day's dose of study agent until after their blood draw.
[10] Phone contact may be substituted by text or email contact if the subject prefers. Contact will be made 60 (± 5 days) post-prostatectomy to capture any late onset adverse events, excluding side effects that are related to prostatectomy.

9.2 Baseline Testing/Pre-Study Evaluation

At the screening/baseline visit, the informed consent form and medical records release form will be signed in order to obtain the biopsy/prostatectomy tissues, pathology reports and prior PSA test results. To minimize participant burden, remote consent may be implemented in compliance to the instructions in Appendix G. This visit will be scheduled between 7-10 AM, when feasible, for men < 45 years of age and prior to 2 PM for men ≥ 45 years of age because of circadian variation in testosterone levels. If the schedule is not feasible, the blood draw may be scheduled for another day. Participants will be evaluated for height, weight, and vital signs (temperature, pulse, and blood pressure), concomitant medications, medical history and baseline symptoms and signs. Baseline blood samples will be collected for CBC-diff, CMP, PSA, TSH, testosterone, and plasma apalutamide assay. Participants will also complete baseline tobacco/alcohol questionnaires and the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) questionnaire, and COVID-19 assessment. Subjects will be instructed on how to complete the Intake Calendar and Adverse Event Diary.

When eligibility is confirmed from lab results, participants will be provided with the study drug in amount sufficient for the entire study duration based on the surgery schedule and the assigned dosing regimen plus an extra week of agent supply. The study drug may be delivered to the subject by study staff or contracted courier. Participant may also pick up the study agent from the clinic.

9.3 Evaluation During Study Intervention

Participants will be contacted by phone or email during the first week of agent intervention to assess compliance and safety and then every 7-10 days for the duration of the study. Participants will be contacted prior to Visit 2 to remind them of the upcoming appointment and to hold that day's dose of study agent until after their blood draw. Participants will be contacted prior to Visit 2 to remind them of the upcoming appointment and to hold that day's dose of study agent until after their blood draw.

9.4 Evaluation at Completion of Study Intervention

Participants will be on agent intervention based on the assigned dosing regimen for 4-8 weeks. Participants may continue to receive the agent intervention for up to 12 weeks if the surgery is delayed.

Within 3 days prior to surgery (end-of-intervention visit), participants will return to the clinic for an end-of-intervention blood draw for CBC-diff, CMP, PSA, TSH, and testosterone, and for plasma apalutamide

assay. This visit will be scheduled between 7-10 AM, when feasible, for men < 45 years of age and prior to 2 PM for men ≥ 45 years of age. Adverse events (AEs), concomitant medications (conmeds) and agent compliance will be assessed. Participants will complete the follow-up tobacco/alcohol questionnaires, EPIC-CP questionnaire, and COVID-19 assessment. In order to assess the plasma trough apalutamide levels, participants will be asked to hold the apalutamide dose on the day of the visit until after the blood draw.

Study agent return, AE diary return, and agent intake calendar return will occur during the end-of-intervention visit if this visit occurs the day before surgery.

9.5 Post-intervention Follow-up Period

A blood sample will be collected 7-14 days post-prostatectomy to assess testosterone and plasma apalutamide levels. Blood draw for testosterone should occur between 7-10 AM for men < 45 years of age and prior to 2 PM for men ≥ 45 years of age. This visit may be combined with the postoperative appointment for catheter removal. Study agent return, AE diary return, and agent intake calendar return will occur during this visit if not done during the end-of-intervention visit.

Participants will be contacted 60 (± 5 days) days post-prostatectomy by their preferred method of contact to capture any late onset adverse events, excluding side effects that are related to prostatectomy (such as erectile dysfunction, urinary incontinence, and negative sexual side effects).

At the discretion of the treating urologist, a testosterone test may be repeated at the 3-month post-surgery standard-of-care visit if the testosterone levels remained elevated at Visit 3. The testosterone results will be captured through a chart review if this was repeated at the 3-month post-op visit.

Pre-intervention biopsy and post-intervention surgical pathology reports will be collected, de-identified, labeled with study ID and participant ID and submitted to the University of Arizona Cancer Prevention Clinical Trials (UA CP-CTNet) Office.

Report Submission Information:
UA CP-CTNet Office
Attn: Frances Epstein
1430 E. Fort Lowell, Suite 304
Tucson, AZ 85719
Phone: (520) 321-7798
Fax: (520) 514-6015
Email: UACC-CPRE@UACC.arizona.edu

Unstained tissue slides (or tissue blocks) from the pre-intervention prostate biopsy and post-intervention prostatectomy tissue will be requested from respective pathology labs for measurement of secondary tissue biomarkers.

9.6 Methods for Clinical Procedures

Blood specimens are collected by venipuncture with standard infectious disease precautionary procedures with attention to eliminating low risks to the subject including infection and bruising.

10. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

10.1 Primary Endpoint

The primary endpoint is to determine the effects of low dose apalutamide on circulating levels of Prostate Specific Antigen (PSA). The percent change of PSA levels from baseline to end-of-intervention will be determined. If the prostate biopsy was performed within 6 weeks prior to the baseline visit, the most recent prior PSA instead of the PSA at the baseline visit will be used for the Baseline value. The proportion of participants with ≥25% decline in PSA levels (from baseline to end-of-intervention) will be determined for each dose cohort.

10.2 Secondary Endpoints

The secondary endpoints, in the order of priority, are to determine the effect of low dose apalutamide on

- Reversibility of testosterone levels 7-14 days post-intervention (post-operative). The post-operative testosterone levels will be compared with the levels at baseline and end-of-intervention within each dose cohort.
- Post-intervention plasma trough apalutamide concentrations. Post-intervention plasma trough apalutamide concentrations will be quantified by a sensitive and specific liquid chromatography-mass spectrometry assay. The correlation between plasma trough apalutamide and the change of PSA levels will be assessed.
- Health-related quality of life (HRQOL). HRQOL will be assessed by a validated questionnaire (EPIC-CP) to allow for efficient and accurate measurement of urinary incontinence, urinary irritation, bowel, sexual, and hormonal HRQOL in prostate cancer patients. Changes (from baseline to end-of-intervention) in the overall score and subscore for each measure will be assessed for each dose group.

10.3 Exploratory Endpoints

- Gleason score of pre- and post-intervention tumor(s). Changes (from most recent biopsy to prostatectomy) in the Gleason score of pre- and post-intervention tumor(s) will be assessed for each dose group. Changes in the Gleason score of pre- and post-intervention tumor(s) will also be assessed in a subgroup of participants where materials are available from pre- and post-intervention tumor(s) with matched location. It is expected that such matched materials will only be available in a subgroup of participants where pathology review can be performed on *ex vivo* prostate tissue sample collected at prostatectomy from the tumor(s) that MRI directed biopsies were collected prior to enrollment.

- Intra-prostatic immune cell infiltration. $CD8^+$, $CD4^+$, and $CD56^+$ positive cells in the prostate tissues will be assessed by immunohistochemistry. Changes (from most recent biopsy to prostatectomy) in these immune cells will be assessed for each dose group. Changes in immune cell infiltration will also be assessed in a subgroup of participants where materials are available from pre- and post-intervention tumor(s) with matched location.

The effects of tobacco/alcohol use on the study endpoints will be assessed by examining the associations between tobacco and alcohol consumption and the effects of apalutamide on the study endpoints.

10.4 Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, AE or serious adverse event (SAE), inadequate agent supply, noncompliance, concomitant medications, or medical contraindication. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. A participant who is taken off-agent either by self or by study personnel will not be replaced by another participant.

10.5 Off-Study Criteria

Participants may go 'off-study' for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, AE/SAE, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, death, determination of ineligibility (including screen failure).

10.6 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

11. CORRELATIVE/SPECIAL STUDIES

11.1 Rationale for Methodology Selection

Plasma trough apalutamide concentrations will be determined by a liquid chromatography-mass spectrometry (LC-MS) method described previously [35]. Quantification of plasma drug levels by LC-MS provides high sensitivity, specificity, and selectivity.

$CD8^+$, $CD4^+$, and $CD56^+$ positive cells in the prostate tissues will be assessed by immunohistochemistry as described previously [17]. Immunohistochemistry is the most validated technique for measuring protein levels of the biomarkers of interest in formalin-fixed paraffin-embedded (FFPE) tissue. It allows analyses of relative expression levels of each biomarker and determination of localization of each marker.

11.2 Comparable Methods

Proposed methods are standard methodologies used in published research studies. The resulting data will be able to be compared to existing data.

12. SPECIMEN MANAGEMENT

12.1 Laboratories

Clinical chemistry and hematology panels will be performed in an institutional or commercial diagnostic laboratory service (i.e., LabCorp, Sonora Quest).

Quantification of plasma apalutamide levels will be performed by the University of Arizona Cancer Center (UACC) Analytical Chemistry Shared Resource. The tissue immunohistochemistry assays will be performed by the UACC Tissue Acquisition and Cellular/Molecular Analysis Shared Resource.

12.2 Collection and Handling Procedures

Blood Samples
Clinical labs
Baseline and End-of-Intervention Visits for CBC with differentials, CMP, PSA, TSH, and testosterone: Approximately 15 ml of blood (fasting or non-fasting) will be drawn to one 3-5 ml EDTA and one 7-10 ml SST or tiger top Vacutainer tubes as directed by the clinical lab, and labeled with the subject name.

Post-operative Visit for testosterone: Approximately 3 ml of blood (fasting or non-fasting) will be drawn to one 3-5 ml SST or tiger top Vacutainer tubes as directed by the clinical lab and labeled with the subject name.

Samples will be processed and stored according to the standard protocol for each. The serum tube (SST or tiger top) will be allowed to clot for approximately 30 minutes at room temperature then centrifuged for serum separation. The EDTA tube (for CBC/diff) will be gently inverted to mix for anticoagulation. All samples will be stored under refrigeration prior to transfer to the commercial laboratory facility on the same day as obtained with a completed lab requisition.

Plasma apalutamide
Baseline, End-of-Intervention and Post-Operative Visits
Approximately 6 ml of blood (fasting or non-fasting) will be drawn to one 6 ml EDTA Vacutainer tube. The EDTA tube will be gently inverted to mix for anticoagulation and then centrifuged for plasma separation. Plasma will be aliquoted into 4 x 2 ml cryovials and stored at -70°C or below until analyses. Samples will be labeled with the study ID, subject ID, and date of collection.

Prostate Tissues
A minimum of 5 and up to 10 unstained tissue slides or tissue blocks from pre-intervention prostate biopsy and prostatectomy will be requested from each institution's pathology department for measurement of tissue biomarkers. When available, slides or blocks from pre- and post-intervention tumor(s) with matched location will be requested. Tissue slides will be labeled with the study ID, subject ID, and date of collection.

12.3 Shipping Instructions

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations. Tissue slides/blocks will be shipped in batches at room temperature. Plasma cryovials will be shipped in batches overnight on dry ice. Tissue slides will be shipped in batches overnight on ice packs. Current shipper and institutional procedures must be followed. Biologic specimens (Category B, UN3373) will be in leak-proof primary and secondary receptacles with puncture resistant packaging and absorbent material. Shipments are to be preceded with phone/email contact to the receiving lab to assure the shipment will be met and processed promptly.

Ship plasma samples and tissue slides/blocks to:

Catherine Cordova c/o Chow Laboratory
University of Arizona Cancer Center, Room 4971
1515 N. Campbell Ave.
Tucson, AZ 85724
(520) 626-5433
ccordova@uacc.arizona.edu

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.

12.4 Tissue Banking

The NCI reserves the right to require the transfer of biologic specimens and data, or true copies of such data, acquired from research supported under this award to an eligible third party. This transfer can occur in order to preserve the specimens and data and/or to continue the research. Third parties supported under this award must be informed of this right

13. REPORTING ADVERSE EVENTS

DEFINITION: An adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not the untoward occurrence is considered drug related. Thus, an AE can include any unfavorable sign (e.g., an abnormal laboratory finding), symptom, or clinical outcome temporally associated with the use of a test drug, active control, or placebo, regardless of whether the event is thought to be related to the drug. An AE can arise with the use of a drug or biologic (e.g., use for a purpose other than FDA-approved indication or in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. A clinically significant lab value is one that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action(s) to be taken**.** Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible. (See the *DCP Baseline and Adverse Event Reporting Guidelines* [https://prevention.cancer.gov/clinical-trials/clinical-trials-management/cp-ctnet-instructions-forms] for more detail on reporting abnormal clinical laboratory values.)

A list of AEs that have occurred or might occur can be found in §8.2 Reported Adverse Events and Potential Risks, as well as the Investigator's Brochure or package insert.

13.1 Adverse Events

13.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are collected must be recorded on the AE CRF whether or not related to study agent.

13.1.2 AE Data Elements:

The following data elements are required for AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade

- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the participant dropped due to the event
- Outcome of the event

13.1.3 Severity of AEs

13.1.3.1 Identify the AE using CTCAE v5.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a severity grading scale for each AE listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AE severity will be assessed according to the grade associated with the CTCAE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v5.0. as stated below.

CTCAE v5.0 general severity guidelines:

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

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.
**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.1.4 Assessment of relationship of AE to treatment

The possibility that the AE is related to study agent will be classified as one of the following: unrelated, unlikely, possible, probable, definite. Criteria for these classifications are provided in DCP's *Serious Adverse Event Report Form: Instructions for Completion and Submission* **(https://prevention.cancer.gov/clinical-trials/clinical-trials-management/cp-ctnet-instructions-forms).**

13.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

13.2 Serious Adverse Events

13.2.1 DEFINITION: Regulations at 21 CFR §312.32 define an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
  (According to FDA safety guidance, an AE is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death. Example: An allergic reaction resulting in angioedema of the larynx, allergic bronchospasm or anaphylaxis is considered life-threatening; however, an allergic reaction resulting only in a localized rash is not life-threatening.)
- In patient hospitalization or prolongation of existing hospitalization
  (NCI, DCP uses admission or stay (including emergency room) equal to or greater than 24 hours as the definition of hospitalization. Exceptions are hospitalization for treatment of a pre-existing condition [unless the condition increased in severity on study], outpatient surgery, planned/elective procedures, and procedures described in the protocol [e.g., pharmacokinetic sampling, surgery] even if the hospital stay is of the described length; however, it does include events resulting from any of these that fulfill other serious outcome criteria, e.g., prolongation of hospitalization or life-threatening.)
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require intervention to prevent one of the other outcomes.

13.2.2 Reporting SAEs to DCP

13.2.2.1 The LAO and all Affiliate Organizations will report SAEs on the DCP SAE Report Form as described in DMACC's CP-CTNet SOP 02-01, found at CP-CTNet SOP 02-01 Reporting Serious Adverse Events (cp-ctnet-dmacc.org) and DCP's *Serious Adverse Event Report Form: Instructions for Completion and Submission* found at https://prevention.cancer.gov/clinical-trials/clinical-trials-management/cp-ctnet-instructions-forms.

13.2.2.2 Contact the DCP Medical Monitor and DCP's Regulatory Contractor within 24 hours of knowledge of the event. Contact via email is preferred, but phone contact is acceptable.

DCP Medical Monitor:
Edward Sauter, MD, PhD
National Cancer Institute, Division of Cancer Prevention
9609 Medical Center Dr., Rm 5E326
Rockville, MD 20850
Phone: (240) 276-7657
Cell: (240) 944-3279
Email: edward.sauter@nih.gov

The contact information for the DCP Regulatory Contractor's Safety Department is: phone: 650-691-4400 x133; email: safety@ccsainc.com).

Include the following information when contacting both the DCP Medical Monitor and the DCP Regulatory Contractor's Safety Department:

- Participant ID
- Date and time of the SAE
- Date and time site notified of SAE
- Name of reporter
- Call back phone number and email
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Suspected drugs (if any)
- Description of the SAE, including attribution to drug

13.2.2.3 The LAO and all Affiliated Organizations will email written SAE reports to the DCP Medical Monitor and the DCP Regulatory Contractor's Safety Department within 48 hours of learning of the event using the Word SAE Report Form.

13.2.2.4 The DCP Medical Monitor and the DCP Regulatory Contractor will determine which SAEs require FDA submission as IND safety reports.

13.2.2.5 The LAO and all Affiliate Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

13.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE Report Form in the appropriate format. Follow-up information should be sent to DCP as soon as available. SAE related to the study agent will be followed until resolved or deemed unlikely to further resolved by the Site PI, or until the subject withdraws consent for further follow-up. SAE unrelated or unlikely to be related to study agent will be followed for 30 days after the last dose of study agent or deemed unlikely to resolve by the Site PI, or until the subject withdraws consent for further follow-up.

14. STUDY MONITORING

14.1 Data Management

This study will report clinical data using Medidata RAVE, a cloud–based clinical trials data management system managed by the DMACC. RAVE will be the database of record for the protocol and subject to NCI and FDA audit. All RAVE users will be trained to use the system and will comply with the instructions in the guidelines provided to the LAO by the DMACC as well as applicable regulatory requirements such as 21 CFR; Part 11.

14.2 Electronic Case Report Forms

The System Variable and Attribute Report (SVAR) template will be used to create the study-specific eCRFs or SVAR workbook. DMACC will contact the LAO to determine if a meeting is needed to discuss

the trial and eCRFs before the DMACC creates the draft SVAR. UA CP-CTNet will use CRF templates from the DMACC and DCP website to develop study-specific CRFs. These templates contain NCI Common Data Elements (CDEs) to facilitate data collection and analysis across studies. The standard template set may require modification to capture the unique data elements of each protocol. NCI CDEs, where available, will be used for all CRF modifications.

DCP will sign-off on the final SVAR workbook prior to study initiation. The SVAR workbook may require changes throughout the conduct of the clinical trial. The need for change may result from protocol amendments or other reasons. Amended SVAR workbooks and attachments will be submitted to the DCP Protocol Information Office.

More detailed information about the SVAR development process is available at: Program Resources | CP-CTNet DMACC website (cp-ctnet-dmacc.org)

14.3 Source Documents

Source documentation for this trial will consist of protocol-specific source documents as well as selected clinical records (such as pathology reports and PSA laboratory values) pertinent for eligibility, medical history and physical findings, adverse events, and study endpoints. Only those specific records will be copied for the source chart to preserve subject confidentiality.

14.4 Data and Safety Monitoring Plan

The University of Arizona Cancer Center (UACC) Data and Safety Monitoring Board (DSMB) will provide oversight for subject safety for all UA CP-CTNet clinical trials consistent with the National Institutes of Health Policy for Data and Safety Monitoring dated June 10, 1998; further guidance statement issued by the NIH on June 5, 2000, and the policy for Data and Safety Monitoring by Data and Safety Monitoring Boards. The UACC DSMB meets quarterly.

Regular study-specific meetings will be used as a forum to review accrual rates, problematic issues relating to accrual and protocol implementation, adverse events occurrence, follow-up, and reporting; submission of all required study reports; and progress and outcomes of laboratory analyses.

14.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

14.6 Record Retention

Clinical records for all participants, including eCRFs, all source documentation (containing evidence of study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as CIRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug

Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

14.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

N/A

15. STATISTICAL CONSIDERATIONS

15.1 Study Design/Description

This is a Phase IIa open label dose-finding trial of low dose apalutamide in prostate cancer patients scheduled to undergo radical prostatectomy. The study is expected to include 2 dose groups. Up to 20 participants will be accrued into each dose group to initiate agent intervention.

The decision of dose de-escalation/escalation will be based on the PSA response. A participant with ≥ 25% decline in serum PSA level is considered as a responder. For participants who do not complete the intervention and without post-intervention PSA value, we will conservatively assume the PSA decline to be <25%, considered as a non-responder.

Accrued participants in the first dose cohort will receive apalutamide 60 mg MWF/wk for 4-8 weeks prior to radical prostatectomy. Based on the PSA response, an additional cohort of participants will receive a de-escalated dosing regimen at 60 mg once per week, or an escalated dosing regimen at 60 mg daily for 4-8 weeks prior to prostatectomy. To improve the efficiency of trial conduct, a continuous monitoring plan will be used for efficacy/futility evaluation after 12 participants have completed the dosing regimen. A PSA response rate of ≥50% is considered sufficient for studying the 60 mg MWF/wk and the 60 mg daily dose in future active surveillance studies. The posterior probabilities of observing a response rate ≥50% are summarized below based on the observed number of responders (N_r) and a non-informative prior for N=12-20 evaluable participants.

N_r	N=12	N=13	N=14	N=15	N=16	N=17	N=18	N=19	N=20
0	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.17	0.09	0.05	0.03	0.01	0.01	0.00	0.00	0.00
2	1.12	0.65	0.37	0.21	0.12	0.07	0.04	0.02	0.01
3	4.61	2.87	1.76	1.06	0.64	0.38	0.22	0.13	0.07
4	13.34	8.98	5.92	3.84	2.45	1.54	0.96	0.59	0.36
5	29.05	21.20	15.09	10.51	7.17	4.81	3.18	2.07	1.33
6	50.00	39.53	30.36	22.72	16.62	11.89	8.35	5.77	3.92
7	70.95	60.47	50.00	40.18	31.45	24.03	17.96	13.16	9.46
8	86.66	78.80	69.64	59.82	50.00	40.73	32.38	25.17	19.17
9	95.39	91.02	84.91	77.28	68.55	59.27	50.00	41.19	33.18
10	98.88	97.13	94.08	89.49	83.38	75.97	67.62	58.81	50.00
11	99.83	99.35	98.24	96.16	92.83	88.11	82.04	74.83	66.82
12	99.99	99.91	99.63	98.94	97.55	95.19	91.65	86.84	80.83
13	NA	99.99	99.95	99.79	99.36	98.46	96.82	94.23	90.54
14	NA	NA	100.00	99.97	99.88	99.62	99.04	97.93	96.08
15	NA	NA	NA	100.00	99.99	99.93	99.78	99.41	98.67
16	NA	NA	NA	NA	100.00	99.99	99.96	99.87	99.64
17	NA	NA	NA	NA	NA	100.00	100.00	99.98	99.93
18	NA	NA	NA	NA	NA	NA	100.00	100.00	99.99
19	NA	NA	NA	NA	NA	NA	NA	100.00	100.00
20	NA	NA	NA	NA	NA	NA	NA	NA	100.00

For the 60 mg MWF/wk dose, if the posterior probability is found to be ≥80% at the evaluation (with the first evaluation starting after 12 evaluable participants), this dose cohort will be closed for efficacy and be de-escalated to 60 mg once a week schedule. If the posterior probability is found to be ≤20% at the evaluation (with the first evaluation starting after 12 evaluable participants), this dose cohort will be closed for futility and be escalated to 60 mg daily dose. If the posterior probability is found to be >20%

and <80%, the evaluation will be repeated with one additional evaluable participant, using the same criteria, up to a total of 20 evaluable participants.

If the regimen is escalated to 60 mg daily dose, the same probability criteria will be used to stop the dose cohort for efficacy or futility.

For the 60 mg once a week schedule, a PSA response rate of ≥25% is considered sufficient for using this regimen as the starting regimen in future active surveillance studies.

The posterior probabilities of observing a response rate ≥25% are summarized below based on the observed number of responders and a non-informative prior for 12-20 evaluable participants.

N_r	N=12	N=13	N=14	N=15	N=16	N=17	N=18	N=19	N=20
0	2.38	1.78	1.34	1.00	0.75	0.56	0.42	0.32	0.24
1	12.67	10.10	8.02	6.35	5.01	3.95	3.10	2.43	1.90
2	33.26	28.11	23.61	19.71	16.37	13.53	11.13	9.13	7.45
3	58.43	52.13	46.13	40.50	35.30	30.57	26.31	22.52	19.17
4	79.40	74.15	68.65	63.02	57.39	51.87	46.54	41.48	36.74
5	91.98	88.83	85.16	81.03	76.53	71.75	66.78	61.72	56.66
6	97.57	96.17	94.34	92.04	89.29	86.10	82.51	78.58	74.36
7	99.44	98.97	98.27	97.29	95.98	94.31	92.25	89.82	87.01
8	99.90	99.78	99.58	99.25	98.76	98.07	97.13	95.91	94.39
9	99.99	99.97	99.92	99.84	99.69	99.46	99.11	98.61	97.94
10	100.00	100.00	99.99	99.97	99.94	99.88	99.77	99.61	99.36
11	100.00	100.00	100.00	100.00	99.99	99.98	99.95	99.91	99.83
12	100.00	100.00	100.00	100.00	100.00	100.00	99.99	99.98	99.96
13	NA	100.00	100.00	100.00	100.00	100.00	100.00	100.00	99.99
14	NA	NA	100.00	100.00	100.00	100.00	100.00	100.00	100.00
15	NA	NA	NA	100.00	100.00	100.00	100.00	100.00	100.00
16	NA	NA	NA	NA	100.00	100.00	100.00	100.00	100.00
17	NA	NA	NA	NA	NA	100.00	100.00	100.00	100.00
18	NA	NA	NA	NA	NA	NA	100.00	100.00	100.00
19	NA	NA	NA	NA	NA	NA	NA	100.00	100.00
20	NA	NA	NA	NA	NA	NA	NA	NA	100.00

Similarly, if the posterior probability is found to be ≥80% at the evaluation (with the first evaluation starting after 12 evaluable participants), this dose cohort will be closed for efficacy. If the posterior probability is found to be ≤20% at the evaluation (with the first evaluation starting after 12 evaluable participants), this dose cohort will be closed for futility. If the posterior probability is found to be >20% and <80%, the evaluation will be repeated with one additional evaluable participant, using the same criteria, up to a total of 20 evaluable participants.

15.2 Randomization/Stratification

N/A.

15.3 Sample Size

The study is expected to include 2 dose groups. Up to 20 eligible participants will be accrued into each dose group to initiate agent intervention. We anticipate accruing 1 participant every two months until all sites are activated. Once all sites are activated, we anticipate accruing 1-2 participants every month, we expect to complete the accrual of each dose cohort in 20 months.

15.4 Primary Objective, Endpoint(s), Analysis Plan

The primary objective of this study is to determine the effects of low dose apalutamide on circulating levels of PSA. Percent changes in circulating levels of PSA from baseline will be measured. If the prostate biopsy was performed within 6 weeks prior to the baseline visit, the most recent prior PSA

instead of the PSA at the baseline visit will be used for the baseline value. The study is expected to have 2 dose groups. The dose level of the second dose cohort may be higher (escalation) or lower (de-escalation) than the first dose group, depending upon the PSA response in the initial cohort. Therefore, for the primary endpoint analysis we conservatively use Bonferroni correction while constructing the credible intervals for two dose groups. Specifically, the proportion of participant with ≥25% decline in PSA levels (from baseline to end-of-intervention) for each dose cohort will be reported along with the 97.5% credible interval (CI) for the response rate based on the posterior distribution of the response rate derived from a non-informative prior for the response rate, which is consistent with the Bayesian approach used for dose escalation/de-escalation. A sample size of 20 participants produces a two-sided 97.5% CI for the response rate with a width no wider than 0.404 (based on an observed response rate of 50%).

Observed response rate	Width of 97.5% CI
5% (i.e. 1 responders)	0.226
10% (i.e. 2 responders)	0.273
15% (i.e. 3 responders)	0.309
20% (i.e. 4 responders)	0.337
25% (i.e. 5 responders)	0.359
30% (i.e. 6 responders)	0.376
35% (i.e. 7 responders)	0.389
40% (i.e. 8 responders)	0.397
45% (i.e. 9 responders)	0.403
50% (i.e. 10 responders)	0.404
55% (i.e. 11 responders)	0.403

In addition, the two-sided 97.5% credible interval (CI) for the mean percentage change in PSA for each dose group will be also constructed based on the posterior distribution of mean percentage change, in which the percentage change is assumed to follow a normal distribution and the prior distribution of the mean percentage change is also assumed to follow a normal distribution.

15.5 Secondary Objectives, Endpoints, Analysis Plans

The secondary objectives are to assess the effects of low dose apalutamide on 1) reversibility of testosterone levels 7-14 days post-intervention (post-operative), 2) post-intervention plasma trough apalutamide concentrations, and 3) health-related quality of life (HRQOL). The exploratory objectives are to determine the effects of apalutamide on intra-prostatic immune cell infiltration and Gleason score and the effects of tobacco/alcohol use on the study endpoints. The reversibility of testosterone levels will be measured by the change of testosterone levels from baseline to post operation. Paired t test will be performed on the changes in testosterone to evaluate the effects of low dose apalutamide for each dose group. Pearson correlation coefficient will be derived to evaluate the correlation between the plasma trough apalutamide levels and the change of PSA levels. HRQOL will be assessed by EPIC-CP. Changes in EPIC-CP (from baseline to end-of-intervention) in the overall score and sub-score for each measure will be derived and paired t test will be performed to evaluate the change for each dose group. Linear mixed effects model with a random intercept accounting within-subject dependence will be performed to compare the change in Gleason score of pre- and post-intervention tumor(s) since a participant can have more than one tumor. Changes in the Gleason score of pre- and post-intervention tumor(s) will also be assessed in a subgroup of participants where materials are available from pre- and post-intervention tumor(s) with matched location. The intra- prostatic immune cell infiltration will be measured by $CD8^+$, $CD4^+$, and $CD56^+$ positive cells in the prostate tissues using immunohistochemistry. Changes (from most recent biopsy to prostatectomy) in these immune cells will be assessed for each dose group by paired t test. In addition, for changes in each of the secondary/exploratory endpoints a 95% CI will be reported for

each of the two dose groups. To explore the effects of tobacco/alcohol use on the endpoints, linear regression with tobacco/alcohol use and dose level indicators as the covariates will be performed for percent changes in PSA and change in EPIC-CP, CD8+, CD4+, and CD56+, respectively. Linear mixed effects model with tobacco/alcohol use and dose level indicators as the covariates will be fitted for the change in Gleason score. For each of the endpoints, the interaction effect between tobacco/alcohol use and dose level (i.e., effect modification or heterogeneity effect) will be tested, as well. If a significant interaction effect is detected, then subgroup analysis will be performed by dose level and reported accordingly.
Due to the exploratory nature of the secondary/exploratory endpoints, we are not planning to account for multiple comparisons but will interpret the findings carefully and report the total number of comparisons, which will then allow one to control for the false discovery rate (FDR) at a specific rate, say, ≤10% via the adjusted p-value method. For both primary and secondary endpoints, data will be transformed before performing the test (paired t test or two-sample t test) if necessary. We do not anticipate observing any serious adverse events based on the dose levels considered for the study. At each study dose level, adverse events will be tabulated by the type of adverse events along with the associated 95% confidence intervals.

15.6 Reporting and Exclusions

All of the participants with endpoint data will be included in the primary analysis. Participants are considered compliant for secondary "per protocol" statistical analysis if they have taken ≥ 80% of their assigned study doses.

15.7 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of apalutamide. Descriptive statistics of the type and frequency of all adverse events will be generated, including 95% confidence intervals.

A continuous monitoring rule for safety will be instituted, to guard against excess toxicity from pre-operative treatment with low dose apalutamide. Based on some pre-specified prior distribution for the unanticipated complication rate, the posterior distribution of the unanticipated complication rate will be derived and used to determine whether to stop the study early due to excessive complications. Specifically, if the probability of the 10^{th} percentile of the posterior distribution of the unanticipated complication rate >5% is greater than 65% at a given time point, the study will be placed on hold to evaluate whether the unanticipated complications are related to apalutamide and referred to the UACC DSMB for evaluation of excess toxicity and recommendations on whether or not to stop the study early. We anticipate a low unanticipated complication rate for this study and, therefore, assume a beta distribution with parameters a = 5 and b = 95 (i.e. a mean complication rate of 5%) for the prior distribution. Below is a table summarizing the probability of the 10^{th} percentile of the posterior probability of the unanticipated complication rate greater than 5% after 10 participants have been treated. If ≤ 3 participants have experienced any unanticipated complications, the probability that the 10^{th} percentile of the posterior distribution > 5% is 0%. If 4 participants have experienced any unanticipated complications, the probability that the 10^{th} percentile of the posterior distribution > 5% is 65.7%. If ≥ 5 participants have experienced any unanticipated complications, the probability that the 10^{th} percentile of the posterior distribution > 5% is 100%.

Observed complication % (n = 10)	Assumed complication rate (prior)
	5% beta(5,95)
10% (i.e., 1 out of 10)	0%
20% (i.e., 2 out of 10)	0%
30% (i.e., 3 out of 10)	0%
40% (i.e., 4 out of 10)	65.7%
50% (i.e., 5 out of 10)	100%

15.8 Evaluation of Response

All subjects with endpoint data will be assessed for response to intervention, based on the endpoints described above in Sections 15.4 and 15.5.

Sub-analyses may be performed on the subsets of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of intervention, major protocol violations, etc.). However, sub-analyses may not serve as the basis for drawing conclusions concerning efficacy, and the reasons for excluding participants from the analysis should be clearly reported.

15.9 Interim Analysis

As described above, a continuous monitoring plan will be used for efficacy/futility evaluation after 12 participants have completed the dosing regimen and the dose cohort will be stopped early for efficacy or futility. Accrual, data collection, and any adverse events will be monitored on a regular basis.

15.10 Ancillary Studies

None.

16. REGULATORY AND ETHICAL CONSIDERATIONS

16.1 Required Documents

Besides the regulatory information that will be entered into the Registration and Credential Repository (see Section 5.1), the following documents are also required:

16.1.1 Documentation of Federalwide Assurance (FWA) number for the LAO and all Affiliate Organizations.

16.1.2 Signed Investigator's Brochure/Package Insert acknowledgement form

16.1.3 Delegation of Tasks Log form for the Lead Accruing Organization and all Accruing Sites signed by the Principal Investigator for each site and initialed by all study personnel listed on the form.

16.2 Informed Consent

All potential study participants will be given a copy of the CIRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding

the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option should be included within the informed consent document.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, and the NCI CIRB. The NCI CIRB approves a model consent for each protocol. Each Signatory Institution inserts their CIRB-approved institutional boilerplate language into the model consent to create the CIRB-approved consent. If the model informed consent document is amended, Signatory Institutions must use the revised model informed consent document and insert their CIRB-approved institutional boilerplate language at the time the change becomes active.

The NCI CIRB is the IRB of record and is the only IRB authorized to approve changes to the protocol or informed consent document. Institutions may require additional oversight that involves the local IRB, but the local IRB is not responsible for any regulatorily-required IRB actions.

16.3 Collection of Regulatory Documents

Regulatory documents will be collected by the DCP regulatory contractor and reviewed for completeness and accuracy.

16.4 Other

This trial will be conducted in compliance with the protocol, the International Conference on Harmonisation's (ICH) Good Clinical Practice (GCP) guidelines, and the applicable regulatory requirements.

17. ROSTER MANAGEMENT

The LAO is responsible for establishing, maintaining, and monitoring all its members that participate in CP-CTNet studies. The LAO must have a "real-time," comprehensive, consolidated roster of all its members with their relevant Cancer Therapy Evaluation Program (CTEP) institution codes, associated investigators, and research staff. This roster information is used for determining compliance with monitoring requirements

The LAO's organizational rosters will be managed by the CP-CTNet Roster Management System website (https://applications.prevention.cancer.gov/cp-ctnet). Requests to add memberships to a roster will be done via this website. All requests require that the following documents be uploaded:

- Consortium Letter of Commitment
- Site Letter of Commitment
- CV/NIH Biosketch

18. FINANCING, EXPENSES, AND/OR INSURANCE

Study procedures performed during study visits will be covered by the study budget. Research tests, including serum and tissue biomarker evaluations, will not be billed to the subject. Subjects may incur minimal out-of-pocket expenses such as transportation but will not be charged for study agent or any study-related activities. Subjects will receive monetary compensation which they may use at their discretion for out-of-pocket cost such as transportation. If injury occurs, medical care will be provided and charged to the subject's insurer.

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APPENDIX A PERFORMANCE STATUS CRITERIA

Karnofsky Performance Scale

Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
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.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B

ALCOHOL AND TOBACCO QUESTIONNAIRE INSTRUCTIONS

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- Data collection will be required for all CP-CTNet studies.
    - Data will be collected at baseline and end of every study. Data may also be collected at follow-up visits as determined by each protocol. If you wish to collect additional information beyond these core elements, you may certainly do so. However, all studies need to collect the basic elements in the attached eCRFs.
    - The eCRFs will be completed by the Site Staff or participant at the time of the designated visit.
- Data will be submitted as part of the final clinical data set.

ALCOHOL ASSESSMENT-- BASELINE

REGISTERING INSTITUTION	PARTICIPANT ID	VISIT TYPE _____	VISIT DATE (MM/DD/YYYY) __ __ / __ __ / __ __ __ __

Instructions:

For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.
When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

1. In your entire life, have you had at least 12 drinks of any kind of alcoholic beverage?

   ☐ Yes
   ☐ No **(End)**
   ☐ Refuse to answer **(End)**
   ☐ Don't know/Not sure

2. In the past 12 months, on average, how often did you drink any type of alcoholic beverage?

   _____ (Enter the number of days you drank based on the timeframe checked below. Enter 0 if you never drank and skip to Question 6.)
   ☐ Week
   ☐ Month
   ☐ Year
   ☐ Refuse to answer
   ☐ Don't know/Not sure

3. In the past 12 months, on those days that you drank alcoholic beverages, on average, how many drinks did you have per day?

   _____ (Enter the average number of drinks per day)

   ☐ Refuse to answer
   ☐ Don't know/Not sure

4. In the past 12 months, on how many days did you have 5 or more drinks of any alcoholic beverage?

   _____ (Enter the number of days you had 5 or more drinks or enter 0 if none.)

☐ Refuse to answer
☐ Don't know/Not sure

5. Was there ever a time or times in your life when you drank 5 or more drinks of any kind of alcoholic beverage almost every day?

☐ Yes
☐ No
☐ Refuse to answer
☐ Don't know/Not sure

6. If you do not currently drink alcoholic beverages, but did in the past, how long has it been since you last drank regularly?

☐ Within the past month (0 to 1 month ago)
☐ Between 1 and 3 months (1 to 3 months ago)
☐ Between 3 and 6 months (3 to 6 months ago)
☐ Between 6 and 12 months (6 to 12 months ago)
☐ Between 1 and 5 years (1 to 5 years ago)
☐ Between 5 and 15 years (5 to 15 years ago)
☐ More than 15 years ago
☐ Don't know/Not sure
☐ Never drank regularly

7. At the heaviest point, either now or in the past, on the days when you drank, about how many drinks did you drink a day on the average?

_____ (Enter the number of drinks a day)

☐ Refuse to answer
☐ Don't know/Not sure

8. How many years have you been drinking (or did drink) regularly?

_____ years

☐ Refuse to answer
☐ Don't know/Not sure

9. At what age did you begin drinking regularly?

_____ years of age

☐ Refuse to answer
☐ Don't know/Not sure

10. What type(s) of alcohol do you drink? (Mark ALL that apply)

☐ Wine
☐ Liquor
☐ Beer
☐ Wine cooler
☐ Other _____ (enter other type(s) of alcohol you drink)

CRF completed by (*check one*):

Study participant _____

Study site staff _____ Staff name (*optional*) _____

Date __ __ / __ __ / __ __ __ __
(MM/DD/YYYY)

ALCOHOL ASSESSMENT - FOLLOW-UP

REGISTERING INSTITUTION	PARTICIPANT ID	VISIT TYPE	VISIT DATE *(MM/DD/YYYY)*
_____	_____	_____	__ __ / __ __ / __ __ __ __

Instructions:

For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

When a number is requested in the response, please enter a whole number (i.e., "4") and not a range or fraction of a number.

1. During the past 30 days, did you drink any alcoholic beverages?

☐ Yes
☐ No **(End)**
☐ Refuse to answer **(End)**
☐ Don't know/Not sure

2. During the past 30 days, how many days per week or per month did you drink any alcoholic beverages, on the average?

_____ (Enter number of days you drank based on the timeframe checked below. Enter 0 if you did not drink.)

☐ Week
☐ Month
☐ Refuse to answer
☐ Don't know/Not sure

3. On the days when you drank, on average, about how many drinks did you have?

_____ (Enter the average number of drinks you had per day.)

☐ Refuse to answer
☐ Don't know/Not sure

4. In the past 30 days, on how many days did you have 5 or more drinks per day?

_____ (Enter the number of days you had 5 or more drinks or enter 0 if none.)

☐ Refuse to answer
☐ Do not know/Not sure

CRF completed by (*check one*):

Study participant _____

Study site staff _____ Staff name (*optional*) _____

Date __ __ / __ __ / __ __ __ __
(MM/DD/YYYY)

TOBACCO ASSESSMENT – BASELINE

REGISTERING INSTITUTION	PARTICIPANT ID	VISIT TYPE	VISIT DATE (MM/DD/YYYY)
_____	_____	_____	__ __ / __ __ / __ __ __ __

Instructions:
When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

Section A. Basic Cigarette Use Information

1. Have you smoked at least 100 cigarettes (5 packs = 100 cigarettes) in your entire life?

☐ Yes
☐ No → **Skip to Section B**
☐ Don't know/Not sure → **Skip to Section B**

2. How old were you when you first smoked a cigarette (even one or two puffs)?

_____ Years old

3. How old were you when you first began smoking cigarettes regularly?

_____ Years old
☐ Check here if you have never smoked cigarettes regularly.

4. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.

_____ Years (If you smoked less than one year, write "1.")

5. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day? (A pack usually has 20 cigarettes in it).

_____ Number of cigarettes per day

6. Do you NOW smoke cigarettes?

☐ Everyday
☐ Some days

☐ Not at all → **Skip to question 8**

7. How soon after you wake up do you smoke your first cigarette?

☐ Within 30 minutes
☐ After 30 minutes

8. How long has it been since you last smoked a cigarette (even one or two puffs)?

First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.

☐ I smoked a cigarette today (at least one puff)
☐ 1-7 days → Number of days since last cigarette _____
☐ Less than 1 month → Number of weeks since last cigarette _____
☐ Less than 1 year → Number of months since last cigarette _____
☐ More than 1 year → Number of years since last cigarette _____
☐ Don't know/Don't remember

Section B. Use of Other Forms of Tobacco

9. Have you ever used other forms of tobacco, not including cigarettes?

☐ Yes
☐ No → **Skip to Section C**

10. How often do you/did you use other forms of tobacco?

☐ Every day → Number of times per day _____
☐ Some days → Number of days _____ per ☐ Week ☐ Month ☐ Year

11. Which of the following products have you ever used regularly?
Check all that apply

☐ Cigarettes
☐ E-cigarettes or other electronic nicotine delivery system
☐ Traditional cigars, cigarillos or filtered cigars
☐ Pipes
☐ Waterpipe
☐ Hookah
☐ Clove cigarettes or kreteks

☐ Bidis
☐ Smokeless tobacco, like dip, chew, or snuff
☐ Snus
☐ Paan with tobacco, gutka, zarda, khaini
☐ Other, Please specify: _____

12. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly?

☐ Within the past month (0 to 1 month ago)
☐ Between 1 and 3 months (1 to 3 months ago)
☐ Between 3 and 6 months (3 to 6 months ago)
☐ Between 6 and 12 months (6 to 12 months ago)
☐ Between 1 and 5 years (1 to 5 years ago)
☐ Between 5 and 15 years (5 to 15 years ago)
☐ More than 15 years ago
☐ Don't know/Not sure
☐ Never used other forms of tobacco regularly

Section C. Second-Hand Smoke Exposure

13. Are you currently living with a smoker?

☐ Yes
☐ No

14. In the past 30 days, have you lived in a place where other people smoked cigarettes indoors?

☐ Yes
☐ No

15. In the past 30 days, have you worked in a place where other people smoked cigarettes indoors?

☐ Yes
☐ No

16. Thinking of all your childhood and adult years, have you ever lived in a place where other people smoked cigarettes indoors?

☐ Yes In total, for about how many years? _____ If less than 1, write "1."
☐ No

17. Thinking of all the years you have worked, have you ever worked in a place where other people smoked cigarettes indoors?

☐ Yes → In total, for about how many years? _____ If less than 1, write "1."
☐ No

CRF completed by (*check one*):

Study participant _____

Study site staff _____ Staff name (*optional*) _____

Date __ __ / __ __ / __ __ __ __
(MM/DD/YYYY)

TOBACCO ASSESSMENT - FOLLOW-UP

REGISTERING INSTITUTION	PARTICIPANT ID	VISIT TYPE	VISIT DATE *(MM/DD/YYYY)*
_____	_____	_____	__ __ / __ __ / __ __ __ __

Instructions:
When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

1. Do you NOW smoke cigarettes?

☐ Everyday
☐ Some days
☐ Not at all → **Skip to Question 3.**
☐ Never smoked → **Skip to Question 4**

2. On average, when you smoked, about how many cigarettes do you (or did you) smoke a day? (A pack usually has 20 cigarettes in it).

_____ Number of cigarettes per day

3. How long has it been since you last smoked a cigarette (even one or two puffs)?

First check which one of the following choices applies to you. Then, if applicable, write a whole number on the line for how many days, weeks, months, or years it has been since your last cigarette.

☐ I smoked a cigarette today (at least one puff)
☐ 1-7 days → Number of days since last cigarette _____
☐ Less than 1 month → Number of weeks since last cigarette _____
☐ Less than 1 year → Number of months since last cigarette _____
☐ More than 1 year → Number of years since last cigarette _____
☐ Don't know/Don't remember

4. Since your last visit, have you used other forms of tobacco, not including cigarettes?

☐ Yes
☐ No (**End)**

5. How often do you/did you use other forms of tobacco?

☐ Every day → Number of times per day _____
☐ Some days → Number of days _____ per ☐ Week ☐ Month ☐ Year

6. Since your last visit, which of the following products have you used? ***Check all that apply***

- ☐ Cigarettes
- ☐ E-cigarettes or other electronic nicotine delivery system
- ☐ Traditional cigars, cigarillos or filtered cigars
- ☐ Pipes
- ☐ Waterpipe
- ☐ Hookah
- ☐ Clove cigarettes or kreteks
- ☐ Bidis
- ☐ Smokeless tobacco, like dip, chew, or snuff
- ☐ Snus
- ☐ Paan with tobacco, gutka, zarda, khaini
- ☐ Other,

Specify_____

7. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly?

- ☐ Within the past month (0 to 1 month ago)
- ☐ Between 1 and 3 months (1 to 3 months ago)
- ☐ Between 3 and 6 months (3 to 6 months ago)
- ☐ Between 6 and 12 months (6 to 12 months ago)
- ☐ Between 1 and 5 years (1 to 5 years ago)
- ☐ Between 5 and 15 years (5 to 15 years ago)
- ☐ More than 15 years ago
- ☐ Don't know/Not sure
- ☐ Never used other forms of tobacco regularly

The following instructions pertain to questions 8 - 10. During each of the following time frames, please indicate whether you smoked cigarettes every day, some days, or not at all.

8. During study treatment

- ☐ Smoked every day
- ☐ Smoked some days
- ☐ Did not smoke at all
- ☐ Don't know/not sure
- ☐ Not applicable

9. After the end of study treatment

- ☐ Smoked every day
- ☐ Smoked some days
- ☐ Did not smoke at all
- ☐ Don't know/not sure
- ☐ Not applicable (I have not completed the study treatment)

10. Since your last visit to this clinic

- ☐ Smoked every day
- ☐ Smoked some days
- ☐ Did not smoke at all
- ☐ Don't know/not sure

CRF completed by (*check one*):

Study participant _____

Study site staff _____ Staff name (*optional*) _____

Date __ __ / __ __ / __ __ __ __
(MM/DD/YYYY)

NATIONAL AND LOCAL RESOURCES TO HELP WITH ALCOHOL ABUSE AND ALCOHOLISM

NIAAA's online guide ***Treatment for Alcohol Problems: Finding and Getting Help*** is written for individuals, and their family and friends, who are looking for options to address alcohol problems. It is intended as a resource to understand what treatment choices are available and what to consider when selecting among them.
https://pubs.niaaa.nih.gov/publications/treatment/treatment.htm

Other resources:

National Institute on Alcohol Abuse and Alcoholism www.niaaa.nih.gov
301–443–3860

National Institute on Drug Abuse www.nida.nih.gov
301–443–1124

National Clearinghouse for Alcohol and Drug Information www.samhsa.gov
1–800–729–6686

Substance Abuse Treatment Facility Locator www.findtreatment.samhsa.gov
1–800–662–HELP

Alcoholics Anonymous (AA) www.aa.org
212–870–3400 or check your local phone directory under "Alcoholism"

Moderation Management www.moderation.org
212–871–0974

Secular Organizations for Sobriety www.sossobriety.org
323–666–4295

SMART Recovery www.smartrecovery.org
440–951–5357

Women for Sobriety www.womenforsobriety.org
215–536–8026

Al-Anon Family Groups www.al-anon.alateen.org
1–888–425–2666 for meetings

Adult Children of Alcoholics www.adultchildren.org
310–534–1815

NATIONAL AND LOCAL RESOURCES TO HELP WITH QUITTING SMOKING

NCI's Smokefree.gov offers science-driven tools, information, and support that has helped smokers quit. You will find state and national resources, free materials, and quitting advice from NCI.

Smokefree.gov was established by the Tobacco Control Research Branch of NCI, a component of the National Institutes of Health, in collaboration with the Centers for Disease Control and Prevention and other organizations.

Publications available from the Smokefree.gov website include the following:

- Clearing the Air: Quit Smoking Today for smokers interested in quitting.
- Clear Horizons for smokers over age 50.
- Staying Smoke-Free for Good for smokers who have recently quit.
- Smoke-free for women, including pregnant women.
- Smoke-free information in Spanish
- Pathways to Freedom: Winning the Fight Against Tobacco for African American smokers.

NCI's Smoking Quitline at **1–877–44U–QUIT (1–877–448–7848)** offers a wide range of services, including individualized counseling, printed information, referrals to other resources, and recorded messages. Smoking cessation counselors are available to answer smoking-related questions in English or Spanish, Monday through Friday, 8:00 a.m. to 8:00 p.m., Eastern time. Smoking cessation counselors are also available through LiveHelp, an online instant messaging service. LiveHelp is available Monday through Friday, 8:00 a.m. to 11:00 p.m., Eastern time.

Your state has a toll-free telephone quitline. Call **1–800–QUIT–NOW (1–800–784–8669)** to get one-on-one help with quitting, support and coping strategies, and referrals to resources and local cessation programs. The toll-free number routes callers to state-run quitlines, which provide free cessation assistance and resource information to all tobacco users in the United States. This initiative was created by the Department of Health and Human Services. For more information about quitlines, speak to an expert on the Smokefree.gov website.

APPENDIX C
EXPANDED PROSTATE CANCER INDEX COMPOSITE FOR CLINICAL PRACTICE (EPIC-CP)

- The EPIC-CP is a valid instrument that enables patient-reported health-related quality of life (HRQOL) to be measured efficiently and accurately in the routine clinical care of prostate cancer patients. The CRFs will be completed by the Site Staff or participant at the time of the designated visit.
- Data will be submitted as part of the final clinical data set.

EXPANDED PROSTATE CANCER INDEX COMPOSITE FOR CLINICAL PRACTICE (EPIC-CP)

REGISTERING INSTITUTION	PARTICIPANT ID	VISIT TYPE	VISIT DATE (MM/DD/YYYY)
_____	_____	_____	__ __ / __ __ / __ __ __ __

Patients: Please answer the following questions by checking the appropriate checkbox. All questions are about your health and symptoms in the **LAST FOUR WEEKS.** Select one answer for each question.

1. Overall, how much of a problem has your urinary function been for you?
   ☐ No problem ☐ Very small problem ☐ Small problem ☐ Moderate problem ☐ Big problem

2. Which of the following best describes your urinary control?
   0 ☐ Total control 1 ☐ Occasional dribbling 2 ☐ Frequent dribbling 4 ☐ No urinary control

   _____

3. How many pads or adult diapers per day have you been using for urinary leakage?
   0 ☐ None 1 ☐ One pad per day 2 ☐ Two pads per day 4 ☐ Three or more pads per day

   _____

4. How big a problem, if any, has urinary dripping or leakage been for you?
   0 ☐ No problem 1 ☐ Very small problem 2 ☐ Small problem 3 ☐ Moderate problem 4 ☐ Big problem

   _____

   Clinicians: Add the answers from questions 2-4 to calculate the Urinary Incontinence Symptom Score (out of 12): ☐

5. How big a problem, if any, has each of the following been for you?	**No problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**
a. Pain or burning with urination……	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
_____ b. Weak urine stream/incomplete bladder emptying…	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
_____ c. Need to urinate frequently ……..	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

_____

Clinicians: Add the answers from questions 5a-5c to calculate the Urinary Irritation/Obstruction Symptom Score (out of 12): ☐

6. How big a problem, if any, has each of the following been for you?	**No problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**
a. Rectal pain or urgency of bowel movements…….	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
_____ b. Increased frequency of your bowel movements…….	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
_____ c. Overall problems with your bowel habits……..	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

_____

Clinicians: Add the answers from questions 6a-6c to calculate the Bowel Symptom Score (out of 12): ☐

7. How would you rate your ability to reach orgasm (climax)?
   0 ☐ Very good 1 ☐ Good 2 ☐ Fair 3 ☐ Poor 4 ☐ Very poor to none

   _____

8. How would you describe the usual quality of your erections?

0 ☐ Firm enough 1 ☐ Firm enough for masturbation 2 ☐ Not firm enough for 4 ☐ None at all

_____

for intercourse and foreplay only any sexual activity

9. Overall, how much of a problem has your sexual function or lack of sexual function been for you?
0 ☐ No problem 1 ☐ Very small problem 2 ☐ Small problem 3 ☐ Moderate problem 4 ☐ Big problem

_____

Clinicians: Add the answers from questions 7-9 to calculate the Sexual Symptom Score (out of 12): ☐

10. How big a problem, if any has each Of the following been for you?	**No problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**
a. Hot flashes or breast tenderness/enlargement	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
_____ (if applicable, circle either hot flashes or breast tenderness/enlargement to indicate which symptom you are experiencing. If both, circle both)					
b. Feeling depressed	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
_____ c. Lack of energy	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

_____

Clinicians: Add the answers from questions 10a-10c to calculate the Vitality/Hormonal Symptom Score (out of 12): ☐

CLINICIANS: Add the five domain summary scores to calculate the Overall Prostate Cancer QOL Score out of 60: ☐

Investigator Signature _____ Date

_____

(mm/dd/yyyy)

Investigator Name (please print)

_____

APPENDIX D
PARTICIPANT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Participant Name:

Diagnosis/Condition:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: DCP UAZ20-01-01

Study Drug(S): Apalutamide

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX E

LIST OF DRUGS IN CATEGORY X DRUG INTERACTIONS

Abemaciclib	Alpelisib	Antihepaciviral Combination Products
Apixaban	Apremilast	Aprepitant
Asunaprevir	Avanafil	Avapritinib
Axitinib	Bedaquiline	Betrixaban
Bortezomib	Bosutinib	Brigatinib
Capmatinib	Cariprazine	Ceritinib
Cobimetinib	Copanlisib	Crizotinib
Dabigatran Etexilate	Daclatasvir	Darolutamide
Dasabuvir	Deflazacort	Delamanid
Dexlansoprazole	Dienogest	Doravirine
DOXOrubicin	Duvelisib	Elbasvir
Elexacaftor, Tezacaftor, and Ivacaftor	Eliglustat	Encorafenib
Entrectinib	Erdafitinib	Esomeprazole
Etravirine	Fedratinib	Flibanserin
Fosaprepitant	Fosnetupitant	Fostamatinib
Fostemsavir	Gemigliptin	Gilteritinib
Glasdegib	Grazoprevir	Ibrutinib
Idelalisib	Indium 111 Capromab Pendetide	Irinotecan Products
Isavuconazonium Sulfat	Istradefylline	Itraconazole
Ivabradine	Ivacaftor	Ivosidenib
Ixazomib	Lansoprazole	Ledipasvir
Lemborexant	Letermovir	Lopinavir
Lorlatinib	Lumacaftor and Ivacaftor	Lumateperone
Lumefantrine	Lurasidone	Lurbinectedin
Macimorelin	Macitentan	Midostaurin
MiFEPRIStone	Naldemedine	Naloxegol
Neratinib	Netupitant	NIFEdipine
Nilotinib	NiMODipine	Nintedanib
Nisoldipine	Olaparib	Omeprazole
Palbociclib	Panobinostat	PAZOPanib
Pemigatinib	Pexidartinib	Pimavanserin
Piperaquine	PONATinib	Praziquantel
Pretomanid	Ranolazine	Regorafenib
Ribociclib	Rimegepant	Ripretinib
Rivaroxaban	Roflumilast	RomiDEPsin
Selpercatinib	Selumetinib	Simeprevir
Sofosbuvir	Sonidegib	SORAfenib
Tasimelteon	Tazemetostat	Telithromycin
Tezacaftor and Ivacaftor	Ticagrelor	Tofacitinib
Toremifene	Trabectedin	Tucatinib
Ubrogepant	Ulipristal	Upadacitinib
Valbenazine	Vandetanib	Velpatasvir
Venetoclax	VinCRIStine (Liposomal)	Vinflunine
Vorapaxar	Voxilaprevir	Zanubrutinib

APPENDIX F

COVID 19 ASSESSMENT INSTRUCTIONS

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- Data collection will be required for all CP-CTNet studies.
    - Data will be collected at baseline and end of every study. All studies need to collect the elements in the attached eCRFs.
    - The eCRFs will be completed by the Site Staff or participant at the time of the designated visit.
- Data will be submitted as part of the final clinical data set.

CP-CTNET COVID-19 BASELINE ASSESSMENT

REGISTERING INSTITUTION	PARTICIPANT ID	VISIT TYPE	VISIT DATE (MM/DD/YYYY)
		_____	__ __ / __ __ / __ __ __ __

Instructions:
The following information is being collected for all Cancer Prevention Clinical Trials Network (CP-CTNet) studies. Only information from before study entry should be reported on this form.

Have you ever had a COVID-19 test?

☐ Yes
☐ No

If Yes, have you ever received a positive test result?

☐ Yes
☐ No
☐ Prefer not to answer

Date of latest positive test: _ _ / _ _ / _ _ _ _
If positive, were you symptomatic?

☐ Yes
☐ No

Have you received a COVID-19 vaccine?

☐ Yes
☐ No
☐ Prefer not to answer

If Yes, which vaccine did you receive for your first dose?

☐ Moderna
☐ Pfizer - BioNTech
☐ Johnson & Johnson
☐ AstraZeneca
☐ Other

If Other, specify: _____

Date of first vaccine dose: _ _ / _ _ / _ _ _ _

Have you received a second vaccine dose?

☐ Yes
☐ No

If Yes, date of second vaccine dose: _ _ / _ _ / _ _ _ _

If No, provide reason:

☐ Not yet due
☐ Second dose not required
☐ Other

If Other, specify: _____

Have you received a booster dose?

☐ Yes
☐ No

1. Date of first booster dose: _ _ / _ _ / _ _ _ _

   Which vaccine did you receive?

   ☐ Moderna
   ☐ Pfizer - BioNTech
   ☐ Johnson & Johnson
   ☐ AstraZeneca
   ☐ Other

   If Other, specify: _____

2. Date of second booster dose: _ _ / _ _ / _ _ _ _

   Which vaccine did you receive?

   ☐ Moderna

☐ Pfizer - BioNTech
☐ Johnson & Johnson
☐ AstraZeneca
☐ Other

If Other, specify: _____

Comments:
_____
_____

CP-CTNET COVID-19 FOLLOW-UP ASSESSMENT

REGISTERING INSTITUTION	PARTICIPANT ID	VISIT TYPE	VISIT DATE (MM/DD/YYYY)
		_____	__ __ / __ __ / __ __ __ __

Instructions:
The following information is being collected for all Cancer Prevention Clinical Trials Network (CP-CTNet) studies. Only use this form to report information that has become available since the last completion of a CP-CTNet COVID-19 Assessment

Since your initial study visit, have you had a COVID-19 test?

☐ Yes
☐ No

If Yes, did you receive a positive test result?

☐ Yes
☐ No
☐ Prefer not to answer

Date of latest positive test: _ _ / _ _ / _ _ _ _

If positive, were you symptomatic?

☐ Yes
☐ No

Since your last study visit, have you received a COVID-19 vaccine?

☐ Yes
☐ No
☐ Prefer not to answer

Indicate the vaccine doses received: (Complete information below about any doses that were received.)

☐ First dose only
☐ Second dose only
☐ Both first and second doses
☐ Booster dose
☐ All three doses

1. Date of first vaccine dose: _ _ / _ _ / _ _ _ _

Which vaccine did you receive?

☐ Moderna
☐ Pfizer - BioNTech
☐ Johnson & Johnson
☐ AstraZeneca
☐ Other

If Other, specify: _____

2. Date of second vaccine dose: _ _ / _ _ / _ _ _ _

Which vaccine did you receive?

☐ Moderna
☐ Pfizer - BioNTech
☐ Johnson & Johnson
☐ AstraZeneca
☐ Other

If Other, specify: _____

3. Date of booster dose: _ _ / _ _ / _ _ _ _

Which vaccine did you receive?

☐ Moderna
☐ Pfizer - BioNTech
☐ Johnson & Johnson
☐ AstraZeneca
☐ Other

If Other, specify: _____

4. Date of booster dose: _ _ / _ _ / _ _ _ _

Which vaccine did you receive?

☐ Moderna
☐ Pfizer - BioNTech
☐ Johnson & Johnson
☐ AstraZeneca
☐ Other

If Other, specify: _____

Comments:
_____
_____

APPENDIX G

REMOTE CONSENT INSTRUCTIONS

1. The participant or their legally-authorized representative (LAR) receives a copy of the informed consent document (e.g., via mail, fax, email, or a web link) ***in advance*** of discussion regarding the study. If mailed, two copies must be mailed so the participant or LAR is able to retain a copy for reference when their signed document is returned to the site and they are waiting to receive the final copy with all necessary signatures back from the site. If an electronic-consent (e-consent) document is provided, the content in the document must be the same as the paper-based consent document.
2. The investigator or designee discusses the study with the potential participant either via telephone or video conferencing. The investigator/designee must have the same consent discussion via telephone/video conferencing that they would have had with the participant or LAR during an in-person meeting. The investigator/designee must also implement a method to ensure the identity of the participant or LAR (e.g., verification of state identification or other identifying documents or use of personal questions or visual methods).
3. If the potential participant or LAR agrees to participation, they sign the consent form and return it to the investigator (e.g., via mail, fax, email, or by signing the e-consent document). If postal mail is used, a pre-paid, self-addressed envelope should be provided to the participant or LAR to mail the signed consent form back to the investigator. The inclusion of a witness in the Remote Consent Procedures is dictated by local institutional policy and must follow FDA and OHRP requirements. When a witness is required, the research record must document the witness' name and that they were present for the informed consent process. The inclusion of the witness' signature on the consent form is dictated by local institutional policy.
4. Once the research team receives the signed informed consent document from the participant or LAR, the investigator/designee who conducted the consent process must sign and date the document using the current date. Under the signature line, the investigator/designee must document whether consent was obtained over the telephone or video conferencing, the date of the telephone/video conference, and the date the signed consent was received. For example, **"Discussed with [participant or LAR name] via [telephone or videoconferencing] on [insert date] and received signed consent form on [insert date]."** Include a brief reason for performing the informed consent discussion over the telephone/videoconferencing.
5. If the site has an informed consent policy that requires the witness to sign the consent document, the witness signs the informed consent. If the site does not have an informed consent policy that requires the signature of the witness on the consent document, then the name of the witness along with the date of the original consenting phone call is recorded in the research records to document the participation of the witness.
6. The date the investigator/designee signs the informed consent document, not the date the consent discussion with the participant or LAR took place, is the official date of informed consent for the participant on the trial.
7. The final informed consent document must be filed in the designated investigator/site regulatory file location. A copy of the final informed consent document, signed by the participant or LAR, the investigator, and the witness (if applicable), must be sent back to the participant via email/scan, fax, or postal mail.
8. **No research activities related to the study can begin until all steps of the informed consent process are complete.**