Janssen Research & Development *

Clinical Protocol

A Multi-center, Open-label, Single-arm Phase 2 Study of the Adjuvant Treatment of Apalutamide and Androgen Deprivation Therapy (ADT) in Treatment-naïve Participants Who Have Undergone Radical Prostatectomy (RP) for Non-metastatic Prostate Cancer and Who Are at High Risk for Metastases

Protocol 56021927PCR2041; Phase 2
AMENDMENT 2

JNJ-56021927 (apalutamide)

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	20-Apr-2021
Amendment 1	12-Aug-2020
Original Protocol	14-May-2020

Amendment 2 (20-April-2021)

Overall Rationale for the Amendment: The main reason for the amendment is to add a sub-study to assess testosterone dynamics when relugolix is administered concurrently with apalutamide. Other clarifications to the main study have also been made.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis	The rationale for sub-study is added.	To add the details of sub-study.
1.1 Synopsis Overall Design; 1.2 Schema; 4.1 Overall Design of Main Study 5.1 Inclusion Criteria 3; 5 Study Population 6.1 Study Intervention Administered	The maximum duration from post radical prostatectomy (RP) to start of study intervention or enrollment in the study is updated from 60 days to between Day 29 and Day 90 post-RP. Screening duration is changed from 60 to 90 days before administration of the study intervention. The window for initiation of study intervention was updated as between Day 29 and Day 90 post-RP.	To reflect the practices where patients may be seen later after surgery and to provide additional clarification in other sections due to updated eligibility criteria.
1.1 Synopsis Number of Participants	Following sentence was added: The sub-study consisting of 12 participants will be in addition to the 94 main ApaRP protocol participants and statistical analyses will be performed separately. Upon completion of the sub-study, participants will be transitioned into the main study beginning at Cycle 2 Day 1.	To add the details of sub-study.
1.1 Synopsis Biomarker Evaluations; 1.3 Schedule of Events and footnote j; 4.1 Overall Design of Main Study 8.6 Biomarkers	RP tissue analysis results may be utilized in addition to the primary biopsy and sent to sponsor's laboratory partner.	To clarify the wordings related to biomarker collection as in some cases RP tissue may be used.
1.2 Schema; 5.1 Inclusion Criteria 5	Definition of high-risk population is updated.	To clarify that high risk can be determined from RP pathology report in addition to biopsy as in some cases only RP tissue

		may be available or may more accurately reflect the disease state.
1.3 Schedule of Events	Post-operative PSA evaluation at screening was separated from PSA evaluation for efficacy.	To separate screening evaluation from efficacy evaluation.
1.1 Synopsis Overall Design; 4.1 Overall Design of the Main Study	The evaluation standards for patients under androgen deprivation were added.	To meet current standards for patients under androgen deprivation.
5.1 Inclusion Criteria 4	Following words in bold were added: have recovered from RP procedure **and have had no worsening in cardiac risk in the peri-operative period** per the clinical judgment of the investigator.	To ensure reassessment of cardiovascular risk prior to reinitiating study intervention after surgery.
1.3 Schedule of Events footnote g 8.2.1 Physical examinations	Following sentence was added for focused physical examination: Any new complaints, symptoms reported by participants or adverse events noted by providers should guide the need and extent of physical examination.	To provide clarity on focused physical examination.
1.2 Schema; 4.1 Overall Design of Main Study 8 Study Assessments and Procedures	"Main study" was added to the sub-section heading. It was clarified that blood volume mentioned is for main study.	To differentiate the main study from sub-study.
5.2 Exclusion Criteria 8	It was specified that malignancies considered cured for more than 24 months are allowed.	To allow participants cured for more than 24 months to enroll in the study.
5.2 Exclusion Criteria 9	Duration of cardiac abnormalities prior to baseline changed from 6 months to 12 months.	To comply with the new guidance from other registrational studies for peri-operative use of apalutamide in clinical trials
8.6 Biomarkers	Following sentence was added: Biopsy tissue is required for risk scores (Prolaris) and is preferred for HRD testing	To clarify type of tissue required for biomarker collection.
10.13 Appendix 13	Description of sub-study protocol, including rationale, schema, endpoints, and schedule of activities was added.	Study testosterone dynamics of novel oral hormonal agent relugolix when administered concurrently with apalutamide.
10.14 Appendix 14	New Appendix with detailed information of sub-study pill diary was added.	To provide the details of the pill dairy required for the sub-study.
10.15 Appendix 15	Amendment summary table for Amendment 1 was moved to Appendix 15.	The older amendment is moved to the appendix.
References	New references were added.	To provide references for new text.
Throughout protocol	Minor grammatical, spelling, and formatting changes are made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Multi-center, Open-label, Single-arm Phase 2 Study of the Adjuvant Treatment of Apalutamide and Androgen Deprivation Therapy (ADT) in Treatment-naïve Participants Who Have Undergone Radical Prostatectomy (RP) for Non-metastatic Prostate Cancer and Who Are at High Risk for Metastases

Apalutamide (ERLEADA®), is an orally available, non-steroidal small molecule, which acts as a potent and selective antagonist of androgen receptors (ARs). Apalutamide is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC) and with metastatic castration sensitive prostate cancer (mCSPC). Apalutamide is currently being studied for the treatment of prostate cancer at all stages.

Given that prostate cancer cells depend on AR for proliferation and survival, a standard treatment for patients with recurrent disease is to lower the level of testosterone by surgical castration or with a gonadotropin releasing hormone (GnRH) agonist or antagonist, commonly referred to as androgen deprivation therapy (ADT).

As a new oral GnRH antagonist (relugolix) has been recently FDA approved, this agent will be part of a sub-study detailed in Section 10.13, Appendix 13.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess if the combination of apalutamide and ADT in participants with high-risk localized prostate cancer improves the BCR-free rate.	• BCR-free rate at 24 months. BCR is defined as a confirmed PSA >0.2 ng/mL.
Secondary	
• To determine the BCR-free rate at 12 months.	• BCR-free rate at 12 months.
• To determine the time to serum testosterone recovery.	• Testosterone recovery rate at 18 and 24 months.
Exploratory	
• To evaluate the incidence of rash.	• Incidence of rash.

Key: ADT=androgen-deprivation therapy; BCR=biochemical recurrence; PSA=prostate-specific antigen

Hypothesis

The primary hypothesis of this study is that adjuvant treatment with apalutamide and ADT will improve the biochemical recurrence (BCR)-free rate at 24 months post radical prostatectomy (RP) in this treatment-naïve, non-metastatic prostate cancer population who are at high risk for the development of metastases compared to historical data from patients without adjuvant treatment.

OVERALL DESIGN

This is a single-arm, open-label, multi-center study of apalutamide and ADT in approximately 94 participants with high risk localized prostate cancer who are treatment naïve, documented to have no evidence of metastatic disease prior to study entry, who are between Day 29 and Day 90 post-RP, whose prostate-specific antigen (PSA) is ≤0.2 ng/mL at study entry and who have recovered from surgery, per the clinical judgment of the investigator. There will be one study intervention group receiving apalutamide for 12 cycles (a cycle is defined as 28 days); the participants will also receive an ADT of investigator's choice

(3-month depot preferred) for 12 months. Treatment with apalutamide and ADT will start following screening and completion of RP and no later than postoperative Day 90. Participants will receive 12 cycles of therapy. During treatment, participants should continuously be re-evaluated for emerging and worsening cardiovascular risk factors per current standards for patients under androgen deprivation. Approximately 30 days post-treatment, a safety follow-up examination will be completed (end of treatment visit). There will be a follow-up period during which serum PSA and testosterone levels will be measured and clinical status monitored every 6 months after the completion of treatment until the end of the study (EOS). The EOS is defined as the date of last participant's enrollment +24 months or discontinuation of all study participants from the study, whichever occurs first. Study enrollment is defined as the day when the participant receives the first dose of apalutamide after having met all prescreening criteria.

A Steering Committee will be commissioned for this study.

NUMBER OF PARTICIPANTS

This study will be conducted in approximately 30 urology practices in the United States and enroll approximately 94 participants. The sub-study consisting of 12 participants will be in addition to the 94 main ApaRP protocol and statistical analyses will be performed separately. Upon completion of the sub-study, participants will be transitioned into the main study beginning at Cycle 2 Day 1.

INTERVENTION GROUPS AND DURATION

Participants will be instructed to take their assigned dose of the study intervention (apalutamide) orally **once daily** for 12 cycles per apalutamide United States Package Insert (ERLEADA® USPI). A treatment cycle is defined as 28 days. There will be one study intervention group receiving apalutamide along with ADT of investigator's choice (3-month depot preferred). Androgen deprivation therapy will be given for 12 months.

EFFICACY EVALUATIONS

Efficacy assessments include serum PSA and testosterone and will be assessed prior to first dose of study intervention and throughout the study per the Schedule of Activities (SoA). A PSA level >0.2 ng/mL, (confirmed within 3-4 weeks), will be considered an indicator of BCR.

BIOMARKER EVALUATIONS

Biomarker samples may be collected as outlined in the SoA. Biomarker analysis is planned to retrospectively evaluate risk scores and other genomic markers and correlate with participants' response to treatment and explore homologous recombinant deficiency (HRD) and efficacy of apalutamide in this subpopulation. To address these objectives, tumor tissue will be collected and sent to sponsor's laboratory partner along with a copy of the full histopathology report of the specimen. Also, whole blood and plasma samples may be collected at baseline, 12 months or end of treatment, and at 24 months or progression (whichever comes first).

SAFETY EVALUATIONS

Participants will be monitored for safety from the beginning of the treatment and at each study visit. Events related to and associated with the recovery from the pre-planned RP will not be collected.

Focused physical examinations including skin assessment will be completed prior to treatment, and at 2, 3, 4, 7, 10, 13, and 14 months. A 12-lead electrocardiogram (ECG) will be conducted prior to treatment to assess for QT prolongation, if not available from pre-operative evaluation. Blood samples specific to the study will be collected only for PSA, testosterone levels, and biomarkers.

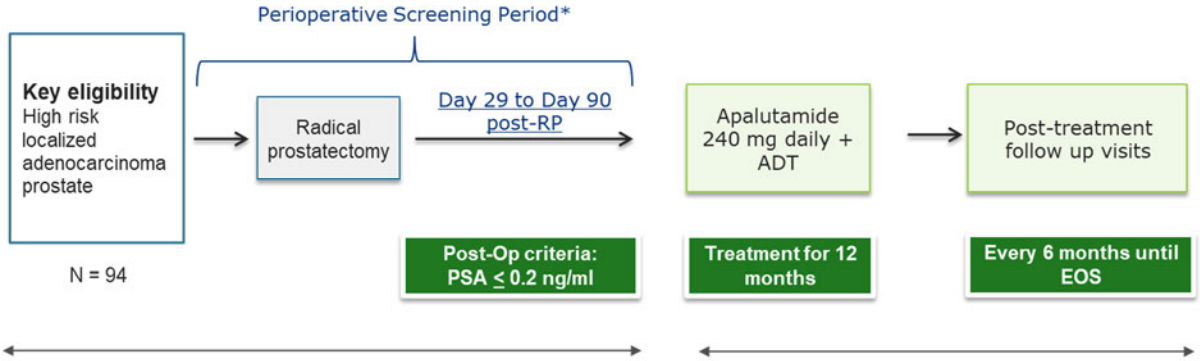
STATISTICAL METHODS

The primary hypothesis of this study is that adjuvant treatment with apalutamide and ADT will improve the BCR-free rate at 24 months in the treatment-naïve, non-metastatic prostate cancer population who are at high risk for the development of metastases compared to historical data from patients without adjuvant treatment (76%).

It is estimated that approximately 94 participants treated for 12 months and followed for an additional 12 months would be required to provide at least 80% power in detecting a 10% absolute increase in BCR-free rate at 24 months from 76% to 86% at a 1-tailed significance level of 0.05. Sample size was calculated using PASS 15 (Power Analysis and Sample Size Software [2017]). Time to BCR (ie, PSA >0.2 ng/mL) will be analyzed using Kaplan-Meier method. The secondary endpoint of testosterone recovery will be analyzed similarly to the primary endpoint. Incidence of rash will be summarized descriptively.

1.2. Schema

Figure 1: Schematic Overview of the Main Study



Definition of High-Risk population:

- PSA ≥20 ng/mL or
- Gleason Score ≥9 in any core on biopsy or
- Gleason Score ≥8 (4+4 or 5+3) in >80% of 2 cores on biopsy or
- Gleason Score = 8 (4+4 or 5+3) in 1 core as long 5 or more other cores with minimum Gleason Score of 4+3 on biopsy

The determination of high risk may be based on pathology report of biopsy or equivalent criteria from radical

* See Section 9.4.5, Safety Analyses for details.

Key: ADT=androgen deprivation therapy; EOS=end of study; N=number of participants; post-op=postoperative; PSA=prostate-specific antigen; RP=radical prostatectomy.

1.3. Schedule of Activities (SoA)

Study Visit	Pre-op Screening	Baseline V1	V2[a]	V3[a]	V4[a]	V5[a]	V6[a]	V7[a]/ET	V8[a] Safety visit	F/U V9[b]	F/U V10[b]	F/U V11[b]	F/U V12[b]
Cycle/Cycle Day		**C1/D1**	**C2/D1**	**C3/D1**	**C4/D1**	**C7/D1**	**C10/D1**	**C13/D1**	**C14/D1**	**C18/D1**	**C24/D1**	**C30/D1**	**C36/D1**
Study Month		**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 7**	**Month 10**	**Month 13**	**Month 14**	**Month 18**	**Month 24**	**Month 30**	**Month 36**
Screening/Administrative													
ICF[c]	X												
Demographics	X												
Review medical history requirements	X												
Phone call		Weekly check	Mid-cycle check	Mid-cycle check									
Inclusion and exclusion criteria met	X												
Post-op Screening PSA	X												
Study Intervention Administration													
Dispense/administer study intervention		X	X	X	X[d]	X[d]	X[d]						
Study intervention accountability			X	X	X	X	X	X					
ADT administration (with 3-month formulation)[e]		X			X	X	X						
Efficacy Evaluations													
PSA[f]					X	X	X	X	X	X	X	X	X
Testosterone		X			X	X	X	X	X	X	X	X	X

Study Visit	Pre-op Screening	Baseline V1	V2[a]	V3[a]	V4[a]	V5[a]	V6[a]	V7[a]/ET	V8[a] Safety visit	F/U V9[b]	F/U V10[b]	F/U V11[b]	F/U V12[b]
Cycle/Cycle Day		**C1/D1**	**C2/D1**	**C3/D1**	**C4/D1**	**C7/D1**	**C10/D1**	**C13/D1**	**C14/D1**	**C18/D1**	**C24/D1**	**C30/D1**	**C36/D1**
Study Month		**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 7**	**Month 10**	**Month 13**	**Month 14**	**Month 18**	**Month 24**	**Month 30**	**Month 36**
Safety Evaluations													
Focused physical examinations[g] including skin assessment		X	X	X	X	X	X	X	X				
12-lead ECG[h]	X												
Pharmacodynamics and Biomarkers													
Plasma samples[i]		X						X			X		
Tumor tissue sample[j]		X											
Pharmacogenomics (DNA)													
DRD status (germline)		X											
Ongoing Participant Review													
Concomitant therapy[k]		X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[l]		X	X	X	X	X	X	X	X	X	X	X	X
Education and counselling on skin care		X	X	X	X	X	X	X					

Note: Race, history of smoking and alcohol intake, height and weight at baseline will be recorded directly in the eCRF and will be considered as source data.

Key: ADT=androgen deprivation therapy; AE=adverse event; C=cycle; CT=computed tomography; D=day; DNA=deoxyribose nucleic acid; DRD=DNA repair deficient; ECG=electrocardiogram; EOS=end of study; ET=end of treatment; F/U=follow-up; ICF=informed consent form; MRI=magnetic resonance imaging; pre-op=preoperative; PET=positron emission tomography; PSA=prostate-specific antigen; SOC=standard of care; USPI=United States Package Insert; V=visit.

Footnotes:

a Beginning with Visits 2 through 8, a window of ±7 calendar days for scheduling will be allowed.

b Beginning with Visit 9 and for all follow-up visits, a window of ±14 calendar days for scheduling will be allowed.

c Must be signed before first study-related activity.

d Provide 3-month supply of apalutamide during Visits 4, 5, and 6.

e ADT first administration will be at baseline and subsequently administered per USPI for total duration 12 months, 3-month depot is the preferred administration. NOTE: If 3-month DEPOT is used, the last dose will be administered at Month 10. If 3-month DEPOT is not used, follow USPI.

f A PSA level >0.2 ng/mL will be an indicator of BCR and will be confirmed within 3 to 4 weeks regardless of study visit and timing. Depending on timing, this may be captured as an unscheduled visit.
g Focused examinations are generally limited to the body systems or regions based on participant's self-assessment and AE reporting. Any new complaints, symptoms reported by participants or adverse events noted by providers should guide the need and extent of physical examination.
h ECG assessment at screening if not available from preoperative information.
i Collected at baseline, 12 months or end of treatment, and at 24 months or progression (whichever comes first).
j Tissue sample to be collected and sent to sponsor's laboratory partner along with a copy of the full histopathology report of the specimen. Biopsy tissue is preferred. See Section 8.6 for further details.
k Collection of concomitant therapies does not begin until time of first dose of apalutamide.
L Collection of AEs does not begin until time of first dose of apalutamide.

2. INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males worldwide.[12] Treatment aimed at eradicating the primary tumor, typically with surgery or radiation, is unsuccessful in 30% of men, who develop recurrent disease that usually manifests first as a rise in prostate-specific antigen (PSA) followed by spread to distant sites.[27] Given that prostate cancer cells depend on androgens for proliferation and survival, a standard treatment for patients with recurrent disease is to lower the level of testosterone by surgical castration or with a gonadotropin releasing hormone (GnRH) agonist or antagonist, commonly referred to as androgen deprivation therapy (ADT).

Apalutamide (ERLEADA®) is an orally available, non-steroidal small molecule, which acts as a potent and selective antagonist of androgen receptors (ARs). To date, apalutamide has been approved for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC) and with metastatic castration-sensitive prostate cancer (mCSPC). Apalutamide is currently being studied for the treatment of prostate cancer at all stages.

For the most comprehensive nonclinical and clinical information regarding apalutamide, refer to the latest version of the Investigator's Brochure (IB)[11] and US Package Insert (ERLEADA® USPI) for apalutamide.

Common terms used throughout the protocol are noted. The term “study intervention” throughout the protocol, refers to apalutamide + ADT. The term "sponsor" refers to the entities listed in the Contact Information page(s), which will be provided as a separate document. The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Men with high risk localized prostate cancer frequently undergo radical prostatectomy (RP)[17] with curative intent. While a significant proportion of patients with clinically localized prostate cancer are cured by definitive local therapy,[22] patients with high-risk features, including Gleason score 8 to 10, positive lymph node involvement, high initial prostate-specific antigen, seminal vesicle invasion and extra prostatic extension have a 40% to 75% chance of disease recurrence in 10 years.[5,16,26] In the National Comprehensive Cancer Network (NCCN) guidelines,[17] there is a Category 1 adjuvant radiation therapy option but no standard adjuvant systemic therapy option for men with most of these clinical features. There is evidence supporting ADT in the adjuvant setting but only for men with node positive prostate cancer.[15] There is also evidence supporting postoperative adjuvant radiation therapy[28] in patients with high and very high risk disease but it is infrequently and inconsistently applied in these situations. Apalutamide and ADT have demonstrated the ability to significantly prolong metastasis-free survival (MFS), radiographic progression free survival (rPFS), and overall survival in 2 large randomized, double blind, placebo controlled registrational trials.[4,25] This study will investigate whether treatment with apalutamide and ADT for 12 months can improve the chance of maintaining participants free of biochemical recurrence (BCR) with a serum PSA ≤0.2 ng/mL 24 months after RP. In other solid tumors, robust adjuvant strategies are available that guide treatment decision-making after surgery.

This guidance is lacking in prostate cancer and this study can help to inform the development of such a strategy for this unmet need.

2.2. Background

High-risk prostate cancer accounts for approximately 15% of newly diagnosed prostate cancers.[3] For patients with high-risk, locally advanced prostate cancer, prostatectomy alone may be inadequate. Cure rates from prostatectomy are less than 25%.[2,15,23] High-risk patients experience the highest recurrence after prostatectomy, with a disease progression rate of approximately 50%.[13] Patients with recurring disease after local therapy require salvage radiotherapy, which is associated with morbidity that has detrimental impact on quality of life. In a retrospective analysis of 379 men who developed a BCR after RP, it was found that patients with a Gleason score of 8 to 10 were more likely to die from prostate cancer than patients with a Gleason score of 7 or less.[7]

Several definitions of high-risk prostate cancer are used in the urological literature. Patients with high-risk localized or locally advanced prostate cancer include those with Gleason scores ≥8, clinical stage ≥cT2c (disease in both or extension outside of the lobes), high baseline PSA ≥20 ng/mL, or involvement of regional nodes. For the current study, high risk is defined by Gleason score or PSA.

For adjuvant use of ADT, prospective randomized studies have shown that early use of long-term ADT extends survival, compared with treatment that is delayed until disease progression.[2,5,6,9,21] In a randomized study in 100 patients to determine whether immediate ADT extends survival in patients with node-positive prostate cancer who have undergone RP and pelvic lymphadenectomy compared with those who received ADT only at disease progression, it was shown that early ADT benefits patients as compared to deferred treatment.[15]

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of apalutamide may be found in the IB and ERLEADA USPI.

As noted in Section 2.1, there is evidence that adjuvant therapy may provide benefit.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess if the combination of apalutamide and ADT in participants with high-risk localized prostate cancer improves the BCR-free rate.	• BCR-free rate at 24 months. BCR is defined as a confirmed PSA >0.2 ng/mL.
Secondary	
• To determine the BCR-free rate at 12 months.	• BCR-free rate at 12 months.
• To determine time to serum testosterone recovery.	• Testosterone recovery rate at 18 and 24 months.

Objectives	Endpoints
Exploratory	
• To evaluate the incidence of rash.	• Incidence of rash.

Key: ADT=androgen-deprivation therapy; BCR=biochemical recurrence; PSA=prostate-specific antigen

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis of this study is that adjuvant treatment with apalutamide and ADT will improve the BCR-free rate at 24 months post-RP in this treatment-naïve, non-metastatic prostate cancer population who are at high risk for the development of metastases compared to historical data from patients without adjuvant treatment.[14]

4. STUDY DESIGN

4.1. Overall Design of the Main Study

This is a single-arm, open-label, multi-center study of apalutamide and ADT in approximately 94 participants with high risk localized prostate cancer who are treatment naïve, documented to have no evidence of metastatic disease prior to study entry, who are between Day 29 and Day 90 post-RP, whose PSA is ≤0.2 ng/mL at study entry and who have recovered from surgery, per the clinical judgment of the investigator.

This study will be conducted in approximately 30 urology practices in the US and enroll approximately 94 participants. There will be one study intervention group receiving apalutamide for 12 cycles; the participants will also receive an ADT of investigator's choice (3-month depot preferred) for 12 months. Treatment with apalutamide and ADT will start following screening and completion of RP and no later than postoperative Day 90. Approximately 30 days post-treatment, a safety follow-up examination will be completed (end of treatment visit). There will be a follow-up period during which serum PSA and testosterone levels will be measured and clinical status monitored every 6 months after the completion of treatment until the end of study (EOS). The EOS is defined as the date of last participant's enrollment +24 months or discontinuation of all study participants from the study, whichever occurs first. Study enrollment is defined as the day when the participant receives the first dose of apalutamide after having met all prescreening criteria.

During treatment, participants should continuously be re-evaluated for emerging and worsening cardiovascular risk factors per current standards for patients under androgen deprivation. Management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension), overweight/obesity, and hyperlipidemia is required for all participants based on recent guidelines.

The timing and frequencies of study assessments are presented in the SoA (Section 1.3). Efficacy assessments include serum PSA and testosterone and will be assessed after the start of apalutamide treatment. A PSA level >0.2 ng/mL (confirmed within 3-4 weeks) is considered an indicator of

BCR. Safety assessments from the time of enrollment and during treatment and end of treatment visit will include focused physical examinations, monitoring of adverse events (AEs). A 12-lead electrocardiogram (ECG) will be conducted at screening to examine QT prolongation, if not available from preoperative evaluation. Safety evaluations will be conducted based on AE reporting. Blood and plasma samples for biomarker analysis as well as tumor tissue will be collected per the Schedule of Activities (SoA).

A Steering Committee will be commissioned for this study. Refer to Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations for details.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

The single-arm, open-label design is appropriate for a Phase 2 study to evaluate the clinical benefit of adjuvant apalutamide with ADT for patients with high-risk localized prostate cancer following RP. The occurrence of rash with apalutamide and subsequent specific management could make blinding impractical. The participants have previously selected to undergo RP as opposed to any other option and their participation in this study with adjuvant treatment could provide added benefit to them.

Following the work conducted by the ICECaP investigators[29] whose results were obtained mostly in patients who had undergone radiation therapy with curative intent, Martini et al[14] described the biochemical and clinical recurrence patterns in a cohort of 3,507 patients with high risk localized prostate cancer who had undergone RP and extended pelvic lymph node dissections. These investigators noted negligible serum PSA (≤0.2 ng/mL) rates of 84% and 76% at 12 and 24 months, respectively after surgery, in the absence of any adjuvant treatment. These findings on biochemical recurrence form the basis for the statistical assumptions and rationale for clinical endpoints in this adjuvant study (see Section 9.2).

Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention and response and can also serve as a marker for disease susceptibility and prognosis.

Biomarker samples may be collected to evaluate progression or help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to this intervention. The goal of the biomarker analyses is to evaluate localized high-risk prostate cancer population and aid in evaluating the intervention-clinical response relationship of apalutamide with ADT.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Participant Input Into Design

As part of the Patient Voice Project, members of the Prostate Cancer Patient Engagement Research Council who are all patients/survivors of prostate cancer favorably reviewed the study design and visit schedule.

The consensus was that the open-label design, without placebo, of this study is preferable to randomized double-blind studies for patients. Additionally, the visit schedule and duration of time on study was not considered "burdensome". Longer follow-up was suggested and follow-up every 6 months until the end of the study was added with subsequent follow-up to be covered by treatment per standard of care.

4.2.2. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

While participants have selected RP independent from this study, the primary ethical concern is that adjuvant therapy with apalutamide following RP is not currently standard of care. The cure rate for patients with high-risk localized prostate cancer is approximately 25%. Apalutamide has been proved to significantly delay metastases and improve overall survival, and has a manageable safety profile.[25] Participants may discontinue from the study if there are signs of disease progression and then be eligible for other forms of treatment including radiation.

An additional ethical concern is germline and other genetic testing which may warrant counselling. This information and potential interventions may affect not only the participant, but his family. Genetic counselling will be made available through the genetic testing facility.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross.[1]

4.3. Justification for Dose

The dose of 240 mg (4 × 60 mg tablets) is the approved dose per ERLEADA USPI.

4.4. End of Study Definition

End of Study Definition

The EOS is defined as the date of last participant's enrollment +24 months or discontinuation of all study participants from the study, whichever occurs first. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

Participants will be considered to have completed the study if they have completed EOS assessments.

Participants who prematurely discontinue study intervention for any reason before study completion will not be considered to have completed the study. If a participant misses a dose for >28 days, consult the sponsor regarding continuation in the study.

5. STUDY POPULATION

The study population will consist of participants that are treatment-naïve, who have undergone RP for non-metastatic prostate cancer, and who are at high risk for metastases, as defined by Gleason score or PSA.

Screening for eligible participants will be performed within 90 days before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. male ≥18 years of age
2. must be willing and able to sign an informed consent form and be able to fully comply with all of the required procedures, restrictions, and prohibitions specified in this protocol
3. Criterion modified per Amendment 2

   3.1 The participant should be

   a. a candidate for RP or status post-RP

   b. eligible to receive study intervention between Day 29 and Day 90 post-RP

   c. post-RP PSA of ≤0.2 ng/mL

   d. has not received other treatment for prostate cancer

4. Criterion modified per Amendment 2

4.1 have recovered from RP procedure and have had no worsening in cardiac risk in the peri-operative period per the clinical judgment of the investigator

5. Criterion modified per Amendment 1

5.1. Criterion modified per Amendment 2

5.2 histologically confirmed adenocarcinoma of the prostate and categorized as high risk for recurrent prostate cancer. High risk can be defined based on PSA alone or biopsy or RP specimen as follows:

- PSA ≥20 ng/mL

  or

- Gleason Score ≥9 in any core on biopsy

  or

- Gleason Score ≥8 (4+4 or 5+3) in >80% of 2 cores on biopsy

  or

- Gleason Score = 8 (4+4 or 5+3) in 1 core as long 5 or more other cores with minimum Gleason Score of 4+3 on biopsy

The determination of high risk may be based on pathology report of biopsy or equivalent criteria from radical prostatectomy.

6. adequate organ function (hepatic, renal, hematologic and cerebral) determined at the discretion of the treating physician

7. Eastern Cooperative oncology Group (ECOG) Performance Status Score of 0 or 1

8. able to take apalutamide per the ERLEADA USPI and able to receive ADT for up to 1 year

9. must be willing to wear a condom when engaging in any activity that allows for passage of ejaculate to another person. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak

10. must be willing to agree not to donate sperm for the purpose of reproduction during the study and for a minimum 90 days after receiving the last dose of study intervention

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified per Amendment 1

   1.1. history or presence of soft tissue/bone metastasis or metastasis in distant lymph nodes (pelvic lymph nodes below the iliac bifurcation that are <2 cm in diameter [short axis] either radiographically or pathologically are allowed.)

2. history of bilateral orchiectomy

3. taking any disallowed therapies or chronic need for prohibited medications (per ERLEADA USPI) as noted in Section 6.8, Concomitant Therapy before the planned first dose of study intervention

4. received an investigational intervention ≤4 weeks before the planned first dose of study intervention

5. history of seizure or any condition that in the opinion of the investigator may predispose to seizure or treatment with drugs known to lower the seizure threshold within 4 weeks prior to starting treatment with apalutamide

6. allergy or hypersensitivity to apalutamide, or excipients, unable or unwilling to take ADT

7. history or presence of psoriasis, neurodermatitis, acneiform rashes or any dermatological condition that in the opinion of the investigator may predispose to confounding with the evaluation and management of study intervention related rash

8. Criterion modified per Amendment 2

   8.1 malignancies (ie, progressing or requiring treatment or treatment change in the last 24 months) other than prostate cancer. The only allowed exceptions are: non-muscle invasive bladder cancer; skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured. Malignancies considered cured for more than 24 months are allowed

9. Criterion modified per Amendment 1

   9.1 Criteria modified per Amendment 2

   9.2 any of the following within 12 months prior to baseline: severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, uncontrolled hypertension, long QT, arterial or venous thromboembolic events (eg, pulmonary

embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias

10. plans to father a child while enrolled in this study or within 12 weeks after the last dose of study intervention

11. any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study, including chronic alcohol use, cytochrome P450 (CYP)3A4 interaction, and drugs known to lower the seizure threshold or cause seizures.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Orchiectomy is prohibited during the entire study.

4. A condom is required for all sexual activity during the study and for 3 months after completion of apalutamide. There is no sperm donation permitted during the study and within 3 months after completion of study treatment. See Section 10.5, Appendix 5, Contraceptive Guidance for further details.

5. If the study participant is engaged in sexual activity with a female of childbearing potential, 2 forms of contraception, including condom use as described above, are required. These include:

    - Oral, injected or implanted methods of contraception including an intrauterine device (IUD) or intrauterine system (IUS)
    - Barrier methods with spermicide

- Vasectomy

5.4. Screening Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent will be used.

Participants who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

5.5. Criteria for Temporary Delaying (Enrolment/Randomization/Administration of Study Intervention) (Not Applicable)

6. STUDY INTERVENTION

6.1. Study Intervention Administered

The study intervention apalutamide, 240 mg (four 60 mg tablets, slightly yellowish to greyish green oblong film-coated tablets, debossed with "AR 60" on one side), will be provided as tablets for oral administration. The window for initiation of study intervention must occur between Day 29 and Day 90 post-RP. Participants will be instructed to take their assigned dose of the study intervention orally **once daily** for 12 cycles per ERLEADA USPI. A treatment cycle is defined as 28 days. Apalutamide can be taken with or without food. If a participant experiences a ≥Grade 3 toxicity or an intolerable side effect, hold dosing until symptoms improve to ≤Grade 1 or original grade, then resume at the same dose or a reduced dose (180 mg or 120 mg), if warranted. If a participant remains off apalutamide for ≥4 weeks, the participant may be withdrawn from the study, after discussing with the sponsor. Participants experiencing treatment related seizure of any grade will have apalutamide permanently discontinued.

Description of Interventions

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF). Study-site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol.

Apalutamide will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients and the ERLEADA USPI.

Investigator's choice of a Food and Drug Administration (FDA)-approved and commercially available ADT, not provided by the sponsor, will be administered per the USPI for 12 months in total duration, during the treatment phase. Three-month depot is the preferred administration. For further information on ADT refer to the USPI.

For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Apalutamide must be stored at controlled temperatures ranging from 15°C to 30°C.

Refer to the ERLEADA USPI for additional guidance on apalutamide and ADT preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Study Site Investigational Product and Procedures Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding (Not Applicable)

6.4. Study Intervention Compliance

Study-site personnel will maintain a log of all study intervention dispensed. Study intervention supplies for each participant will be inventoried and accounted for.

6.5. Dose Modification

Any dose adjustment should be overseen by medically qualified study-site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

In case a dose modification is necessary, the study intervention will be administered per Section 10.9, Appendix 9, Recommendations for Management of Drug-related Rash.

6.6. Continued Access to Study Intervention After the End of the Study (Not Applicable)

6.7. Treatment of Overdose

For this study, any dose of apalutamide greater than 240 mg within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific intervention for an overdose. There is no specific antidote and treatment should consist of general supportive measures.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for adverse event (AE)/serious adverse event (SAE).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.
- Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Concomitant therapies must be recorded throughout the study from the time of first dose of study intervention to the last study visit. Concomitant therapies should also be recorded beyond 30 days after last study visit only in conjunction with new or worsening AEs and SAEs that meet the criteria outlined in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication.

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

Prohibited concomitant therapies, outlined in Section 10.6 Appendix 6, include treatment with any AR blocker or CYP17 inhibitor for the treatment of prostate cancer. Sipuleucel-T, pembrolizumab, radium-223, strontium-89, samarium-153, saw palmetto and any agent under investigation and not currently approved by the FDA for any indication are also prohibited. Concomitant therapy restrictions are outlined in Section 10.7, Appendix 7, Restricted Concomitant Medications.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- Noncompliance with study intervention administration
- Participants experiencing treatment-related seizure of any grade will have apalutamide permanently discontinued

If a participant discontinues study intervention for any reason before the end of the study, then the last scheduled study assessments should be obtained and scheduled assessments off study intervention should be continued. If a participant misses doses for >28 days, consult the sponsor regarding continuation in the study. If a participant discontinues study intervention due to disease progression, the subsequent treatment including radiation will be captured in the eCRF, if known. Additional participants will not be entered to ensure the protocol-specified number of participants complete the study.

7.1.1. Rechallenge

If a participant experiences a ≥Grade 3 toxicity or an intolerable side effect, hold dosing until symptoms improve to ≤Grade 1 or original grade, then resume at the same dose or a reduced dose, if warranted per Section 10.9, Appendix 9, Recommendations for Management of Drug Related Rash.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

- Investigator's discretion
- Seizure
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion) as local regulations permit.

Prior to a participant withdrawing consent for follow-up, the investigator should offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described below. Withdrawal of consent should be an infrequent occurrence in clinical studies, therefore, prior to the start of the study, the sponsor and the investigator should discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the research samples:

- The collected samples will be retained and used in accordance with the participant's original informed consent.
- The participant may withdraw consent for research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample has been destroyed.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main informed consent form (ICF).

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to study entry, attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

Participants will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

7.4. National Disaster/Extra Ordinary Circumstances

If appropriate, site visits may be replaced with telephone visits during a national disaster or extra ordinary circumstances, with site visits resuming as soon as possible thereafter. Telephone visits will be recorded in the source documentation and eCRF. If a visit included blood collection, the collection and testing may be done at a facility closer to the participant. A copy of the laboratory report, along with the reference ranges must be obtained for the source documentation and provided with the eCRF. Study intervention may be dispensed by alternative methods (for example shipped to participants). Refer to Section 10.12, Appendix 12, Guidance on Study Conduct during the COVID-19 Pandemic, for details related to the COVID pandemic that may also be applied to other national disasters or extra ordinary circumstances.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, biomarker, safety measurements applicable to this study.

The PSA assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant perceptions.

Blood collections should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

The total blood volume for the main study is approximately 55 mL.

Repeat or unscheduled samples may be taken for technical issues with the samples.

Sample Collection and Handling

Refer to Section 1.3, Schedule of Activities for the timing and frequency of all sample collections.

Study-Specific Materials

The investigator will be provided with the following information:

- IB and ERLEADA USPI for apalutamide and USPI for ADT
- Pharmacy Manual/Study Site Investigational Product and Procedures Manual
- National Cancer Institute Common- Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0
- Response Evaluation Criteria in Solid Tumors (RECIST) guidelines Version 1.1
- Electronic data capture (eDC) Manual
- eSource Manual
- ICF template

8.1. Efficacy Assessments

Efficacy assessments include serum PSA and testosterone and will be assessed prior to first dose of study intervention and throughout the study per the SoA. A PSA level >0.2 ng/mL (confirmed within 3-4 weeks) will be considered an indicator of BCR.

8.2. Safety Assessments

Participants will be monitored for safety from the beginning of the treatment and at each study visit. Events related to and associated with the recovery from the pre-planned RP will not be collected.

Details regarding the Steering Committee are provided in Committees Structure in Section 10.3 Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Section 10.4, Appendix 4, Adverse Events,

Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA.

8.2.1. Physical Examinations

Focused physical examinations including skin assessment will be completed prior to treatment, and at 2, 3, 4, 7, 10, 13, and 14 months. Focused examinations are generally limited to the body systems or regions based on participant's self-assessment and AE reporting. Any new complaints, symptoms reported by participants or adverse events noted by providers should guide the need and extent of physical examination.

8.2.2. Vital Signs

Vital signs are to be assessed per standard of care or as warranted by AEs.

8.2.3. Electrocardiograms

A 12-lead ECG will be conducted prior to treatment to assess for QT prolongation, if not available from pre-operative evaluation. During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. The only study-specified laboratory assessments are PSA and testosterone.

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety

information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

Monitoring of AEs will be performed at 1, 2, 3, 4, 7, 10, 13, 14 months, at each follow-up visit, and during phone calls with the participants. All AEs and special reporting situations, whether serious or non-serious, will be reported from the time after the participant receives the first dose of apalutamide until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be emailed to the to the appropriate sponsor contact person by study-site personnel.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Participants who are not able to respond verbally, may be asked to write a brief description of how they have been feeling.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4 Adverse Events, Serious Adverse Events, Product Quality Complaints,

and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AE to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

The plan for monitoring and analyzing the anticipated events is specified in the IB.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the United States requirements.

8.3.5. Pregnancy

All initial reports of pregnancy in partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Cardiovascular and Death Events

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving apalutamide. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of apalutamide for Grade 3 and 4 events.

8.3.7. Disease-Related Events and Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfil the SAE definition (refer to Adverse Event Definitions and Classifications in Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting). Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study intervention than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study

intervention is enhancing disease progression, should be reported per the usual reporting requirements.

8.3.8. Adverse Events of Special Interest

For apalutamide, there are no non-serious AEs of special interest identified.

Rash is an AE of special interest to be assessed by CTCAE criteria and following the specific rash management plan in Appendix 9, Recommendations for Management of Drug related Rash.

8.4. Pharmacokinetics (Not Applicable)

8.5. Genetics

Genetics will be evaluated by DNA repair deficient (DRD) germline testing using whole blood sample.

8.6. Biomarkers

Biomarker samples may be collected as outlined in the SoA. Biomarker analysis is planned to retrospectively evaluate risk scores and other genomic markers and correlate with participants' response to treatment and explore HRD status and efficacy of apalutamide in this subpopulation. To address these objectives, tumor tissue will be collected and sent to sponsor's laboratory partner along with a copy of the full histopathology report of the specimen. Biopsy tissue is required for risk scores (Prolaris) and is preferred for HRD testing Also, whole blood and plasma samples may be collected at baseline, 12 months or end of treatment, and at 24 months or progression (whichever comes first).

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded tumor sample for the successful completion of the protocol specified analyses, the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study intervention(s) or diseases being investigated.

8.7. Immunogenicity Assessments (Not Applicable)

8.8. Health Economics (Not Applicable)

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

The primary hypothesis of this study is that adjuvant treatment with apalutamide and ADT will improve the BCR-free rate at 24 months in the treatment-naïve, non-metastatic prostate cancer population who are at high risk for the development of metastases compared to historical data without adjuvant treatment (76%).[14]

9.2. Sample Size Determination

It is assumed that BCR-free rate follows an exponential distribution with a constant hazard rate. It is estimated that approximately 94 participants accrued over approximately 1 year, treated for 12 months and followed for an additional 12 months would be required to provide at least 80% power in detecting a 10% absolute increase in BCR-free rate at 24 months of 76% to 86% at a 1-tailed significance level of 0.05. The null hypothesis of 76% BCR-free rate at 24 months for the historical data of no adjuvant treatment is an estimate based on published data.[14] Sample size was calculated using PASS 15 (Power Analysis and Sample Size Software [2017]).[20]

9.3. Populations for Analysis Sets

For analysis purpose, the following sets are defined:

- All safety analyses will be performed using the Treated set. The Treated set will consist of all participants who received at least 1 dose of apalutamide.
- All efficacy analyses will be performed using the Modified Intent-to-Treat set. The Modified Intent-to-Treat set consist of all participants who satisfy all of the following:
  - Met all eligibility criteria and are enrolled in the study
  - Received at least 1 dose of apalutamide
  - Had a baseline PSA and at least 1 post-treatment PSA assessment.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Primary endpoint test of hypothesis will be performed at 1-sided significant level 0.05; a 2-sided alpha level of 0.10 will be used to provide all confidence intervals.

9.4.2. Primary Endpoint

Time to BCR (ie, PSA >0.2 ng/mL) will be analyzed using Kaplan-Meier method. The BCR -free rate at 24 months will be estimated with the 90% confidence interval. Null hypothesis of BCR free- rate of 76% will be rejected if the lower limit of the 90% confidence interval exceeds 76%. Participants who do not have any occurrence of PSA >0.2 ng/mL, will be considered as censored at their last time of PSA measurement.

9.4.3. Secondary Endpoint

The secondary endpoint of testosterone recovery will be analyzed similarly to the primary endpoint. The testosterone recovery, defined as a serum testosterone ≥150 ng/dL, will be analyzed using Kaplan-Meier method. The testosterone recovery at 24 months will estimated together with 95% confidence interval.

9.4.4. Exploratory Endpoint

Incidence of rash will be summarized descriptively.

9.4.5. Safety Analyses

All safety analyses will be made on the Safety Population.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days is considered to be treatment emergent. All reported treatment emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or a serious AE.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst AE grade experienced by the participant during the study will be provided as shift tables.

9.4.6. Other Analyses

Biomarkers Analyses

Participants with biomarker samples will be evaluated for high-risk genomic classifiers and HRD status. A subgroup analysis will be performed to assess the treatment effect in participants stratified by risk classifiers and HRD status.

The association of biomarkers with clinical response endpoints or survival may be assessed using appropriate statistical methods (eg, analysis of variance [ANOVA], categorical, or survival models) depending on the endpoints. Analyses may be performed within and between each intervention group. Other clinical covariates (such as baseline tumor characteristics and participant demographics) may also be included in the model. Association of biomarkers with clinical response or relevant time-to-event endpoints will also be explored in the overall population. Results of these exploratory analyses will be presented in separate technical reports.

9.5. Interim Analysis (Not Applicable)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ADT	androgen deprivation therapy
ADL	Activities of Daily Living
AE	adverse event
AR	androgen receptor
ANOVA	analysis of variance
BCR	biochemical recurrence
BCRP	breast cancer resistance protein
BSA	body surface area
COVID-19	coronavirus disease 2019
CSPC	castration-sensitive prostate cancer
CT	computed tomography
CYP	cytochrome P450
DBL	database lock
DES	diethylstilbestrol
DRD	DNA repair deficient
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EOS	end of study
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin releasing hormone
HRD	homologous recombinant deficiency
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
mCSPC	metastatic castration-sensitive prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MFS	metastasis-free survival
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nmCRPC	non-metastatic castration-resistant prostate cancer
OATP1B1	organic anion transporter 1B1
PET	positron emission tomography
PASS	Power Analysis and Sample Size Software
P-gp	P-glycoprotein
PQC	product quality complaint
PSA	prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
RP	radical prostatectomy
rPFS	radiographic progression free survival
SAE	serious adverse event
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction

UGT	uridine diphosphate glucuronosyl transferase
USPI	United States Package Insert

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Clinical Laboratory Tests

Prostate-specific antigen and testosterone tests will be performed by the local laboratory.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials

- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of samples for research included in the ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in the US.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1, Participant Input Into Design.

10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that

the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the participant's or his legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

10.3.4. Data Protection

Privacy of Personal Data

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

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

The informed consent obtained from the participant (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and

confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand apalutamide with ADT, to understand localized high-risk prostate cancer, to understand differential intervention responders, and to develop tests/assays related to apalutamide with ADT and localized high-risk prostate cancer. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.3.6. Committee Structure

Steering Committee

A Steering Committee will be established to provide guidance and supervision for the study, including ensuring the continued safety of the participants enrolled in this study. The committee chair will have medical expertise in the relevant therapeutic area. Committee membership responsibilities, authorities, and procedures will be documented in its charter.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding apalutamide or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of apalutamide, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of smoking, all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum
- History of alcohol intake, including type, usage, amount, and frequency.
- Height and weight at baseline

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in thee CRF.

10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.12. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigators should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonisation [ICH][10])

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

Note: The sponsor collects AEs from the time after the participant receives the first dose of apalutamide (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

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

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

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For apalutamide, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all AE.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity grade will be made using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, where ‘grade’ refers to the severity of the AE.

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care (ADL)

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

For additional information, refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017.

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without participant exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number

Serious Adverse Events

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

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

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study intervention than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study intervention is enhancing disease progression, should be reported per the usual reporting requirements.

10.4.6. Product Quality Complaint Handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure

appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive Guidance

Participants' female partners must follow contraceptive measures as outlined as below. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.4, Appendix 4 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
[b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
[c] Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Prohibited Concomitant Medications

Apalutamide

Drugs known to lower the seizure threshold or cause seizures are prohibited and a representative list is included below:

- Aminophylline/theophylline
- Atypical antipsychotics (eg, clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperidine (pethidine)
- Phenothiazine antipsychotics (eg, chlorpromazine, mesoridazine, thioridazine)
- Tricyclic antidepressants (eg, amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)

Other prohibited therapies include the following:

- Investigational agents
- Any other prior or current treatment for prostate cancer which includes but not limited to
  - Abiraterone acetate or other CYP17 inhibitors
  - Other hormonal agents for the treatment of prostate cancer
  - Other antineoplastic agents
  - Radiation therapy
  - 5-α-reductase inhibitors
  - Chemotherapy
  - Immunotherapy or vaccine therapy for cancer treatment
  - Other anti-androgens (eg, bicalutamide, nilutamide, flutamide, cyproterone acetate, enzalutamide)
  - Bisphosphonates or denosumab unless for management of osteoporosis
  - Systemic ketoconazole (or other azole drugs such as fluconazole or itraconazole)
  - Diethylstilbestrol (DES) or similar
  - Other preparations such as pomegranates or pomegranate juice or saw palmetto, which are thought to have endocrine effects on prostate cancer
  - Radiopharmaceuticals such as strontium (^{89}Sr) or samarium (^{153}Sm) or similar analogs such as radium-223 (^{223}Ra)
  - Spironolactone

If the permissibility of a specific drug/treatment is in question, please contact the sponsor.

10.7. Appendix 7: Restricted Concomitant Medications

- Investigators should refer to the IB (Sections 4.3.4 and 5.10) and associated addenda for complete details on the drug interaction potential of apalutamide.
- Medications that inhibit CYP2C8 or CYP3A4: Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl apalutamide). No initial dose adjustment is necessary; however, consider reducing the apalutamide dose based on individual tolerability. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.
- Effect of apalutamide on drug metabolizing enzymes: Apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of apalutamide with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of efficacy if medication is continued. Concomitant administration of apalutamide with medications that are substrates of uridine diphosphate 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 efficacy.
- Effect of apalutamide on drug transporters: Apalutamide was clinically shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporter 1B1 (OATP1B1). Concomitant use of apalutamide with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with apalutamide, and evaluate for loss of efficacy if medication is continued.
- Long-term use of systemically administered corticosteroids during the study is not allowed. Short-term use (≤4 weeks, including taper) and locally administered steroids (eg, inhaled, topical, ophthalmic, and intra-articular) are allowed, if clinically indicated.
- See Section 10.8, Appendix 8, Medications with the Potential for Drug-drug Interactions, for a complete list of medications prohibited while on active treatment with apalutamide.
- Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, and alternative therapies must be documented on the eCRF. The principal investigator should be alerted if the participant is taking any agent found in Appendix (a listing of medications with the potential for drug-drug interaction).

10.8. Appendix 8: Medications with the Potential for Drug-drug Interactions

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

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

Generic Name	Brand Name**
thioridazine	Detril; Elperil; Melleril; Ridazin; Ridazine; Thiodazine; Thioril; Sonapa
ziprasidone	Geodon; Li Fu Jun An; Pramaxima; Si Bei Ge; Ypsila; Zeldox; Zipwell; Zypsila; Zypsilan

****Note: This document is intended as an aid in identifying prohibited meds but may not be all inclusive**.

10.9. Appendix 9: Recommendations for Management of Drug-related Rash

- In the combined data of two randomized, placebo-controlled clinical studies, rash associated with apalutamide was most commonly described as macular or maculopapular. (Please refer to the current IB- for further details.)
- Evaluate causality of the rash ie, Is it related to apalutamide? Or another form of rash such as shingles, sunburn, etc.
  - If not considered related to apalutamide, evaluate and treat according to the etiology.
  - If possibly related to apalutamide, grade the severity of rash per the NCI-CTCAE Version 5.0 below and treat according to Dose Modification and Management Guidelines.

Rash maculo-papular	A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis.
Grade 1	Macules/papules covering <10% body surface area (BSA) with or without symptoms (eg, pruritus, burning, tightness)
Grade 2	Macules/papules covering 10 to 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental Activities of Daily Living (ADL); rash covering >30% BSA with or without mild symptoms.
Grade 3	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL.

NCI-CTCAE Version 5.0; Published: 27 November 2017.

Toxicity Severity	**Dose Modification and Management Guidelines**
If there is blistering or mucosal involvement, stop apalutamide immediately and contact the sponsor. Standardized photography to be undertaken by the study-site personnel. Educate on gentle skin care. Initiate dermatological treatment.	
Grade 1 or Grade 2	**Continue apalutamide at the same dose:** o High potency topical steroid lotion bid eg, fluocinonide 0.05%, clobetasol 0.05%, or betamethasone 0.05% AND o Oral antihistamines hydroxyzine: 10 mg bid for Grade 1 or 25 mg bid for Grade 2, or equivalent. **Monitor for change in severity, contact the participant at minimum every 2 weeks:** o If rash is stable or improves, continue current management and monitoring until rash resolves. o If rash worsens, follow guidance for Grade 3.

Toxicity Severity	Dose Modification and Management Guidelines
If there is blistering or mucosal involvement, stop apalutamide immediately and contact the sponsor. Standardized photography to be undertaken by the study-site personnel. Educate on gentle skin care. Initiate dermatological treatment.	
Grade 3	**Hold apalutamide until rash is Grade ≤1** o Oral steroids Prednisone 0.5 to 1 mg/kg/day for 20 days or equivalent with maximum dose of 100 mg/day AND o High potency topical steroid lotion or solution bid eg, fluocinonide 0.05%, clobetasol 0.05%, or betamethasone 0.05% AND o Oral antihistamines (hydroxyzine 25 mg bid or equivalent). o Reassess after 2 weeks (by site staff). **After 2 weeks of management (as above):** **If the rash is the same or has worsened** o Continue to hold apalutamide and refer the participant to a dermatologist. **If rash improves to Grade 2:** o Continue to hold apalutamide, continue current management. o Reassess after 1 week (by site staff). After 1 week: o If after 1-week rash is still Grade 2, continue to hold apalutamide and refer the participant to a dermatologist. o If rash has improved to Grade ≤1, see below. **If rash is Grade ≤1:** o Reinitiate apalutamide at half the dose (120 mg) for 2 weeks o Continue oral antihistamines for 1 week o Start tapering oral steroids o Continue topical treatment until rash resolves o Return to full dose after 2 weeks of half dose apalutamide and if rash remains ≤1 If the proposed total oral steroid use will exceed 28 days, contact the sponsor. If after 28 days of starting the treatment, rash has not resolved to Grade ≤1, contact the sponsor

10.10. Appendix 10: Phone calls with Participants

It is recommended to use a standardized questionnaire as noted below during phone calls. The questions serve as a guidance for documenting presence and severity of rash. All participants will receive a call weekly in the first month of treatment and then mid-cycle (ie, biweekly) after Visit 2 through Visit 3 and thereafter if the participant has rash (per Section 10.9, Appendix 9, Recommendations for Management of Drug-related Rash). Participants should be encouraged to call the study site anytime they notice a rash or if the rash worsens.

Guide for discussion during phone calls:

- Ask if the participant is willing to continue the study
- Collect information on the participant's compliance with oral administration of study intervention
- Collect information on the participant's current health status including discussion of concomitant medications and adverse events including any skin rash
  - Have you noticed any skin rash since the start of the treatment (or since the last site visit or phone call)?
    - If this is the first occurrence of rash, please schedule a site visit for the participant as soon as possible
  - If yes, do you have any symptoms associated with the rash? (eg, pruritus, tingling, burning, tightness)
  - What is the severity of the symptoms? (none, mild, moderate, severe, very severe)
  - Are the symptoms improving or worsening?
  - (If applicable) Have you been regularly applying the skin lotion or solution prescribed to you for skin rash?
  - Remind the participant about the gentle skin care instructions
- Schedule the next call (if applicable)

10.11. Appendix 11: Instructions for Gentle Skin Care

1. Light emollient (lotion) applied daily as required after any other prescribed topical steroid lotion has had time to dry.
2. Use an antiseptic-containing soap substitute or a mild pH-neutral soap (eg, Cetaphil).
3. Avoid strong sun and weather extremes.
4. Use sunblock (SPF 50) when outdoors.
5. Avoid long, hot baths, showers and saunas. Use tepid water for bathing.
6. Avoid alcohol-based and fragranced skin-care products as these may exacerbate dry skin.
7. For participants with pre-existing eczema: intensify usual skin care routine.

10.12. Appendix 12: Guidance on Study Conduct during the COVID-19 Pandemic

The measures outlined in this appendix are temporary, while access to sites may be restricted. As restrictions are lifted, the decision to revert back to the protocol specified procedures should be discussed and agreed with the sponsor.

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, the study intervention will be discontinued, and study follow-up will be conducted.

If a potential participant had RP surgery delayed due to the COVID-19 situation and was given ADT as a bridging measure until the participant could be scheduled for surgery, the participant may still be considered for the study, if all other inclusion/exclusion criteria are met. Each individual case will need to be discussed with the study sponsor for approval prior to entry into the study.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

To ensure participant safety and minimize disruption to completion of protocol scheduled visits, we recommend the following when it is not safe to complete a scheduled visit at the site due to the coronavirus pandemic:

- Arrange an appointment to conduct the visit as well as collect information on the participant current health status, adverse events and concomitant medications over the phone or other remote technology (Facetime, WhatsApp etc) as allowed by local regulations.
- Document all communication with participants and protocol related activities completed remotely in the source and eDC as required.
- Document all missed assessments, discontinuations of study interventions and withdrawal from the study. Missed assessments will be captured in the clinical trial management system for protocol deviations, with the actual visit date documented or reason for withdrawals specified; discontinuations of study interventions and withdrawal from the study will be captured with the prefix "COVID-19-RELATED" in the eCRF.

Safety and Disease Evaluation Visits:

Protocol required laboratory tests may be performed at a nearby hospital or doctor´s office when they cannot be done at the site.

- For participants who are unable or unwilling to leave their homes to complete protocol scheduled visits due to the coronavirus pandemic, the visits should be postponed until it is deemed safe to return to the site or local hospital.
- It is strongly recommended to schedule regular phone consultations to assess any new/ongoing adverse events including skin rash, fatigue, seizures, falls and fractures. Participants should be encouraged to check their blood pressure at home regularly and report any new symptoms to the study team urgently. Advise participants to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur.
- If a participant is unable to visit study site or designated laboratory, serum PSA and testosterone testing can be done at a local laboratory. Protocol required biomarker and pharmacogenomics sampling can be done at the site as soon as the situation permits.
- Please ensure any evaluations are documented in the source and eDC. Identify the assessments as "missed or delayed due to COVID-19".

Changes in Study Intervention:

- Study intervention (apalutamide) should be continued in the protocol specified manner. If a participant is unable to receive the drug as specified in the protocol, please call the sponsor to discuss.
- Androgen Deprivation Therapy (ADT) which is administered concurrently should be continued (1-month or 3-month depot formulations given intramuscular or subcutaneously per the information in the package insert). If a participant is unable to visit the study site, please

arrange a visit to a nearby hospital or doctor´s office or a home visit by a trained provider to administer the ADT at home.

Keep Communications Open (within-site, sponsor-site, site-participant):

- Please maintain up-to-date contact information for one another (site colleagues, sponsor contacts, participants) and keep communication channels open, including in circumstances where site staff/participants are experiencing restrictions in physical workplace or study visit attendance.

Source Data Verification/Monitoring:

- On-site monitoring visits may not be possible due to local regulations, restrictions and guidance. In these cases, the Site Manager will arrange to conduct site monitoring visits and activities remotely. Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

10.13. Appendix 13: Sub-Study Protocol

10.13.1. Protocol Summary

A sub-study will be conducted assessing the coadministration of apalutamide and relugolix in treatment-naïve participants who have undergone radical prostatectomy (RP) for non-metastatic prostate cancer and who are at high risk for metastases.

Apalutamide (ERLEADA®) is an orally available, non-steroidal, small molecule, which acts as a potent and selective antagonist of androgen receptors (ARs). Apalutamide is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC) and metastatic castration-sensitive prostate cancer (mCSPC). Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.

Relugolix (ORGOVYX™) is an orally available GnRH receptor antagonist approved by the FDA on December 18, 2020 for the treatment of adult patients with advanced prostate cancer.

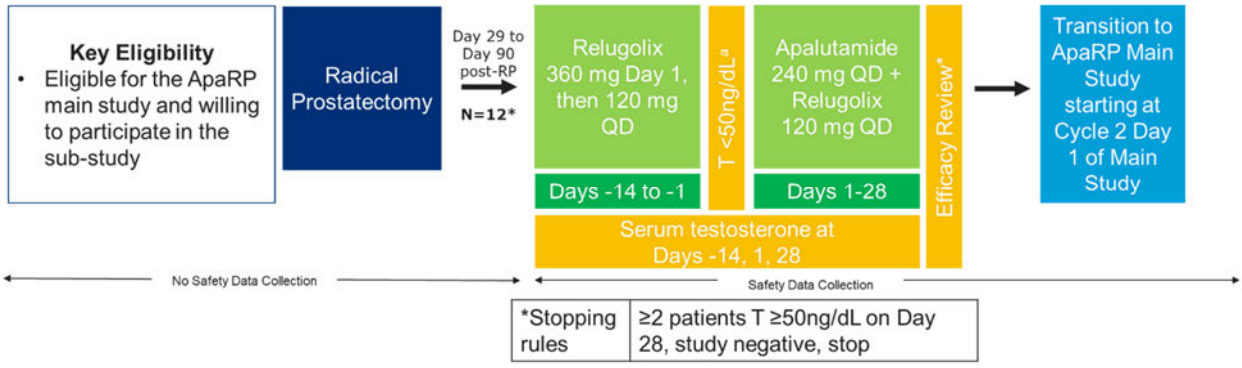
Given the recent approval of relugolix and the fact that apalutamide is indicated in combination with a GnRH analog, there is a need to understand the effect of combining relugolix and apalutamide on testosterone suppression.

This is a single-arm, open-label, multi-center sub-study of apalutamide and relugolix in 12 participants with high risk localized prostate cancer who are treatment naïve, documented to have no evidence of metastatic disease prior to study entry, who are between Day 29 and Day 90 post-RP, whose PSA is ≤0.2 ng/mL at study entry, and who have recovered from surgery, per the clinical judgment of the investigator. There will be one study intervention group receiving relugolix monotherapy for 2 weeks followed by coadministration with apalutamide for 1 cycle (28 days). Serum testosterone will be measured on Day –14 (ie, the day of starting relugolix administration), Day 1 (ie, the day of starting coadministration with apalutamide), and Day 28. The primary endpoint is the percentage of participants maintaining testosterone <50 ng/dL through Day 28, and the secondary endpoint is safety (adverse events) through Day 28. Upon completion of the sub-study, participants will be transitioned into the main ApaRP study protocol beginning at Cycle 2 Day 1.

Refer to subsequent sections for details on objectives and endpoints, hypothesis, overall design, number of participants, intervention groups and duration, efficacy evaluations, and safety evaluations.

10.13.2. Schema

Figure 2: Schematic Overview of the Sub-Study



10.13.3. Schedule of Activities (SoA)

ApaRP Relugolix Sub-Study **participants join main ApaRP SoA after sub-study (starting Day 29 [C2D1 apa])*															
Study Visit	**Pre-op Screening**	**Sub-Study V1**				**Sub-Study V2**								**Sub-Study V3**	**Transition to main ApaRP protocol starting at Cycle 2 Day 1**
Calendar Day		**Day -14****	**Day -13 to Day -8**	**Day -7**	**Day -6 to Day -1**	**Day 1**	**Day 2 to Day 6**	**Day 7**	**Day 8 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21**	**Day 22 to Day 27**	**Day 28**	
Study Window						+3[a]								+3	
Screening/Administrative															
Sub-study informed consent form (ICF)[b]	x*														
Demographics	x*														
Review medical history requirements	x*														
I/E criteria met	x*														
Post-op PSA	x*														
Study Intervention Administration															
Dispense/administer study intervention (apalutamide)						x	x	x	x	x	x	x	x	x	
Dispense/administer study intervention (relugolix)		x[c]	x	x	x	x	x	x	x	x	x	x	x	x	
Check-in on medication compliance[d]				x		x		x		x		x		x	
Sub-study participant medication diary[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	
Efficacy Evaluations															
Testosterone		x				x[f]								x[f]	
Safety Evaluations															
Focused physical examination including skin assessment[g]		x*													
12-lead ECG	x					x								x	
Pharmacodynamics and Biomarkers															
Plasma samples[h]		x*													
Tumor tissue sample[i]		x*													
Pharmacogenomics (DNA)															
DRD status (germline)		x*													
Ongoing Participant Review															
Concomitant therapy[j]		continuous													
Adverse events[k]		continuous													
Education and counselling on skin care						continuous									

Key: ADT=androgen deprivation therapy; AE=adverse event; DNA=Deoxyribonucleic Acid; DRD=DNA repair deficient; ECG=electrocardiogram; ICF=informed consent form; I/E criteria=inclusion exclusion criteria; PSA=prostate-specific antigen

Footnotes:

*as required for main ApaRP study

**study Day -14 starts on date of administration of relugolix treatment

a If delaying sub-study visit 2 by up to 3 days, please advise the patient to continue relugolix until castrate levels of testosterone are confirmed and coadministration with apalutamide has started.

b The sub-study ICF must be signed before first study-related activity and will cover the sub-study and the main study.
c Relugolix administered as 360 mg on first day of treatment (Day –14), followed by 120 mg on subsequent days.
d If not occurring during an in-person visit, the study team should call the participant to ask about medication compliance.
e Should be completed daily by the participant during sub-study treatment and provided to the study team at each sub-study visit (form located in Section 10.14, Appendix 14).
f If participant's testosterone ≥50 ng/dL on Day 1 or Day 28, stop relugolix, switch to intramuscular ADT, and switch to main ApaRP study.
g Focused examinations are generally limited to the body system or regions based on participant's self-assessment and AE reporting. Any new complaints, symptoms reported by participants or adverse events noted by providers should guide the need and extent of physical examination.
h Collected at baseline, 12 months or end of treatment, and at 24 months or progression (whichever comes first) as part of the main ApaRP study.
i Tissue sample to be collected and sent to sponsor's laboratory partner along with a copy of the full histopathology report of the specimen. See Section 8.6 for further details.
j Collection of concomitant therapies does not begin until time of first dose of relugolix.
k Collection of AEs does not begin until time of first dose of relugolix.

10.13.4. Introduction

10.13.4.1. Study Rationale

Relugolix (ORGOVYX™) is an orally available gonadotropin-releasing hormone (GnRH) receptor antagonist approved by the FDA on December 18, 2020 for the treatment of adult patients with advanced prostate cancer. Relugolix is administered at a loading dose of 360 mg on the first day of treatment, followed by 120 mg taken orally once daily. Relugolix is metabolized primarily by CYP3A and is a substrate for intestinal P-glycoprotein (P-gp). Clinical studies with rifampin, a combined P-gp and strong CYP3A inducer, decreased the AUC and C_{max} of relugolix by 55% and 23%, respectively. Consequently, the relugolix label suggests avoiding coadministration with combined P-gp and strong CYP3A inducers and if unavoidable, to increase the dose of relugolix to 240 mg once daily.[19]

Apalutamide is a strong inducer of CYP3A4 and a weak inducer of P-gp. Concomitant use of apalutamide with medications that are primarily metabolized by CYP3A4 and/or a substrate of P-gp can result in lower exposure of these medications. Apalutamide has been shown to reach steady state concentrations at 4 weeks.[7]

Given relugolix is the first and only approved oral GnRH antagonist and apalutamide is indicated in combination with a GnRH analog, there is a need to understand the clinical implications of combining relugolix and apalutamide in the clinic. Achieving and maintaining a castrate level of serum testosterone (<50 ng/dL) while on ADT is considered the gold standard assessment of achieving castration with GnRH analogs. Data from 899 participants (from Phase 1, 2, and 3 studies) with both relugolix and testosterone concentration data were combined for PopPK and PopPK/PD analyses.[18] In simulated testosterone concentrations, relugolix dosed as low as 40 mg once daily following a loading dose of 360 mg achieved a median testosterone <50 ng/dL within 10 days.[18] Relugolix dosed at 120 mg once daily following a loading dose of 360 mg achieved a testosterone <50 ng/dL in 90% of the simulations within 10 days.[18] In the registrational Phase 3 HERO study of relugolix dosed at 120 mg once daily after a loading dose of 360 mg, the cumulative probability of testosterone suppression to <50 ng/dL on Day 4 and Day 15 were 56% and 98.7%, respectively.[24]

As part of the Phase 3 HERO study, concomitant medications that could possibly affect testosterone were tracked. Seventeen (3%) participants received concomitant enzalutamide with relugolix.[19] Similar to apalutamide, enzalutamide is a strong CYP3A4 inducer.[30] In vitro, enzalutamide and N-desmethyl enzalutamide are inhibitors of P-gp.[30] Despite the potential drug-drug interaction, no clinically significant differences in the pharmacokinetics of relugolix were observed when coadministered with enzalutamide.[19] Additionally, no clinically relevant differences were noted in the incidence or types of adverse events (AE) before or after concomitant use of enzalutamide.[18]

Given the similarities in the metabolism of apalutamide and enzalutamide and the fact that relugolix achieved a median testosterone <50 ng/dL within 10 days dosed as low as 40 mg once daily following a loading dose of 360 mg, we hypothesize coadministration of apalutamide 240 mg

once daily with relugolix as indicated (120 mg once daily following a loading dose of 360 mg) will achieve and maintain castrate testosterone levels (<50 ng/dL) without the need to increase the relugolix dose.

For the most comprehensive nonclinical and clinical information regarding relugolix or apalutamide, refer to the latest version of their respective US Package Inserts (USPI).

10.13.4.2. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of apalutamide may be found in the ERLEADA® USPI.[7] More detailed information about the known and expected benefits and risks of relugolix may be found in the ORGOVYX™ USPI.[19]

The perceived benefit of relugolix is the convenience of oral administration versus intramuscular injections that require supervision of a physician as indicated with other GnRH analogs. Throughout the course of this 6-week sub-study, serum testosterone levels will be assessed on multiple occasions and participants will be removed from the sub-study if castrate levels of testosterone are not achieved. Safety will be monitored by AE reporting. With established safety profiles, close monitoring, and the low risk of short-term reduced relugolix effect on testosterone, the benefit of assessing the coadministration of apalutamide and relugolix outweighs the potential risks associated with each intervention.

10.13.5. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess if the addition of apalutamide to relugolix is able to maintain castrate levels of testosterone.	• Percentage of participants maintaining testosterone <50 ng/dL through Day 28.
Secondary	
• To evaluate the safety of coadministering apalutamide and relugolix at their indicated doses.	• Adverse events through Day 28.

HYPOTHESIS

The primary hypothesis of this sub-study is that coadministration of apalutamide 240 mg once daily with relugolix 120 mg once daily (following a loading dose of 360 mg) will achieve and maintain castrate levels of testosterone (<50 ng/dL).

10.13.6. SUB-Study Design

10.13.6.1. Overall Design

This is a single-arm, open-label, multi-center sub-study of apalutamide and relugolix in 12 participants with high risk localized prostate cancer who are treatment naïve, documented to have no evidence of metastatic disease prior to study entry, who are between Day 29 and Day 90 post-RP, whose PSA is ≤0.2 ng/mL at study entry, and who have recovered from surgery, per the

clinical judgment of the investigator. Upon completion of the sub-study, participants will be transitioned into the main ApaRP study protocol beginning at Cycle 2 Day 1.

The sub-study will be conducted in approximately 6 urology practices already conducting the main ApaRP study. There will be one study intervention group receiving relugolix monotherapy for 2 weeks followed by coadministration with apalutamide for 1 cycle (28 days). Treatment with relugolix will start following screening and completion of RP and no later than postoperative Day 90. Coadministration of apalutamide will start 14 days after initiation of relugolix monotherapy. Serum testosterone will be measured on Day –14 (ie, day of starting relugolix administration), Day 1 (ie, the day of starting coadministration with apalutamide), and Day 28. If a participant does not achieve a serum testosterone <50 ng/dL on Day 1 following 14 days of relugolix monotherapy, relugolix will be discontinued and the participant will switch to intramuscular ADT and the main ApaRP study and that participant will be replaced in the sub-study. If a participant achieves a serum testosterone <50 ng/dL on Day 1 following 14 days of relugolix monotherapy, coadministration with apalutamide will begin. As assessed on Day 28, if the coadministration of apalutamide and relugolix achieves and maintains a serum testosterone <50 ng/dL through Day 28 of the sub-study, participants will be given the opportunity to continue relugolix and apalutamide as part of the main ApaRP study. If the coadministration of apalutamide and relugolix does not achieve and maintain a testosterone <50 ng/dL through Day 28 of the sub-study in 2 or more participants, all participants on the sub-study will discontinue relugolix and switch to intramuscular ADT plus apalutamide as part of the main ApaRP study.

The sub-study will have 12 participants. If 2 or more participants have a testosterone ≥50 ng/dL on Day 28, the sub-study will be considered negative and all participants will switch to intramuscular ADT in the main ApaRP protocol. If 0 or 1 participant has a testosterone ≥50 ng/dL, the sub-study will continue until all 12 participants have been enrolled.

If a participant ends the sub-study early (ie, due to treatment non-compliance or not achieving a testosterone <50 ng/dL on Day 1 after relugolix monotherapy), that participant will be replaced in order to enroll 12 participants total. If the sub-study is terminated early due to lack of efficacy (ie, ≥2 participants have a testosterone ≥50 ng/dL on Day 28) or safety (ie, ≥2 participants have prolonged QTc (>ULN) on Day 28), no further participants will be enrolled into the sub-study.

The timing and frequencies of study assessments are presented in the sub-study SoA (Section 10.13.3, Appendix 13). Efficacy assessments include serum testosterone and will be assessed at baseline (Day -14), after 14 days of relugolix monotherapy (Day 1), and after 28 days of coadministration of apalutamide and relugolix. A serum testosterone <50 ng/dL is considered castrate and the gold standard for indicating castration while on ADT. Study enrollment is defined as the day when the participant receives the first dose of relugolix monotherapy after having met all prescreening criteria. Adverse events will be assessed continuously from the time of enrollment and during treatment. A 12-lead electrocardiogram (ECG) will be conducted at screening, after 14 days of relugolix monotherapy, and after 28 days of apalutamide and relugolix coadministration, to examine QT prolongation. If any participant has a prolonged QTc at either Day 1 or Day 28, that participant will be removed from the study completely and replaced in the sub-study. If

2 participants have prolonged QTc at Day 28 the sub-study will terminated and any participants currently on the combination of relugolix and apalutamide will be evaluated for potentially changing to intramuscular ADT.

A diagram of the study design is provided in Section 10.13.2, Appendix 13, Schema.

10.13.6.2. Scientific Rationale for Study Design

The single-arm, open-label design is appropriate to evaluate the pharmacodynamic effect of a new oral ADT medication with apalutamide. Additionally, stopping rules can be quickly implemented with this design (see Section 10.13.6.1, Appendix 13 Overall Design for stopping rules).

Scientific Rationale for the main ApaRP study design can be found in Section 4.2, Scientific Rationale of the main protocol.

10.13.6.3. Justification for Dose

The dose of 240 mg once daily apalutamide and 120 mg once daily relugolix following a loading dose of 360 mg relugolix are approved doses per their respective USPIs.

10.13.6.4. End of Study Definition

End of Study Definition

The sub-study EOS is defined as the date of the last participant's enrollment in the sub-study +6 weeks or discontinuation of all study participants from the sub-study, whichever occurs first. All participants will be transitioned to the main ApaRP study following the sub-study EOS visit.

Study Completion Definition

Participants will be considered to have completed the sub-study if they have completed EOS assessments. Participants who prematurely discontinue sub-study intervention for any reason before sub-study completion will not be considered to have completed the sub-study. If a participant misses a dose for ≥3 days, the investigator should consult the sponsor regarding continuation of the sub-study.

10.13.7. Study Population

The sub-study population will use the criteria of the main ApaRP study. Refer to Section 5 of the main ApaRP protocol for details of the study population. Participants must also be willing to participate in the sub-study and should not have any allergy, hypersensitivity, or contraindications to the administration of relugolix per the ORGOVYX USPI.

10.13.8. Study Intervention

10.13.8.1. Study Intervention Administered

Apalutamide

The sub-study intervention apalutamide, 240 mg (four 60 mg tablets, slightly yellowish to greyish green oblong film-coated tablets, debossed with "AR 60" on one side), will be provided as tablets for oral administration. Participants will be instructed to take their assigned dose of the sub-study intervention orally once daily for 28 days per the ERLEADA USPI. Apalutamide can be taken with or without food. If a participant experiences a ≥Grade 3 toxicity or an intolerable side effect, hold dose until symptoms improve to ≤Grade 1 or original grade, then resume at the same dose or a reduced dose (180 mg or 120 mg), if warranted. If a participant remains off apalutamide for ≥3 days, the participant may be withdrawn from the sub-study and switched to the main ApaRP study after discussing with the sponsor. Participants experiencing treatment related seizure of any grade will have apalutamide permanently discontinued.

Relugolix

The sub-study intervention relugolix, 120 mg with a loading dose of 360 mg (three 120 mg tablets, light red, almond-shaped, film-coated, debossed with "R" on one side and "120" on the other side), will be provided as tablets for oral administration. Participants will be instructed to take their assigned dose of the sub-study intervention orally once daily for 42 days per the ORGOVYX USPI. Relugolix can be taken with or without food. If a participant misses relugolix for ≥3 days, the participant may be withdrawn from the sub-study and switched to the main ApaRP study after discussing with the sponsor.

Description of Interventions

Sub-study interventions administration must be captured in the source documents and the electronic case report form (eCRF). Sub-study site personnel will instruct participants on how to store sub-study interventions for at-home use as indicated for this protocol.

Apalutamide will be manufactured and provided under the responsibility of the sponsor. Refer to the IB[11] for a list of excipients and the ERLEADA USPI.

Relugolix, an FDA approved and commercially available oral ADT, not provided by the sponsor, will be administered per the ORGOVYX USPI during the sub-study and the main ApaRP study if participants continue relugolix coadministration (see Section 10.13.6.1, Appendix 13, Overall Design for details of relugolix continuation in the main ApaRP study). For further information on relugolix refer to the ORGOVYX USPI. For a definition of apalutamide overdose, refer to Section 6.7, Treatment of Overdose, in the main ApaRP protocol.

10.13.8.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Refer to the respective USPIs for guidance on apalutamide and relugolix preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all sub-study interventions received at the site are inventoried and accounted for throughout the sub-study. The sub-study interventions administered to the participant must be documented on the intervention accountability form. All sub-study interventions will be stored and disposed of according to the sponsor's instructions. Sub-study site personnel must not combine contents of the sub-study intervention containers.

Sub-study interventions must be handled in strict accordance with the protocol and the container labels, and must be stored at the sub-study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused sub-study interventions and sub-study interventions returned by the participant must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused sub-study interventions, or used returned sub-study interventions for destruction, will be documented on the intervention return form. When the sub-study site is an authorized destruction unit and sub-study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Sub-study interventions should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Sub-study interventions will be supplied only to participants participating in the sub-study. Returned sub-study interventions must not be dispensed again, even to the same participant. Sub-study interventions may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the sub-study intervention from, nor store it at, any site other than the sub-study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused sub-study interventions are provided in the Study Site Investigational Product and Procedures Manual.

10.13.8.3. Study Intervention Compliance

Sub-study site personnel will maintain a log of all sub-study interventions dispensed. Sub-study interventions supplied for each participant will be inventoried and accounted for.

10.13.8.4. Dose Modification

Any dose adjustment should be overseen by medically qualified study-site personnel (principal or sub-investigator unless an immediate safety risk appears to be present).

In case a dose modification of apalutamide is necessary, apalutamide will be administered per ApaRP main protocol Section 10.9, Appendix 9, Recommendations for Management of Drug-related Rash.

10.13.8.5. Treatment of Overdose

Refer to the main ApaRP protocol Section 6.7, Treatment of Overdose.

10.13.8.6. Concomitant Therapy

Concomitant therapies must be recorded throughout the sub-study from the time of first dose of sub-study intervention (Day -14) to the last sub-study visit (Day 28). Concomitant therapies occurring after sub-study EOS will be captured as part of the main ApaRP protocol (Section 6.8, Concomitant Therapy).

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the sub-study intervention must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

Prohibited concomitant medications are outlined as part of the main ApaRP study in Section 10.6, Appendix 6, Prohibited Concomitant Medications. Concomitant therapy restrictions are outlined in Section 10.7, Appendix 7, Restricted Concomitant Medications.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

10.13.9. Discontinuations of study intervention and Participant discontinuations/withdrawal

10.13.9.1. Discontinuation of Study Intervention

A participant's sub-study interventions must be discontinued if:

- The participant withdraws consent to receive sub-study interventions
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue sub-study interventions
- Noncompliance with sub-study interventions administration
- The sub-study is terminated (Refer to Section 10.13.6.1, Appendix 13, Overall Design for details)
- Participants experiencing treatment-related seizure of any grade will have apalutamide permanently discontinued

If a participant discontinues sub-study interventions for any reason before the end of the sub-study, then the last scheduled sub-study assessments should be obtained. If a participant misses doses of either sub-study intervention for ≥3 days, the investigator should consult the sponsor regarding

continuation in the sub-study. If a participant discontinues sub-study interventions due to disease progression, the subsequent treatment including radiation will be captured in the eCRF, if known.

10.13.9.2. Rechallenge

Refer to the main ApaRP study protocol Section 7.1.1, Rechallenge for details.

10.13.9.3. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the sub-study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Investigator's discretion
- Seizure
- Death

When a participant withdraws before sub-study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the sub-study is withdrawal of consent, then no additional assessments are allowed. Refer to main ApaRP protocol Section 7.2, Participant Discontinuation/Withdrawal From the Study and Section 7.2.1, Withdrawal From the Use of Research Samples for further details.

10.13.9.4. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to study entry, attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

Participants will be considered lost to follow-up if they fail to return for scheduled visits and are unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. Refer to main ApaRP protocol Section 7.3 Lost to Follow-up for further details.

10.13.9.5. National Disaster/Extra Ordinary Circumstances

Refer to main ApaRP protocol Section 7.4, National Disaster/Extra Ordinary Circumstances for details.

10.13.10. Study Assessments and Procedures

Overview

The sub-study Schedule of Activities summarizes the frequency and timing of efficacy and safety measurements applicable to this sub-study. Refer to Section 10.13.3, Appendix 13, Schedule of Activities for the timing and frequency of sample collections.

Blood collections should be kept as close to the specified time as possible. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

The total blood volume for the sub-study is approximately 30 mL.

Repeat of unscheduled samples may be taken for technical issues with the samples.

Sub-Study-Specific Materials

The investigator will be provided with the following information in addition to what is provided as part of the main ApaRP protocol (refer to Section 8, Study-Specific Materials for details):

- ICF sub-study template
- Sub-study pill diary (found in Section 10.14, Appendix 14)

10.13.10.1. Efficacy Assessments

Efficacy assessments include serum testosterone and will be assessed prior to the first dose of relugolix monotherapy (Day -14), prior to starting apalutamide coadministration (Day 1), and following 28 days of apalutamide and relugolix coadministration, per the sub-study SoA. A testosterone level <50 ng/dL will be considered an indicator of castration.

10.13.10.2. Safety Assessments

Participants will be monitored for safety from the beginning of the study treatment (Day -14) and at each sub-study visit. Events related to and associated with the recovery from the pre-planned RP will not be collected.

Adverse events will be reported and followed by the investigator as specified in the main ApaRP protocol Section 8.3, Adverse Events and Serious Adverse Events and Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the sub-study must be recorded on the AE section of the eCRF.

Any clinically significant abnormalities persisting at the end of the sub-study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The sub-study will include the evaluations of safety and tolerability included in the main ApaRP protocol as noted in Section 8.2.1, Physical Examinations, and 8.2.2, Vital Signs.

10.13.10.2.1. Electrocardiograms

A 12-lead ECG will be conducted at screening, after 14 days of relugolix monotherapy, and after 28 days of apalutamide and relugolix coadministration, to examine QT prolongation. During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television,

cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

10.13.10.2.2. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the sub-study.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to the main ApaRP protocol Section 8.3, Adverse Events and Serious Adverse Events, Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

10.13.11. Statistical Considerations

Statistical analysis will be done by the sponsor or under the authority of the sponsor.

The primary hypothesis of this sub-study is that coadministration of apalutamide 240 mg once daily with relugolix 120 mg once daily (following a loading dose of 360 mg) will achieve and maintain castrate levels of testosterone (<50 ng/dL). Clinical decision rule is that if 2 or more participants have a testosterone ≥50 ng/dL on Day 28, the sub-study will be considered negative. The 95% 1-sided upper limit for the observed incidence of proportion of patients not able to maintain castrate levels is 22.1% if no participant out of 12 has a testosterone ≥50 ng/dL and 33.9% if 1 participant out of 12 has a testosterone ≥50 ng/dL. Percentage of participants maintaining testosterone <50 ng/dL through Day 28 will be summarized descriptively.

Once one cycle (28 days) of the coadministration of apalutamide and relugolix has completed, the participants will transition to the treatment schedule of the main ApaRP protocol beginning at Cycle 2 Day 1. Safety data collected during the coadministration of apalutamide and relugolix will be summarized descriptively. Data for participants transitioned to the main ApaRP protocol schedule will be summarized at the end of the study using methods similar to the main protocol analysis.

10.14. Appendix 14: Sub-Study Pill Diary

1. Record the date, time, and the number of study medication tablets you took
2. Bring this pill diary to your clinic visits

INSTRUCTIONS:

***Day -14 ONLY: Take *three* tablets relugolix (360 mg)** by mouth with or without food

Days -13 through -1: Take *one* tablet relugolix (120 mg) one time a day by mouth with or without food

Days 1 through 28: Take *one* tablet relugolix (120 mg) AND *four* tablets apalutamide (240 mg) one time a day by mouth with or without food

Day	Date	Time	# of relugolix pills	# of apalutamide pills	NOTES *(optional)*
-1	*07/01/2021*	*09:00*	*1*	*0*	*This is an example.*
Take ONLY relugolix Days -14 through -1					
-14*				*0*	**Remember to take 3 relugolix tablets today ONLY**
-13				*0*	
-12				*0*	
-11				*0*	
-10				*0*	
-9				*0*	
-8				*0*	
-7				*0*	
-6				*0*	
-5				*0*	
-4				*0*	
-3				*0*	
-2				*0*	
-1				*0*	
There is no break in treatment. Take relugolix AND apalutamide Days 1 through 28					
1	*07/15/2021*	*09:00*	*1*	*4*	*This is an example.*
1					
2					
3					
4					
5					
6					
7					
8					
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10.15. Appendix 15: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (12 August 2020)

Overall Rationale for the Amendment: The main reason for the amendment is to add visit windows, administrative changes, and specify the unit for prostate-specific antigen (PSA) level for high risk population.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis Overall Design; 4.1 Overall Design; 4.4 End of Study Definition	Definition of end of study (EOS) is updated to: "The EOS is defined as the date of last participant's enrollment +24 months or discontinuation of all study participants from the study, whichever occurs first."	Clarified the definition of EOS to allow some participants to have follow-up visits beyond 24 months from enrollment.
1.1 Synopsis Overall Design, Intervention Groups and Duration; 4.1 Overall Design; 6.1 Study Intervention Administration	Text is added to define treatment with apalutamide; text has been reworded to define treatment duration of 12 cycles for apalutamide.	To define treatment cycles and treatment duration.
1.1 Synopsis Overall Design, Intervention Groups and Duration; 6.1 Study Intervention Administration	Text is added to mention the use of study intervention (apalutamide) as per its United States Package Insert (USPI).	Added text to accommodate prospective changes in apalutamide label.
1.1 Synopsis Biomarker Evaluations; 8.6 Biomarkers	Text added to specify that full histopathology report will be sent along with the primary biopsy specimen to sponsor's laboratory partner.	To clarify the steps in biomarker assessment.
1.3 Schedule of Activities (SoA)	Updated footnote j to: "Tissue sample to be collected from the primary biopsy and sent to sponsor's laboratory partner along with a copy of the full histopathology report of the biopsy specimen."	
1.2 Schema; 5.1 Inclusion criteria	Figure 1 and inclusion criterion 5 are updated to include the unit of PSA level as ng/mL.	Added the unit of PSA for clarity.
1.3. Schedule of Activities (SoA)	'Focused physical examinations including skin assessment' is added at Baseline.	Text added to be consistent with Inclusion criterion 4 have recovered from radical prostatectomy (RP) procedure, per the clinical judgement of the investigator.
1.3. Schedule of Activities (SoA)	Footnote is updated to add recording of alcohol intake directly in the eCRF.	Text added to record history of alcohol intake directly into the eCRF in alignment with lifestyle restrictions #1).
Appendix 3, 10.3.10 Source Documents	Text to include history of alcohol intake including type, usage, amount, and frequency is added to the list of data that will be recorded directly into the electronic Case Report Form (eCRF).	

Section number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	New footnotes a and b are added to allow a visit window of ±7 calendar days for Visits 2 through 8 and a visit window of ±14 calendar days, Visit 9 onwards for all follow-up visits. The subsequent footnotes are rearranged alphabetically and are updated in the SoA.	Visit windows are added to allow scheduling flexibility.
1.3 Schedule of Activities (SoA)	New footnote i added for plasma samples: "Collected at baseline, 12 months or end of treatment, and at 24 months or progression (whichever comes first)."	Added to clarify the guidance of 'whichever comes first'
1.3. Schedule of Activities (SoA)	New footnotes k and l are added to start collection of concomitant therapies and adverse events (AEs) from the time of first dose of apalutamide.	Added the day of commencing concomitant therapy and AE collection to be consistent throughout the protocol and in agreement with Global Medical Safety (GMS) to collect AEs beginning with dosing (and not to collect AEs that could be associated with RP).
8.3.1 Time Period and Frequency for Collecting AE and SAE Information; Appendix 4, 10.4.1 AE Definitions and Classifications	Reporting of AEs from the time after enrollment is changed to Reporting of AEs from the time after the participant receives the first dose of apalutamide.	
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Text added to mention that AEs will additionally be monitored during phone calls with the participants.	To include all timepoints for AE monitoring.
5.2. Exclusion Criteria	Exclusion criterion 1 is updated to exclude presence of soft tissue/bone metastasis or metastasis in distant lymph nodes. Exclusion Criteria 9 is updated with "any of the following within 6 months prior to baseline" at the beginning of the sentence.	To clarify the metastasis criterion. Rearranged the wording to clarify that the 6 months period applies to all the conditions listed therein.
7.1. Discontinuation of Study Intervention	Text is added to record the subsequent therapy, if known, in the eCRF for participants discontinuing the study intervention due to disease progression.	Added instructions to record subsequent therapy.
	Deleted the text: "Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant."	To disallow reassignment of study intervention as this is not relevant for an open-label study.
7.2.1 Withdrawal From the Use of Research Samples; Appendix 3, 10.3.1 Regulatory and Ethical Considerations	'Optional research sample' is changed to 'research sample' and the sentences are reworded accordingly.	The provision to keep research samples optional is deleted as this is not considered optional collection.
7.2.1 Withdrawal From the Use of Research Samples	Paragraph on "withdrawal from optional research samples while remaining in the main study" is deleted.	The paragraph is not applicable as the provision to keep research samples optional is deleted.
	Provision of separate Informed Consent Form (ICF) for optional research is deleted.	Separate ICF is not applicable for research samples as the details are included in the main ICF.
8.3.8 Adverse Events of Special Interest	Added text: "For apalutamide, there are no non-serious AEs of special interest identified."	To provide background information on apalutamide AEs of special interest.

Section number and Name	Description of Change	Brief Rationale
	"Rash is an AE of clinical interest" is changed to "Rash is an AE of special interest".	Text is modified for consistency with the heading.
Appendix 4, 10.4.3 Severity Criteria	Text to grade AEs as per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 is added. Text to grade AEs into mild, moderate, and severe is deleted.	Changed the AE grading criteria to be consistent with the standard for oncology studies.
Appendix 10, 10.10 Phone Calls With Participants	Added new bullet points to the 'Guide for discussion during phone calls'	Added additional bullets for clarity on guidance for phone calls.
Throughout protocol	Minor grammatical, spelling, and formatting changes are made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

JNJ-56021927 (apalutamide)
Clinical Protocol 56021927PCR2041 Amendment 2

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Scientific Affairs, LLC

Signature: PPD

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 20 April 2021