PILLAR
(PSMA Imaging Leveraged for Local/Regional Therapy and Androgen Receptor Targeted Therapy)

A Randomized, Phase II Study of Apalutamide +/- Stereotactic Body Radiotherapy (SBRT) in Castration-Resistant Prostate Cancer Patients with Oligometastatic Disease on PSMA-PET Imaging

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Principal Investigator (Sponsor-Investigator)
Rahul Aggarwal, MD
University of California San Francisco

[redacted]

Statistician
Li Zhang, PhD

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Protocol Signature Page

Protocol No.: 175519

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).

2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.

3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.

4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.

5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

Protocol Signature Page – Participating Sites

Protocol No.: 175519

Participating Site(s)

Principal Investigator Name:	Principal Investigator Name:
Institution Name:	Institution Name:
Address:	Address:
Telephone: E-mail:	Telephone: E-mail:

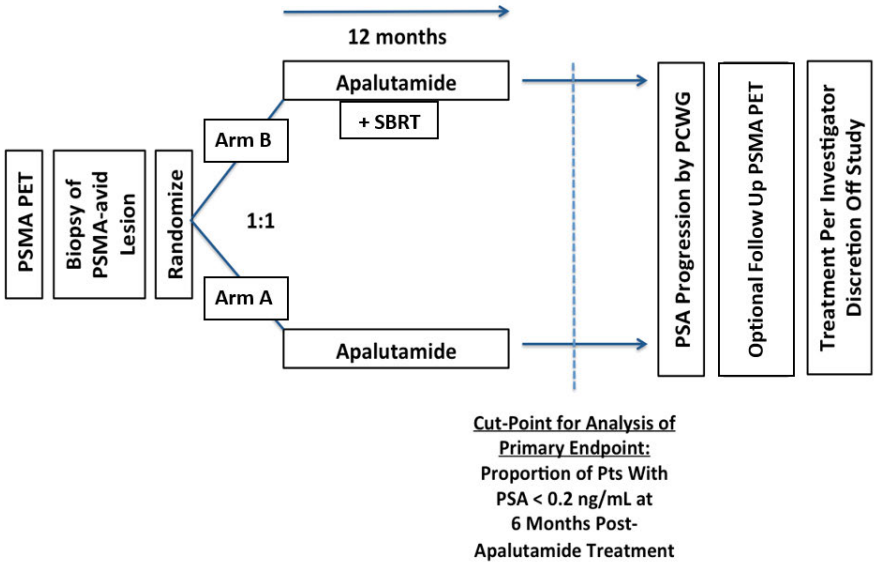
I have read this protocol and agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), Institutional Review Board regulations, and all national, state and local laws and/or requirements of the pertinent regulatory requirements.

Principal Investigator	**Site**
Printed Name	Institution Name
Signature	Date

Abstract

Title	A Randomized, Phase II Study of Apalutamide +/- Stereotactic Body Radiotherapy (SBRT) in Castration-Resistant Prostate Cancer Patients with Oligometastatic Disease on PSMA-PET Imaging
Patient population	The study population includes men 18 years of age or older with CRPC. Key eligibility criteria include: • Histologically confirmed prostate adenocarcinoma. • Progressive, castration-resistant prostate cancer with ongoing castration therapy during the course of study treatment. • At least one but no more than 5 discrete PSMA-avid radiation fields on baseline PSMA-PET scan amenable to SBRT in judgment of treating clinician. • No prior abiraterone acetate, enzalutamide, apalutamide, or docetaxel initiated in CRPC setting.
Rationale for Study	Apalutamide is a next-generation anti-androgen that binds directly to the ligand-binding domain of AR, impairing nuclear translocation and DNA binding. Apalutamide binds AR with 5-fold greater affinity than bicalutamide, and induces partial or complete tumor regression in both castration-sensitive and castration-resistant prostate cancer. The efficacy of AR targeting agents in conventionally defined non-metastatic disease has been demonstrated in several phase 2 trials. In the non-metastatic castration resistant prostate cancer (NM-CRPC) subset (n =51) of the phase 2 study of apalutamide, the 12-week PSA response (≥ 50% decline from baseline) was 91%. While phase 3 trials are still maturing (e.g. ARN-509-003) it is assumed that these trials are very likely to establish the utility of agents like apalutamide in prolonging the metastasis-free interval in patients with NM-CRPC. There has been considerable erosion in the size of the population of patients with NM-CRPC. In part, this reflects more frequent conventional imaging driven by PSA testing. However, the impact seen to date on the proportion of patients with NM-CRPC is dwarfed by the anticipated exponential growth of targeted imaging. Prostate Specific Membrane Antigen (PSMA) PET is the most sensitive imaging modality available. The significant increase of PSMA PET scanning in other parts of the world provides insight to the anticipated uptake of PSMA scanning in the US. It is anticipated that the US will have tremendous market penetration by PSMA PET scanning. Although PSMA PET has largely been evaluated in early stage hormone-sensitive disease, at UCSF we have begun to evaluate PSMA PET scanning in patients with CRPC who have progressive disease by PSA criteria, but who do not have evidence of metastatic disease on conventional (bone scan and CT

	abdomen/pelvis) imaging - the SPARTAN population. In our first group of roughly 25 "SPARTAN eligible" patients with undergoing PSMA PET scanning, approximately 50% were found to have oligometastatic disease (defined by convention as 5 or fewer lesions), whereas 25% were found to have widely metastatic disease (> 5 lesions), and 25% did not have detectable lesions (unpublished data). Thus, it is conceivable that had SPARTAN patients undergone targeted imaging with PSMA PET, approximately 75% of patients would have been ineligible and would have been found to have metastatic disease by PSMA PET. Despite this anticipated dramatic stage migration, there is no consensus regarding the appropriate treatment for patients with oligometastatic CRPC. Reasonable options that are being tested in these patients include stereotactic body radiotherapy (SBRT), surgical resection of limited nodal disease, and systemic therapy with androgen receptor targeted therapy, including AR inhibitors such as apalutamide. SBRT is an advancing treatment approach made possible by recent advancements in radiation delivery, which allow for precise treatment within any anatomical region of the body. As a result, the capacity to deliver tumor killing radiation doses in a single or few outpatient radiation treatments is now possible. In addition, by minimizing the irradiation of surrounding healthy tissue, it should also be possible to decrease the rate of complications. Intracranial stereotactic body radiation therapy (SBRT) has been shown to be a highly effective treatment for brain lesions13. Data suggests SBRT provides high rates of local progression-free survival (92-93% at 3 to 5 years post-SBRT) in metastatic hormone-sensitive prostate cancer, as well as high rates of local control (90-100%) in other cancers as well. Toxicity has been minimal in multiple U.S., European and Japanese trials of extracranial stereotactic radiotherapy to the lung, liver, spine, pelvis and abdomen despite the use of very high biological equivalent doses for patients with both organ confined and metastatic cancer. The impending dramatic stage migration from PSMA PET imaging and the current lack of consensus regarding appropriate therapies represents an opportunity to establish the role of apalutamide in the treatment of what is likely to become the fastest growing population of prostate cancer patients. It is clear that PSMA PET imaging will be utilized much more frequently in the future, and likely become a standard of care with respect to imaging. The increased usage of PSMA PET will inevitably result in a significant increase in the number of patients with "oligometastatic" castration-resistant prostate cancer. The goal of this study is to assess the efficacy of apalutamide in this patient population, and determine if the addition of stereotactic body radiotherapy can improve outcomes. The proposed treatment represents a logical combination of the current state-of-the-art systemic targeting of AR, the current state-of-the-art radiation therapy, and the current state-of-the-art imaging for prostate cancer lesions. The study schema is shown on the following page.
Primary Objective	To demonstrate whether the proportion of patients with an

	undetectable serum PSA at 6 months following cessation of apalutamide is higher with addition of SBRT to PSMA-avid oligometastatic sites of disease compared to the group of patients receiving apalutamide monotherapy.
Secondary Objectives	**1.** To compare the time to PSA progression by PCWG criteria between treatment arms **2.** To evaluate the safety and tolerability of apalutamide in combination with SBRT.
Exploratory Objectives	*1. To evaluate the genomic factors associated with the presence of oligometastatic disease* *2. To evaluate the association between somatic and germline genomic alterations with outcomes on protocol therapy* *Note: The italicized objectives above were discontinued in Protocol v. 8.0. See Section 7.3 for additional information.* **3.** To characterize the metastatic pattern at baseline and atprogression in these patients and to determine whether features of the baseline PSMA-PET scan are associated with treatment outcomes.
Study Design	This is a randomized (1:1), open-label, phase II clinical trial evaluating the efficacy and safety of apalutamide with or without SBRT to all visible lesions in men with CRPC and oligometastatic disease based upon PSMA-PET imaging. Patients will complete up to 52 weeks of treatment with apalutamide in the absence of disease progression, and will subsequently be followed until PSA progression as defined by PCWG criteria. Following development of PSA progression, patients may undergo repeat PSMA-PET imaging. Treatment at the time of progression will be at the discretion of the treating physician, and can include SBRT for those patients deemed appropriate candidates (whether or not they received prior SBRT) and/or any FDA approved systemic therapy. 

Number of Patients	60 (apalutamide: 30; apalutamide + SBRT: 30)
Duration of Therapy	Patients will continue protocol treatment until the first occurrence of one of the following: • Disease progression by PCWG3 criteria • Unacceptable adverse event(s) related to apalutamide or SBRT • Completion of treatment (52 weeks for apalutamide) • Patients decides to withdraw from the study • Significant patient non-compliance with protocol • General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.
Duration of Follow up	Patients will continue on study in follow up until disease progression by PCWG3 or withdrawal from study, whichever occurs first.
Duration of Study	The anticipated study duration is approximately 36 months.
Study Drugs/ Treatments	• Apalutamide will be administered orally on a continuous daily dosing regimen, at a starting dose of 240 mg once daily (4 x 60-mg tablets), until the completion of 12 months of treatment, unacceptable toxicity, or PSA progression, whichever occurs soonest. • SBRT will be delivered by treating radiation oncologist according to standard institutional practice for up to 5 PSMA-avid radiation fields. SBRT must be initiated within 90 days following initiation of apalutamide therapy. SBRT will be delivered in 1 to 5 fractions, and the dose and fractionation schedule will depend on the size and location of the lesion/radiation field and the surrounding normal tissue constraints in accordance with AAPM Task Group 101 recommendations. Typical doses include 16 – 24 Gy in 1 fraction, 40 – 50 Gy in 4 fractions, and 40 – 60 Gy in 5 fractions.
Safety Assessments	Patients will be assessed for adverse events (AEs) at each monthly clinic visit while on the study treatment. Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Type, incidence, severity, timing, seriousness, and relatedness of AEs, and laboratory abnormalities will be reported.
Efficacy Assessments	Disease assessments will be performed as scheduled according to the calendar, regardless of treatment delays resulting from toxicity. PSA measurements will be performed every 4 weeks until the time of

	PSA progression by PCWG criteria. PSMA-PET imaging will be performed at baseline and is optional at the time of PSA progression.
Primary Endpoint	▪ Proportion of patients with undetectable serum PSA (< 0.2 ng/mL) at 6 months following completion of apalutamide therapy (18 months from date of randomization).
Secondary Endpoints	1. Time to PSA progression by PCWG criteria 2. Feasibility and Safety of apalutamide and concurrent SBRT
Exploratory Endpoints	*1. Association between genomic factors and presence of oligometastatic disease* *2. Association between somatic and germline genomic alterations with clinical outcomes* *Note: The italicized objectives above were discontinued in Protocol v. 8.0. See Section 7.3 for additional information.* 3. Association between baseline PSMA-PET scan uptake and distribution of lesions with treatment outcomes.
Statistical Analysis/ Sample Size Justification	The primary efficacy is based on the primary endpoint of the study, the proportion of patients with undetectable PSA (PSA < 0.2 ng/mL) 6 months following completion of 12 months of apalutamide therapy (18 months from date of randomization). Assuming a 10% inevaluable/drop-out rate per treatment arm, a sample size of 60 patients (30 patients/arm) provides 84% power to detect a difference in proportion of patients with undetectable PSA of 25% in the apalutamide + SBRT arm vs. 2.5 % in the apalutamide monotherapy arm, with a unidirectional level of significance of 0.10 (Fisher's exact test). Patients who discontinue apalutamide prior to completion of 12 months of therapy for reasons other than disease progression by PCWG criteria will be considered inevaluable for this analysis.

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
CTV	clinical tumor volume
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FCBP	female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute

List of Abbreviations

ORR	overall response rate
PD	disease progression
PK	pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
PTV	planning target volume
QOL	Quality of Life
RBC	red blood cell (count)
SBRT	stereotactic body radiation therapy
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ULN	upper limit of normal
WBC	white blood cell (count)

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1 BACKGROUND AND OVERALL STUDY RATIONALE

Apalutamide is a next-generation anti-androgen that binds directly to the ligand-binding domain of AR, impairing nuclear translocation and DNA binding1, and is FDA approved for the treatment of non-metastatic castration resistant prostate cancer and metastatic castration sensitive prostate cancer. Apalutamide binds AR with 5-fold greater affinity than bicalutamide, and induces partial or complete tumor regression in both castration-sensitive and castration-resistant human prostate cancer xenograft models.

The efficacy of AR targeting agents in conventionally defined non-metastatic disease has been demonstrated in several phase 2 trials as well as the phase 3 study of apalutamide versus placebo. In the non-metastatic castration resistant prostate cancer (NM-CRPC) subset (n =51) of the phase 2 study of apalutamide, the 12-week PSA response (≥ 50% decline from baseline) was 89%2. In the phase 3 study, the median metastasis-free survival with apalutamide versus placebo was (40.5 vs. 16.2 months, $p < 0.001$).3

There has been considerable erosion in the size of the population of patients with NM-CRPC. In part, this reflects more frequent conventional imaging driven by PSA testing. However, the impact seen to date on the proportion of patients with NM-CRPC is dwarfed by the anticipated exponential growth of targeted imaging.

Prostate Specific Membrane Antigen (PSMA) PET is the most sensitive imaging modality available4-6. The significant increase of PSMA PET scanning in other parts of the world provides insight to the anticipated uptake of PSMA scanning in the US. It is anticipated that there will be tremendous market penetration by PSMA PET scanning in the US.

Although PSMA PET has largely been evaluated in early stage hormone-sensitive disease, at UCSF we have begun to evaluate PSMA PET scanning in patients with CRPC who have progressive disease by PSA criteria, but who do not have evidence of metastatic disease on conventional (bone scan and CT abdomen/pelvis) imaging - the SPARTAN population. In our first group of 25 "SPARTAN eligible" patients with undergoing PSMA PET scanning, approximately 50% were found to have oligometastatic disease (defined by convention as 5 or fewer lesions), whereas 25% were found to have widely metastatic disease {> 5 leions), and 25% did not have detectable lesions (unpublished data). Thus, it is conceivable that had SPARTAN patients undergone targeted imaging with PSMA PET, approximately 75% of patients would have been ineligible and would have been found to have metastatic disease by PSMA PET.

Despite this anticipated dramatic stage migration, there is no standard of care for patients with oligometastatic CRPC. Reasonable options that are being tested in these patients include SBRT, surgical resection of limited nodal disease, and systemic therapy with androgen receptor targeted therapy, including AR inhibitors such as apalutamide. SBRT is an advancing treatment approach made possible by recent advancements in radiation delivery, which allow for precise treatment within any anatomical region of the body7,8. As a result, the capacity to deliver tumor killing radiation doses in a single or few outpatient radiation treatments is now possible9-18. In addition, by minimizing the irradiation of surrounding healthy tissue, it should also be possible to decrease the rate of complications. Intracranial stereotactic body radiation therapy (SBRT) has been shown to be a highly effective treatment for brain lesions19. Data suggest SBRT provides high rates of local progression-free survival (92-93% at 3 to 5 years post-SBRT) in metastatic hormone-sensitive prostate cancer, as well as high rates of local control (90-100%) in other cancers 20,21. Toxicity has been minimal in multiple U.S., European and Japanese trials of extracranial stereotactic radiotherapy to the lung, liver, spine, pelvis and abdomen despite the use of very high biological equivalent doses for patients with both organ confined and metastatic cancer.

Thus, the impending dramatic stage migration due to PSMA PET imaging and the current lack of standard therapies represent an opportunity to establish the role of apalutamide in the treatment of what is likely to become the fastest growing population of prostate cancer patients. It is clear that PSMA PET imaging will be utilized much more frequently in the future, and likely become a standard of care with respect to imaging.

Increasingly, as more sensitive imaging technology is developed, “non-metastatic” M0 CRPC will be shown to in fact be comprised of a certain population of patients with oligometastatic disease, thereby identifying a group of patients with potentially curable disease.

The underlying hypothesis being tested by this study is that the beneficial impact of apalutamide can be augmented by the use of concurrent SBRT in patients with oligometastatic CRPC.

1.1 APALUTAMIDE

Apalutamide is an orally available, potent and selective AR antagonist that acts by inhibiting the action of androgen, nuclear translocation of the AR and DNA binding to androgen response elements and unlike bicalutamide, it exhibits no significant agonist activity i inAR-overexpressing prostate cancer cells.

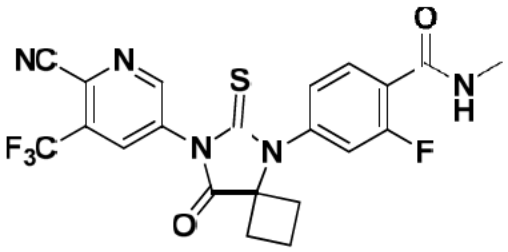
Complete information for apalutamide (JNJ-56021927) can be found in the Investigator’s Brochure, the safety reference document for this study, as well as the US Package Insert [redacted]

1.1.1 Molecular Formula and Chemical Class

Apalutamide drug substance is a white to off-white crystalline solid.

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

Chemical Structure:



Molecular Formula: $C_{21}H_{15}F_4N_5O_2S$

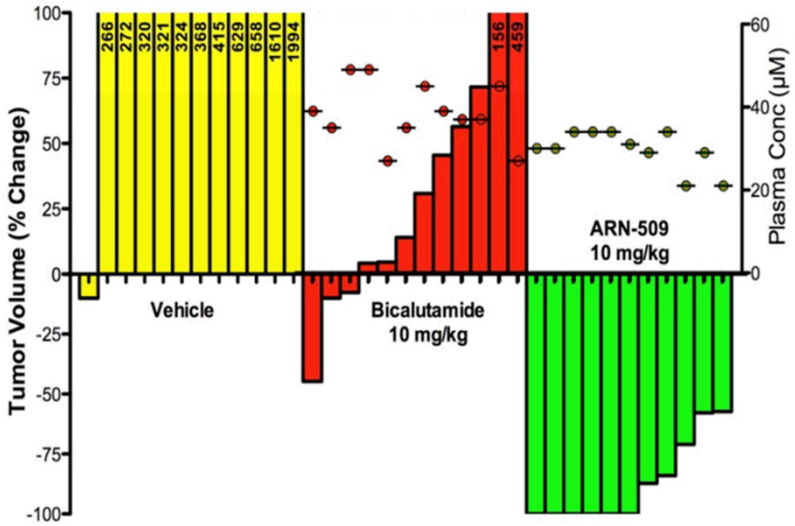
Molecular Weight: 477.44

1.1.2 Pre-Clinical Development Overview

The mechanism of action of apalutamide is through antagonism of androgen action and inhibition of AR nuclear translocation and DNA binding to androgen response elements, a mechanism that is distinct from the first generation anti-androgen, bicalutamide. Unlike bicalutamide, it shows no significant agonist properties in an in vitro model of CRPC (e.g., AR-over-expressing prostate cancer cells; LNCaP/AR cells). Gene transcription of the androgen-driven genes, PSA and TMPRSS2, is inhibited by apalutamide and results in concentration-dependent reduction of these protein levels in vitro. Apalutamide was also

shown to reduce proliferation of CRPC cells as well as increase apoptosis and necrosis in vivo. These effects are supported by the anti-tumor activity of apalutamide observed in murine tumor models of CRPC. In these models, apalutamide showed dose-dependent tumor growth inhibition and tumor regression that were superior to bicalutamide. Figure 1 depicts the percent change in tumor volume and plasma concentrations (filled circles above waterfall plot) of bicalutamide and apalutamide on Day 28.

Figure 1 Tumor Growth Inhibition in Castration-resistant LNCaP/AR-Luc Xenograft Model after 28 Days of Treatment with Bicalutamide or apalutamide (ARN-509)



Apalutamide is a low clearance molecule with a moderate volume of distribution and high bioavailability (when dosed with a lipid-based formulation). Apalutamide was found to have a very low turnover when incubated for up to 120 minutes with rat, dog, and human liver S9 fraction and liver microsomes. The primary in vivo metabolites were formed by N-demethylation and amide hydrolysis in the rat and dog. In vitro, CYP3A4 may be partially involved in the metabolism of apalutamide.

Apalutamide and its primary metabolite ARN000308 (M3) are inducers of human CYP2B6 and CYP3A4 in hepatocytes at concentrations up to 30 μM. Apalutamide is a moderately potent inhibitor of human cytochrome P450 isoform CYP2C8 (IC_{50}=13.9 μM), but a weak inhibitor of the other major isoforms (IC_{50}>25 μM); M3 is also a weak inhibitor of CYP major isoforms (IC_{50}>25 μM).

Four metabolites have been identified with different proportions between species. All four were assessed for their on-target effects against the androgen receptor. Metabolite M1 was found to be essentially inactive as an AR antagonist, while metabolites M2 and M4 were approximately 30-fold less potent against AR than apalutamide. Metabolite M3 was the most potent AR antagonist, but was still 3-fold less potent than apalutamide. Metabolite M3 is considered the predominant metabolite, with a longer elimination half-life than apalutamide.

In vitro and in vivo studies to assess cardiovascular, CNS, and respiratory system effects of apalutamide did not reveal any concerns.

Single-dose and repeat-dose toxicology studies up to 13 weeks of dosing have been conducted in male Sprague Dawley (SD) rats and male Beagle dogs (repeat-dose studies only).

Acute administration of apalutamide at 1,000 mg/kg was well tolerated in SD rats, with no morbidity, mortality or significant effects on body weight or serum chemistry markers.

In repeat-dose toxicology studies, apalutamide was well tolerated at doses up to

100 mg/kg/day in the 13-weeks study in SD rats and 10 mg/kg/day in Beagle dogs. In male SD rats, lethality was observed at doses of 150 mg/kg/day and greater. The morbidity/mortality observed at these doses occurred within the first 5 days of dosing; however, animals that did survive at these higher doses, appeared to develop a tolerance for the test article with extended exposure. Clinical signs observed in the moribund animals were piloerection, hypothermia, breathing abnormalities, dehydration, and decreased activity. The cause of the morbidity/mortality in male rats could not be determined by pathologic examination. Key clinical pathology changes at doses of 150 mg/kg/day or greater included significant increases in cholesterol (greater than 200% from controls), decreases in erythrocytes, hemoglobin and hematocrit, and increases in reticulocytes, platelets, leukocytes, lymphocytes, basophils, and aPTT. The increase in cholesterol is attributed to the anti-androgen activity of apalutamide and is believed to be responsible for the stated hematologic changes. Examination of red blood cell morphology revealed changes that were consistent with excess cholesterol being transferred to the outer membrane of the erythrocytes, resulting in a mild hemolytic anemia. Pharmacologic effects were also observed in the male accessory sex organs (epididymides, prostate, seminal vesicles and to a lesser degree, the testes) at apalutamide doses as low as 50 mg/kg/day. Other target organs in the rat that were observed at apalutamide doses of 150 mg/kg/day or higher included adrenals (also at 50 mg/kg/day), liver, pituitary, thyroid, spleen, salivary glands, mammary gland, and stomach. With the exception of the salivary glands and stomach, the effects on those organs are also believed to be due to the anti-androgen effect of apalutamide and in many cases are specific to the physiology of the rat.

Once daily oral gavage dosing of apalutamide for 13 weeks was well tolerated in male rats up to 100 mg/kg/day, i.e. the highest dose tested. Pharmacologic changes characteristic of

anti-androgen compounds were noted in the adrenal gland, pituitary gland, spleen, mammary gland, seminal vesicles, testes, prostate, and epididymides, while changes in the spleen and bone marrow correlated with a mild regenerative anemia. The 100 mg/kg/day dose level was considered to be the no observed adverse effect level (NOAEL) and was associated with steady-state (Day 91) plasma C_{max} and $AUC_{0\text{-}24h}$ values of 30.1 µg/mL and 521 µg•h/mL, respectively, for the parent compound.

In male Beagle dogs, seizures necessitating humane euthanasia occurred at apalutamide doses of 25 mg/kg/day and greater, 7 to 14 days after dosing was initiated. Daily administration of 25 mg/kg/day of apalutamide resulted in tremors and seizures in 3 of 8 animals after 1 week of dosing. The average apalutamide concentration at the time of first observation of central nervous system (CNS) toxicity was determined to be 30.2 µg/mL, which was about 4-fold higher than the mean apalutamide steady-state C_{max} (7.55 µg/mL) at the Phase 3 dose of 240 mg/day measured during repeated dosing in subjects with CRPC. It is likely that the convulsive seizures observed in dogs at very high doses are the result of apalutamide's functional antagonism of the $GABA_A$ receptor. This is similar to what has been observed with other second generation AR antagonists. The 10 mg/kg/day dose was considered to be the NOAEL in the 28-day study, and was associated with an apalutamide

C_{max} of 13.2 µg/mL and an $AUC_{0\text{-}24}$ of 290 µg•h/mL. Other clinical pathology and target organ changes were limited to increases in cholesterol (up to 50% compared to controls) and effects on the epididymides, prostate and testes at all doses tested and attributed to the anti- androgen effect of apalutamide.

Once daily oral capsule administration of apalutamide for 13 weeks was well tolerated in male dogs up to 10 mg/kg/day, i.e. the highest dose tested. Gross and microscopic pathology changes and organ weight changes characteristic of anti-androgen compounds were noted in the pituitary gland, prostate, testes, and epididymides; these changes were reversible and were attributable to the expected pharmacologic effect of apalutamide. Based upon the lower body weight performance in the group receiving 10 mg/kg/day, the 5 mg/kg/day dose was considered to be the NOAEL. Corresponding steady-state (Day 91) plasma C_{max} and

$AUC_{0\text{-}24h}$ values were 10.3 µg/mL and 202 µg•h/mL, respectively, for the parent compound.

Preclinical studies have demonstrated the absence of genotoxic, clastogenic, and phototoxic properties for apalutamide and its pharmacologically active metabolite ARN000308 (M3). ARN000066 (M4), an inactive metabolite of apalutamide, tested negative in an in vitro bacterial reverse mutation (Ames) assay, but was weakly positive in an in vitro chromosome aberration test in human peripheral blood lymphocytes. However, the totality of nonclinical data supports the lack of an in vivo genotoxic potential of ARN000066 (M4).

1.1.3 Overview of Clinical Studies

In addition to Study ARN-509-003, apalutamide is also being evaluated in Phase I studies in healthy men and Phase I/II, Phase II, and Phase III studies in patients with prostate cancer.

Study ARN-509-001 is an ongoing Phase I/II study in patients with progressive advanced CRPC. In the Phase I portion of the study, 30 patients with mCRPC received at least 1 dose of apalutamide at escalating dose levels: 3 patients each at 30, 60, 90, 120, 180, 240, 390, 480 mg/day, and 6 patients at 300 mg/day. Three subgroups are being evaluated in the Phase 2 portion (Group 1: NM-CRPC; Group 2: mCRPC without previous ketoconazole, abiraterone acetate, enzalutamide or chemotherapy [for mCRPC]; and Group 3: mCRPC post abiraterone acetate, no previous chemotherapy [for mCRPC]). All patients received apalutamide orally once daily, except those in the 300, 390, and 480 mg cohorts who received a twice-daily dosing regimen due to the higher pill burden at those levels. The results of the Phase 1 portion of the study from 30 patients with mCRPC demonstrated that treatment with apalutamide resulted in PSA declines at all dose levels tested. Eighteen subjects (60%) had a ≥50% or higher maximum decrease in PSA from baseline and 6 (20%) had ≥90% maximum decrease. Ten patients had measureable soft tissue disease at baseline; 5 (50%) subjects maintained stable disease response for more than 6 months, 1 (10%) subject experienced disease progression, and the remaining 4 subjects had indeterminate responses. Apalutamide was well tolerated, with only 1 dose-limiting toxicity (DLT) at the 300 mg dose level (Grade 3 treatment-related abdominal pain). The event lasted 6 days and resolved with dose interruption and subsequent dose reduction to 240 mg (120 mg twice daily). Three additional subjects were treated at the 300 mg dose level with no reported DLTs. No seizures were reported at any dose level. The maximum tolerated dose (MTD) was not determined. The PK profile is linear and dose-proportional.

Sixteen subjects participated in an evaluation of AR binding in vivo using

16β-[18F] fluor-α-dihydrotestosterone (FDHT) positron emission tomography (PET)/CT scan. Apalutamide treatment reduced FDHT uptake across all dose levels (30 to 390 mg dose levels). A plateau was reached at approximately 120 mg (with FDHT uptake near background) indicating saturation of AR binding. The mean plasma trough levels associated with this dose (2.5 µg/mL) were at the lower end of the range that produced tumor regression in the LNCaP/AR mouse model. Steady state plasma levels at the 240 mg dose level (3 to 6 µg/mL) were more in the range sufficient to elicit a tumor response in the mouse xenograft model. Therefore, the 240 mg daily regimen was chosen for Phase 2 and Phase 3 dosing.

Apalutamide was rapidly absorbed, with measurable plasma concentrations within 30 minutes after ingestion of a single oral dose of 1 to 16 soft gelatin capsules (total apalutamide dose, 30 to 480 mg). On average, peak plasma concentrations occurred 2 to 3 hours after administration in each dose group. The increases in plasma C_{max} values and in the area under the plasma concentration curve (AUC) were linear and dose proportional. Plasma apalutamide concentrations declined slowly, with a mean half-life value at steady-state of 4 days.

The percentage of patients with PSA reductions of ≥ 50% at 12 weeks in patients with NM-CRPC was 89%[2]. Similar data were observed after 24 weeks. The data available to date indicate that apalutamide shows durable PSA responses in NM-CRPC and early mCRPC (before treatment with abiraterone acetate or chemotherapy). Apalutamide also has activity in a subgroup of patients with mCRPC that have progressed on abiraterone actetate. For the NM-CRPC subgroup, the median time to PSA progression was 24.0 months (16.3 – NR).

In the NM-CRPC subgroup (n =51), the most frequent treatment-related adverse events reported in >10% are fatigue (61%), diarrhea (43%), and nausea (39%)[2]. No deaths were reported in this subgroup as of the safety cutoff.

In the phase 3 study, the median metastasis-free survival with apalutamide versus placebo was (40.5 vs. 16.2 months, $p < 0.001$).[3]

1.2 STEREOTACTIC BODY RADIATION THERAPY IN OLIGOMETASTATIC PROSTATE CANCER

The definition of oligometastatic prostate cancer has varied across studies. Multiple uncontrolled and prospective studies had defined as ranging from ≤ 3 to ≤ 5 lesions in various studies[21]. A recent retrospective analysis of pooled individual data from patients with castration-sensitive recurrent prostate cancer following definitive local therapy, with up to three positive lesions on baseline scan, to determine the efficacy of this treatment strategy. SBRT was defined as a radiotherapy dose of at least 5 Gy per fraction to a biologically effective dose (BED) of at least 80 Gy. A total of l19 patients were treated for 163 metastatic lesions (lymph node, n = 72; bone n = 43; visceral met n = 2). The 3-year and 5-year local progression free survival rate was 93% and 92%, respectively. A lower radiotherapy dose predicted for higher local recurrence rate. The median distant progression-free survival time was 21 months (95% CI 15-27 months)[19]. A recent review highlighted 5 additional retrospective studies demonstrates the safety of SBRT to oligometastatic sites of disease, as well as the high rates of local control ranging from 90-100%[20].

Two major limitations of the currently available data are randomized studies with and without SBRT to begin to address whether addition of SBRT impacts intermediate- and long-term outcomes, as well as limited data available in the oligometastatic castration-resistant prostate cancer setting. The current study was designed to address these gaps and evaluate the role of SBRT in oligometastatic CRPC in a randomized fashion, with treatment of up to five bone and nodal radiation fields.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To demonstrate whether the proportion of patients with an undetectable serum PSA at 6 months following cessation of apalutamide is higher with addition of SBRT to PSMA-avid oligometastatic sites of disease compared to the group of patients receiving apalutamide monotherapy.

2.2 SECONDARY OBJECTIVES

1. To compare the time to PSA progression by PCWG criteria between treatment arms
2. To evaluate the safety and tolerability of apalutamide in combination with SBRT.

2.3 EXPLORATORY OBJECTIVES

1. *To evaluate the genomic factors associated with the presence of oligometastatic disease via exome sequencing.*
2. *To evaluate the association between somatic and germline genomic alterations including but not limited to AR amplification and point mutations and alterations in DNA damage response pathway with outcomes on protocol therapy*

   Note: The italicized objectives above were discontinued in Protocol v. 8.0. See Section 7.3 for additional information.
3. To characterize the metastatic pattern at baseline and at progression in these patients and to determine whether features of the baseline PSMA-PET scan are associated with treatment outcomes.

3 STUDY DESIGN

3.1 STUDY OVERVIEW AND RATIONALE

This is a randomized, open-label, phase II clinical trial evaluating the efficacy and safety of apalutamide with or without SBRT in patients with oligometastatic castration-resistant prostate cancer detected on PSMA-PET scan imaging. A randomized design was chosen to begin to address the clinically relevant question as to whether the addition of SBRT improves outcomes as compared to systemic therapy alone for men with oligometastatic prostate cancer. We chose to utilize PSMA-PET as opposed to conventional imaging to define oligometastatic disease based on the improved sensitivity of this imaging modality, enabling earlier detection of oligometastatic disease.

The justification of assigned therapy by treatment arm is as follows:

(1) SBRT: There is no standard timing for the use of SBRT for patients with oligo-metastatic disease. Therefore, it is appropriate to undertake SBRT either at the time of starting apalutamide as part of study treatment, or later, as post-study therapy. We chose to utilize SBRT as compared to more conventional radiation treatment schedule due to the higher rates of local control observed with higher doses of radiation therapy in prior studies of radiation in oligometastatic prostate cancer.

(2) Apalutamide therapy: Apalutamide is not considered SOC therapy in this group of patients, and consequently will be provided by the study. Apalutamide is being used in both arms of the study in order to maintain equipoise with regards to PSA endpoints. The optimal duration of concurrent androgen pathway inhibitor treatment in conjunction with ADT remains undefined. The SPARTAN study has studied maintenance of apalutamide therapy until radiographic disease progression, and not for a fixed time period as in this study.

However the optimal duration of apalutamide therapy in this setting has not been determined. Extrapolation from other studies evaluating the use of AR targeted therapy in hormone-naive prostate cancer patients with recurrent, but non-extensive disease suggests that the approach selected is appropriate. Clinical trials testing AR targeted therapy in conjunction with "salvage" radiotherapy in men with progressive disease following prostatectomy have utilized AR targeted therapy from 6 months (Carrie et al, Lancet Oncol 2016) to 24 months (Shipley et al, NEJM, 2017.) Furthermore, in a trial of intermittent androgen deprivation in patients with non-metastatic disease progression following radiation therapy, one year of systemic therapy was used (Crook et al, NEJM, 2012). One year of apalutamide therapy will therefore be used in both arms. Shorter duration is felt inadequate for patients with potentially metastatic disease, whereas longer duration would delay read out of results.

Although SBRT is an appropriate therapeutic approach in selected patients with oligometastatic prostate cancer, its utility has not been rigorously demonstrated. It is hypothesized that the addition of SBRT to apalutamide will result in clinically meaningful benefit, with improvement in time to subsequent metastasis, and potentially in an overall survival benefit. However, before embarking on a large phase 3 trial, an intermediate signal of activity is required. Only a very small proportion (2.5%) of patients with non-metastatic CRPC treated with apalutamide alone reach a serum PSA level of < 0.2 ng/mL. A nadir PSA of < 0.2 ng/mL has previously been shown to be strongly associated with long-term survival, and therefore represents a reasonable intermediate endpoint for a randomized phase 2 study. Positive results from the current study would form the strong justification for a follow-on randomized phase 3 study to investigate whether addition of SBRT impacts long-term treatment outcomes including radiographic progression-free and overall survival.

3.1.1 Number of Subjects

A total of 60 subjects may participate in this study. Thirty subjects will be enrolled to the apalutamide monotherapy arm, and 30 patients will be enrolled to the apalutamide + SBRT arm.

3.2 STUDY OUTCOMES

3.2.1 Primary Endpoints

Proportion of patients with undetectable serum PSA (< 0.2 ng/mL) at 6 months following completion of apalutamide therapy (18 months from date of randomization).

3.2.2 Secondary Endpoints

1. Time to PSA progression by PCWG criteria
2. Feasibility and safety of apalutamide and concurrent SBRT

3.2.3 Exploratory Endpoints

1. *Association between genomic factors and presence of oligometastatic disease*
2. *Association between somatic and germline genomic alterations with clinical outcomes*

   Note: The italicized objectives above were discontinued in Protocol v. 8.0. See Section 7.3 for additional information.

3. Association between baseline PSMA-PET scan uptake and distribution of lesions with treatment outcomes.

4 PATIENT SELECTION

The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. It is expected that all patients will be treated according to local standard of care, including radiation therapy if needed for local disease, prior to enrolling.

No waivers will be granted for eligibility criteria deviations.

Patients considered screen failures may be subsequently rescreened. Rescreening must be discussed with and approved by the Principal Investigator on a case-by-case basis. Patients who are determined to be eligible for the study after rescreening must sign a new informed consent form (ICF) and be assigned a new patient number.

4.1 INCLUSION CRITERIA

1. Histologically or cytologically confirmed adenocarcinoma of the prostate.
2. Progressive, castration-resistant prostate cancer demonstrated during continuous ADT, defined as 3 PSA rises at least 1 week apart, with a minimum PSA > 0.2 ng/mL obtained during Screening.
3. At least one but no more than 5 discrete PSMA-avid radiation fields on baseline PSMA-PET scan. All PSMA-avid lesions in radiation fields must be amenable to SBRT in judgment of treating radiation oncologist. There are no restrictions on site of lesion/radiation field (e.g. bone, lymph node, prostate, visceral). Equivocal lesions/radiation fields on PSMA PET scan that are not definitive for metastasis will not count towards the limit of 5 radiation fields and will not undergo SBRT.
4. Surgically or medically castrated, with testosterone levels of <50 ng/dL during Screening. If the patient is medically castrated, continuous dosing with LHRH analogue must have been initiated at least 4 weeks prior to randomization and must be continued throughout the study to maintain castrate levels of testosterone including post-treatment follow up period.
5. No prior systemic treatment initiated for the treatment of castration resistant prostate cancer, including abiraterone acetate, enzalutamide, apalutamide, darolutamide, other novel AR or CYP17 antagonist, or docetaxel.
6. Patients receiving bone loss prevention treatment with bone-modifying agents (e.g. denosumab, zoledronic acid) must be on stable doses for at least 4 weeks prior to randomization
7. Patients who received a first generation anti-androgen (e.g., bicalutamide, flutamide, nilutamide) as most recent treatment must have at least a 6-week washout prior to randomization and must show continuing disease (PSA) progression (an increase in PSA) after washout.
8. At least 4 weeks or 5 half-lives, whichever is shorter, must have elapsed from the use of any anti-cancer therapy, other than LHRH analog or first generation antiandrogen, prior to randomization
9. At least 4 weeks must have elapsed from major surgery or radiation therapy prior to randomization
10. Age ≥ 18 years

11. Eastern Cooperative Oncology Group (ECOG) Performance Status grade 0 or 1

12. Resolution of all acute toxic effects of prior therapy or surgical procedure to Grade 1 or baseline prior to randomization

13. Adequate organ function as defined by the following criteria:

    a. Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 x upper limit of normal (ULN)

    b. Total serum bilirubin ≤1.5 x ULN. In subjects with known or suspected Gilbert's syndrome, if total bilirubin is >1.5 × ULN, direct bilirubin is ≤1.5 × ULN

    c. Glomerular filtration rate ≥ 45 ml/min based on Cockroft-Gault equation

    d. Absolute neutrophil count (ANC) ≥ 1500/microliter

    e. Platelets ≥ 75,000/microliter

    f. Hemoglobin ≥ 9.0 g/dL

    g. Serum albumin ≥ 3.0 g/dL

14. Signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the trial prior to randomization.

15. Willingness and ability to comply with scheduled visits, treatment plans, laboratory and radiographic assessments, and other study procedures, including ability to swallow study drug tablets and long-term follow-up.

16. Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.

4.2 EXCLUSION CRITERIA

1. Presence of visceral lesions (e.g. lung, liver) detectable on baseline imaging or bone lesions requiring focal radiation treatment at the time of study entry

2. History of seizure or condition that may pre-dispose to seizure (e.g., prior stroke within 1 year prior to randomization, brain arteriovenous malformation, Schwannoma, meningioma, or other benign CNS or meningeal disease which may require treatment with surgery or radiation therapy.

3. Concurrent therapy with any of the following (all must have been discontinued or substituted for at least 1 week prior to randomization, except for medications known to lower seizure threshold which must be discontinued or substituted at least 4 weeks prior to randomization):

    a. Medications known to lower the seizure threshold (for a complete list please see Appendix 5)

b. Herbal (e.g., saw palmetto) and non-herbal (e.g., pomegranate) products that may decrease PSA levels.

c. Systemic (oral/IV/IM) corticosteroids. Patients on chronic stable dose of steroids at an equivalent dose of prednisone ≤ 10 mg daily may be permitted to enroll at the discretion of Principal Investigator.

d. Any other experimental treatment on another clinical trial.

4. Any of the following within 6 months prior to randomization: Severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias

5. Uncontrolled hypertension at study entry. Patients with a history of uncontrolled hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment.

6. Gastrointestinal disorder affecting absorption.

7. Secondary malignancy requiring active treatment except for non-melanoma skin cancer and superficial bladder cancer.

8. Any medical condition that would be a contra-indication to radiation therapy, such as inflammatory bowel disease.

9. Spinal cord compression or impending spinal cord compression

10. Any other condition that, in the opinion of the Investigator, would impair the patient's ability to comply with study procedures.

4.3 DURATION OF THERAPY

Protocol therapy will continue until the first occurrence of any one of the following:

- Disease progression by PCWG3 criteria
- Unacceptable adverse event(s) related to apalutamide or SBRT
- Completion of treatment (52 weeks)
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.4 DURATION OF FOLLOW UP

For safety follow up, patients will be followed for adverse events until 30 days after completion of treatment, removal from study, or until death, whichever occurs first. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower.

Patients will be followed on study until confirmed PSA progression by PCWG criteria.

4.5 RANDOMIZATION PROCEDURES

Once eligibility is confirmed, subjects will be randomized with equal probability to 1 of the 2 treatment arms. Balance in treatment assignment will be achieved using a randomized block design. Randomization will be carried out via computer generated random assignment. All subjects must commence treatment within 7 calendar days after randomization. Study sites will email the Eligibility Checklist to the Lead site (UCSF) in order to obtain the subject's treatment assignment. Once subject eligibility is confirmed by the lead site, an email with the treatment assignment number will be provided to the study site.

4.6 STUDY TIMELINE

The estimated study duration is approximately 36 months, 18 months for accrual and 18 months of study follow up.

5 STUDY TREATMENTS

5.1 RANDOMIZATION

After patients have provided their written informed consent, completed all screening assessments and received confirmation of eligibility, they will be randomized into the study. All patients must commence treatment within 7 calendar days after randomization.

5.2 BLINDING

There is no blinding for this study.

5.3 FORMULATION

5.3.1 Apalutamide

Refer to the Investigator's Brochure for a list of excipients.

5.3.2 Packaging, Storage, and Labeling

The apalutamide 60-mg tablets will packaged in 120-count, 160 cc high-density polyethylene (HDPE) bottles with child-resistant caps. Bottles will include desiccant.

Each bottle of study drug will be labeled with the required regulatory agency warning statement, the protocol number, the Sponsor's name, and directions for patient use and storage. The Investigator will ensure that the study drug is stored in appropriate conditions in a secure location with controlled access. For clinical formulation-specific and batch-specific storage instructions, see the packaging label.

5.3.3 Drug Administration

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

5.3.4 Cycle Management

For the purposes of the study, a treatment cycle will consist of 4 weeks (28 days).

It is anticipated that individual patients may occasionally forget to take a dose. In those cases, missed doses should only be replaced if the patient remembers within a 12-hour window. After that, patients should just take the next dose the following day, without compensating for the missed dose (including vomited doses). In the event of dose delays due to transient toxicity, tumor assessments should remain on schedule independent of cycle length.

5.3.5 Dose Modifications

Intra-patient dose interruptions and/or reductions will be permitted provided that study discontinuation criteria have not been met (please see Section 10).

- Patients experiencing treatment-related seizure of any grade will have study drug permanently discontinued.
- For patients experiencing Grades 1-2 treatment-related adverse events, short treatment breaks can be instituted as per the discretion of the Investigator until the severity of the toxicity decreases to Grade 1 or returns to baseline. If toxicity recurs, dose reductions to the next lower dose level will be allowed as per the discretion of the Investigator.
- For patients experiencing Grade 3 treatment-related adverse events other than seizure, study drug should be held. If the severity of the toxicity decreases to Grade 1 or returns to baseline within two weeks, study treatment may be resumed at the next lower dose level, except for clinically insignificant laboratory abnormalities that resolve within two days on optimal treatment, in which case dose reduction is not required. If toxicity recurs at Grade 3 or higher, the dose of apalutamide should be reduced to the next lower dose level. A maximum of 2 dose level reductions will be allowed (Table 1).
- For patients experiencing Grade 4 treatment-related adverse events, except for clinically insignificant laboratory abnormalities that resolve within two days on optimal treatment, study treatment must be permanently discontinued.
- Any patient requiring > 14 days delay in treatment due to study treatment-related AEs should discontinue treatment of the study treatment thought to be responsible for the AE.

Table 1 Apalutamide Dose Levels

Dose Level	Total Daily Dose	Number of 60-mg Tablets (QD)
0	240 mg	4
-1	180 mg	3
-2	120 mg	2

Doses reduced for study treatment-related toxicities should generally not be re-escalated, however, re-escalation back to the previous dose level may be permitted at the discretion of the Principal Investigator.

Rash

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

Table 2 Apalutamide Dose Modification

Severity	Intervention

Grade 1	• Continue apalutamide at current dose • Initiate dermatological treatment[a]: ○ Topical steroid cream AND ○ Oral Antihistamines • Monitor for change in severity[a]
Grade 2 (or symptomatic Grade 1)[b]	• Hold apalutamide for up to 28 days • Initiate dermatological treatment[a] ○ Topical steroid cream AND ○ Oral Antihistamines • Monitor for change in severity[a] ○ If rash or related symptoms improve, reinitiate apalutamide when rash is Grade≤1. Consider dose reduction at a 1 dose level reduction[c].
Grade 3[d]	• Hold apalutamide for up to 28 days • Initiate dermatological treatment[a] ○ Topical steroid cream AND ○ Oral Antihistamines AND Consider short course of oral steroids • Reassess after 2 weeks, and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the subject to a dermatologist ○ Reinitiate apalutamide at a 1 dose level reduction[e] when rash is Grade≤1. ○ If the dose reduction will lead to a dose less than 120mg, the study drug must be stopped (discontinued) • If after 28 days, rash has not resolved to Grade≤1, discontinue study drug
Grade 4	• Permanently discontinue apalutamide • Inpatient admission for IV steroids and dermatology consultation

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

a Obtain bacterial/viral cultures if infection is suspected

b Subject presents with other rash related symptoms such as pruritus, stinging, or burning

c 1 dose level reduction = 60mg (1 apalutamide tablet)

d If there is blistering or mucosal involvement, stop apalutamide dosing immediately

e If a subject previously started oral corticosteroids, continue for at least 1 week after resumption of reduced dose of apalutamide. If the proposed total oral steroid use will exceed 28 days, contact Principal Investigator.

5.4 STUDY DRUG ACCOUNTABILITY

The initial study drug shipment will be shipped after all required regulatory documentation has been received by the manufacturer and a Clinical Trial Agreement fully executed.

The study drug will only be dispensed to patients who meet the eligibility criteria and are randomized to a treatment arm in the trial. An accurate and current accounting of the dispensing and return of study drug for each patient will be maintained on an ongoing basis by the Investigator or his/her designated personnel. The number of study drug dispensed and returned by the patient will be recorded on the Investigational Product Accountability Log. The study monitor will verify these documents throughout the course of the study.

The disposition of any unused study drug should be performed per institutional guidelines. The Investigator must ensure that all investigational product is destroyed in compliance with the applicable environmental regulations, institutional policy, and any other special instructions provided by the manufacturer. Drug destruction must be adequately documented.

5.5 MEASURES OF TREATMENT COMPLIANCE

At each clinic visit, patients will be asked to return any remaining study drug from the previous dosing cycle as well as all used and unused study drug containers.

The overall treatment compliance will be defined as the total dose in mg taken during the study divided by the expected total dose in mg. Patients completing their last cycle on capsules should continue with a maximum of 8 capsules per day and patients on tablets should have a maximum of 4 tablets per day.

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

5.6 STEREOTACTIC BODY RADIATION

SBRT must be initiated within 90 days following initiation of apalutamide therapy for patients randomized to this treatment arm.

For the purposes of planning an SBRT treatment, CT- and/or MRI-simulation will be performed with fabrication of a radiation therapy immobilization device (such as a vacuum lock bag) which will be custom made for each patient. For tumors located in the upper abdomen or thorax, respiratory motion will be considered with methods including four-dimensional CT study or respiratory control to improve tumor targeting accuracy for those tumors that may be subject to respiratory motion.

The treating radiation oncologist will identify the location of the tumor. Gross tumor volume (GTV) delineation will be performed on sequential axial computed tomography images. An SBRT treatment plan will be developed based on tumor geometry and location. The clinical tumor volume (CTV) will typically equal the GTV or ITV (internal target volume). The dose will be prescribed to the minimal isodose line that completely covers the planning target volume (PTV) PTV (=CTV plus a 5 mm margin), except in cases where dose constraints to neighboring organs necessitates under dosage of the PTV. Adjacent normal structures including but not limited to the heart, esophagus, aorta, spinal cord, kidneys, rectum, bowel, liver, and stomach within 5 cm of the CTV will be identified for the purpose of limiting incidental radiation to these structures.

SBRT will be delivered in 1 to 5 fractions, and the dose and fractionation schedule will depend on the size and location of the lesion(s)/radiation field and the surrounding normal tissue constraints in accordance with AAPM Task Group 101 recommendations. Typical doses include 16 – 24 Gy in 1 fraction, 30 – 60 Gy in 3 fractions, and 30 – 60 Gy in 5 fractions. For example, while isolated osseous lesions may be treated in a single fraction (depending on location), lesions in the lung and liver will be treated in 3 to 5 fractions depending on their size (5 fractions for ≥ 3 cm) or location (central tumors in close proximity to the mediastinum).

Within three weeks of the initial treatment planning imaging study, SBRT will be administered using image-guidance. A vacuum lock bag (or equivalent immobilization approach) will be used to minimize movement of the chest, spine, and abdomen during treatment. During treatment, real time cone beam CT images of the patient's body site of interest will be obtained. Cone beam CT scan will be obtained immediately prior to treatment and will be repeated until the treatment shift, required to align the CT planning scan and the cone beam CT scan performed on the day of treatment cone beam CT, is within tolerance for the body site.

Equivocal lesions/radiation fields on PSMA PET scan that are not definitive for metastasis will not count towards the limit of 5 radiation fields and will not undergo SBRT. Patients will be evaluated for adverse events/toxicities during their treatment.

6 CONCURRENT MEDICATIONS

All patients should be maintained on the same medications throughout the entire study period, as medically feasible, with minimum introduction of new chronic therapies. Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded on the CRF. Standard medical treatment as applicable is allowed except for treatments noted in the eligibility criteria and/or listed in the prohibited medications section below.

Continuous treatment with a LHRH analogue or surgical castration is mandatory for all patients in order to maintain castrate concentrations of testosterone (<50 ng/dL). The choice of LHRH analogue is at the discretion of the investigator. Dose and dose schedule (without interruption) will be consistent with the prescribing information and should only be adjusted if clinically indicated to maintain castrate concentrations of testosterone. Maintenance of castrate level of testosterone is mandatory during both the On-Treatment and Post-Treatment periods of the study.

All patients should receive oral calcium and vitamin D supplementation while receiving apalutamide. For patients at high estimated fracture risk based on baseline DXA bone density scan (> 3% estimated 10 year risk of hip fracture or > 20% major osteoporotic fracture per FRAX calculator (https://www.sheffield.ac.uk/FRAX/), treatment with a bone-modifying agent (e.g. alendronate) should be administered as per institutional guidelines.

6.1 PROHIBITED MEDICATIONS AND TREATMENTS

As a class effect, androgen receptor antagonists have been associated with seizures due to an off-target mechanism of action ($GABA_A$ inhibition). Patients will be closely monitored for seizures, but as a precautionary measure, drugs known to decrease the seizure threshold and/or cause seizure will be prohibited while on study. A list of these medications can be found in Appendix 5.

6.2 RESTRICTED THERAPIES

Investigators should refer to the apalutamide Investigator's Brochure (Sections 4.3.3.3 and 5.10) and associated addenda for complete details on the drug interaction potential of apalutamide. Highlights of drug interaction are summarized below.

- Strong CYP3A4 inducers: the potential for drug-drug interactions with apalutamide has not been tested clinically. Strong inducers of CYP3A4 (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, efavirenz, tipranavir, St. John's wort) should be avoided as much as possible. Additional information is provided in Appendix 5.

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

- Strong CYP2C8 inhibitors (eg, gemfibrozil) should be used with caution with apalutamide.

- The potential for drug-drug interaction between apalutamide and warfarin (e.g., Coumadin) is unknown at present. If a patient is taking warfarin, re-assess (prothrombin) PT/(international normalized ratio) INR as clinically indicated and adjust the dose of warfarin accordingly.

- Corticosteroids (Oral, IV, or IM): due to possible resistance mechanisms, which may be contributed by glucocorticoid receptor signaling, concurrent use of corticosteroids during the study should be avoided whenever possible. Short term use of steroids (≤ 4 weeks) will be allowed if clinically indicated, however, its use must be tapered off as soon as possible.

6.3 LIFESTYLE GUIDELINES

To avoid risk of drug exposure through the ejaculate (even men with vasectomies), patients must use a condom during sexual activity while on study drug and for 3 months following the last dose of study drug. Donation of sperm is not allowed during the study and for 3 months following the last dose of study drug.

There are no data on the use of apalutamide in pregnancy. Maternal use of an anti-androgen is expected to produce changes in hormone levels that may affect fetal development. It is not known if apalutamide or its metabolites are present in semen.

If the patient is engaged in sexual activity with a woman of childbearing potential, a condom is required along with another effective contraceptive method consistent with local regulations regarding the use of birth control methods for patients participating in clinical studies and their partners. Highly effective forms of contraception include:

- established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine (IUS) system;

- barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
- vasectomy;
- true abstinence (an option when this is in line with the preferred and usual lifestyle of the patient).

Two highly effective forms of contraception are required during the study and for 3 months after the last dose of study drug.

7 STUDY PROCEDURES AND GUIDELINES

A Schedule of Activities representing the required testing procedures to be performed during the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and any other authorizations must be signed and dated by the patient or patient's legal representative.

7.1 CLINICAL ASSESSMENTS

7.1.1 Demographics

Demographic information (e.g., date of birth, race) will be recorded at Screening.

7.1.2 Medical History

Relevant medical history, including history of current disease, other pertinent clinical conditions, and information regarding underlying diseases will be recorded at Screening.

7.1.3 Physical Examination

A complete physical examination will be performed by either the Investigator or a sub-Investigator at Screening. Qualified staff (e.g., nurse practitioner or physician assistant) may complete either a full or abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and followed by a physician or other qualified staff at the next scheduled visit. All physical exams may be performed over a telemedicine visit.

7.1.4 Vital Signs

Heart rate and blood pressure will be recorded after resting for 5 minutes at Screening and every scheduled visit during treatment and at the end of treatment. If the physical exam is a telemedicine visit, BP and heart rate will be self-reported by the patient.

7.1.5 Performance Status

The Eastern Cooperative Oncology Group (ECOG) performance status scale will be used (Appendix 3) and will be assessed at Screening and every subsequent clinic visit.

7.1.6 Adverse Events

Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03), timing, seriousness, and relatedness (Appendix 4). Adverse events will be assessed at every clinic visit.

7.1.7 Concomitant Medications/Therapies

All concomitant medication and concurrent therapies will be documented from screening until 30 days after the last dose of study drug. Name, indication for administration, and dates of medication or therapy will be captured.

7.1.8 Tumor Assessments

Whole body PSMA-PET imaging will be performed within 42 days of randomization during the Screening period. PSMA PET imaging may use Ga-PSMA-11 or other PSMA PET tracer. Either PSMA PET/MR or PET/CT is allowed. A certified trained nuclear medicine physician will evaluate the baseline PSMA-PET scan for purposes of eligibility determination to verify whether there are ≥ 1 but ≤ 5 discrete radiation fields. A treating radiation oncologist will review baseline scans to determine whether the lesion(s) identified on baseline PSMA PET scan are amenable to SBRT.

If more than 5 radiation fields are identified on baseline PSMA PET scan the patient will be deemed Screen Failure and will be treated per investigator discretion.

Patients will undergo optional follow up PSMA PET scan at the time of PSA progression by PCWG criteria. PSA progression will be defined as an increase of at least 2 ng/mL and 25% above the nadir or baseline on study, whichever is lower, confirmed by repeat PSA measurement at least 2 weeks later.

7.1.9 Tumor Biopsy (DISCONTINUED)

An optional biopsy and biomarker blood collection was to be conducted under the PROMOTE study (CC155518, IRB# 15-18365), as an optional enrollment option. The PROMOTE study has closed to accrual and will no longer be able to financially support the biopsy, biomarker collection, and downstream correlatives. Therefore, we are discontinuing the biopsy and biomarker blood collection moving forward described in the italicized paragraph below (as of Amendment 8.0). Any specimens collected under prior protocol versions (i.e., prior to implementation of Amendment 8.0) may continue to be stored and/or used as permitted according to the PROMOTE study protocol and ICF.

Patients will undergo optional baseline image-guided core needle tumor biopsy of PSMA-avid metastatic lesion if lesion is safely accessible. Lesions will be chosen based upon the strength of the evidence suggesting the presence of metastasis and with the goal of minimizing patient risk. Soft tissue lesions should be prioritized for biopsy. If the Radiologist in charge of the procedure cannot identify a lesion amenable for biopsy, the patient will still be treated on study.

Patients undergoing biopsy must have a PT or INR and a PTT ≤ 1.5 times the institutional ULN within 14 days prior to biopsy. Patients on warfarin, aspirin, or other anti-coagulants may undergo biopsy, provided they are deemed able to tolerate discontinuation of anti-coagulation for one week prior to the baseline biopsy. Conversion to low molecular weight heparin prior to biopsy is permitted per local standard operating procedures, provided there is agreement regarding the procedure between the treating physician, the interventional radiologist and the PI.

The biopsies will be performed in an interventional radiology suite with radiological guidance (typically CT or MRI) in accordance with the standard operating procedure according to institutional standards. Once the target lesion(s) identified, up to six (6) biopsies will be performed. Preferably, a 16 gauge Bonopty™ needle or biopsy needle with an equivalent 16g bore will be used to biopsy the metastatic lesion. If the lesion is a bone metastasis, the Bonopty needle will be passed through the cortical bone and into the target lesion. Optimal results are obtained when the biopsies are performed on medullary bone directly adjacent to blastic lesion. Soft tissue biopsies should be taken so that a core of approximately 10 to

20 mm in length is obtained. Core biopsies will be extracted: up to 3 will be placed in neutral-buffered formalin and up to 3 will be immediately frozen on a pre-frozen bed of OCT (Optimal Cutting Temperature compound used for frozen sections), covered with additional OCT, and kept on dry ice or at -80° C.

7.2 CLINICAL LABORATORY MEASUREMENTS

Blood will be obtained at the time points described in the Schedule of Activities. Appendix 2 lists all of the specific tests that will be performed.

Investigators may have additional blood tests performed for the purpose of planning treatment administration, dose modification, or following adverse events.

7.2.1 PSA

Serum PSA will be measured using local laboratory during Screening, on C1D1, on D1 of every cycle thereafter during the 12 month treatment period, and every 28 days during follow up until the date of confirmed PSA progression by PCWG3 criteria.

7.3 EXPLORATORY BIOMARKERS (DISCONTINUED)

An optional biopsy and biomarker blood collection was to be conducted under the PROMOTE study (CC155518, IRB# 15-18365), as an optional enrollment option. The PROMOTE study has closed to accrual and will no longer be able to financially support the biopsy, biomarker collection, and downstream correlatives. Therefore, we are discontinuing the biopsy and biomarker blood collection moving forward described in the italicized paragraph below (as of Amendment 8.0). Any specimens collected under prior protocol versions (i.e., prior to implementation of Amendment 8.0) may continue to be stored and/or used as permitted according to the PROMOTE study protocol and ICF.

Metastatic tumor biopsy tissue acquired at UCSF will undergo genomic characterization as described in UCSF protocol CC# 155518. In brief, *freshly frozen tissue will undergo laser capture microdissection and exome/transcriptome sequencing. Formalin-fixed paraffin embedded tissue will undergo pathologic evaluation and targeting next-generation sequencing using CLIA-certified laboratory. Whole blood for exploratory analysis of circulating nucleic acids including analysis of circulating tumor DNA and long noncoding RNA (lncRNA) will be collected on C1D1, every 3 cycles during protocol treatment, at the end of study treatment, and at the time of PSA progression. Germline mutation testing to evaluate for alterations in BRCA2 and other DNA repair pathway genes will be performed at baseline if patients give optional consent for testing. Germline mutation testing is not performed in a CLIA environment and, therefore, will not be reported back to patients.*

PSMA imaging characteristics including the number, distribution and avidity of metastatic lesions will be characterized by trained nuclear medicine physician.

8 STUDY ASSESSMENTS BY VISIT (APPENDIX 1)

8.1 SCREENING (WITHIN 42 DAYS OF RANDOMIZATION, UNLESS OTHERWISE SPECIFIED)

- Review the study with the patient (patient's legal representative) and obtain written informed consent
- Collect archival primary prostate cancer tissue (optional)

- PSMA (prostate specific membrane antigen) PET scan. Imaging may use Ga-PSMA-11 or other PSMA PET tracer. Either PET/MR or PET/CT is allowed (within 12 weeks of randomization).
- Record demographics data
- Record medical history, including history of prostate cancer, diagnosis date, and prior treatments
- Record concomitant medications
- Perform a physical examination
- Perform and record vital signs and ECOG performance status grade
- Collect blood for clinical laboratory assessments including hematology tests, total bilirubin (and direct bilirubin if total bilirubin > 1.5 ULN), ALT, AST, alkaline phosphatase, BUN or creatinine, albumin, and LDH.
- Collect blood for PSA
- Collect blood for testosterone
- Collect blood for Thyroid Stimulating Hormone (TSH)
- Obtain DXA bone density scan (femoral neck and lumbar spine)
- If patient is confirmed eligible by the medical monitor, randomize patient and proceed to Cycle 1 Day 1 visit (randomization can occur on C1D1 or within 7 days prior to C1D1)

8.2 CYCLE 1 DAY 1

- Record changes to concomitant medications
- Record any adverse events
- Perform abbreviated physical examination
- Perform and record vital signs and ECOG performance status
- Collect blood for clinical laboratory assessments including hematology tests, total bilirubin (and direct bilirubin if total bilirubin > 1.5 ULN), ALT, AST, alkaline phosphatase, BUN or creatinine, and LDH. Screening evaluations can be used if done within 4 days of Cycle 1 Day 1.
- Collect blood for PSA
- Collect blood for TSH
- Dispense study drug

8.3 DAY 1 OF CYCLES 2-4, THEN DAY 1 OF EVERY 2 CYCLES STARTING FROM CYCLE 5 THROUGH C13 (C5, C7, C9, C11, C13) (+/- 7 days) UNLESS OTHERWISE SPECIFIED

- Record any adverse events
- Record changes to concomitant medications

- Dispense study drug
- Assess study drug compliance
- Perform abbreviated physical examination
- Perform and record vital signs and ECOG performance status
- Collect blood for clinical laboratory assessments (including hematology tests, total bilirubin (and direct bilirubin if total bilirubin > 1.5 ULN), ALT, AST, alkaline phosphatase, BUN or creatinine, and LDH.
- Collect blood for PSA measurement (Day 1 of every treatment cycle)
- Stereotactic body radiation therapy administered 60 days following initiation of apalutamide therapy
- Collect blood for thyroid stimulating hormone test every 4 cycles starting Cycle 5 Day 1 (C5D1, C9D1, C13D1).

8.4 END OF TREATMENT VISIT

- Record any adverse events
- Record changes to concomitant medications
- Assess study drug compliance
- Perform abbreviated physical examination
- Perform and record vital signs and ECOG performance status
- Collect blood for clinical laboratory assessments (including hematology tests, total bilirubin (and direct bilirubin if total bilirubin > 1.5 ULN), ALT, AST, alkaline phosphatase, BUN or creatinine, and LDH.
- Collect blood for PSA measurement
- Collect blood for TSH

8.5 SAFETY FOLLOW-UP (30 DAYS FOLLOWING THE LAST DOSE OF STUDY DRUG)

- Record any adverse events
- Record changes to concomitant medications

8.6 POST-TREATMENT PERIOD UNTIL CONFIRMED PSA PROGRESSION BY PCWG CRITERIA

- Collect blood for PSA measurement every 28 days (+/- 7 days) until confirmed PSA progression by PCWG3 criteria. In the event of disease progression per PCWG3 or initiation of a new non-protocol therapy, patients will be discontinued from the study, and further PSA tracking will no longer be required

8.7 AT CONFIRMED PSA PROGRESSION (+ 28 day window)

- PSMA PET scan (optional)

- All patients can be treated at their physician's discretion as standard of care, after coming off study treatment.
- Perform and record ECOG performance status

9 ADVERSE EVENT REPORTING REQUIREMENTS

9.1 DEFINITIONS

9.1.1 Adverse Events (AE)

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

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

Examples of AEs include but are not limited to:

- Clinically significant abnormal laboratory findings (see below)
- Clinically significant signs and symptoms
- Changes in physical examination findings
- Worsening of signs and symptoms of the malignancy under study. *Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as an adverse event, unless the outcome is fatal during the study or within the safety reporting period – see definition of serious adverse event below.*
- Signs or symptoms resulting from dose overdose, dependency, withdrawal, abuse, and/or misuse
- Drug interactions
- Exposure in utero (pregnancy)

For laboratory abnormalities, the criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing outside of protocol-stipulated dose adjustments or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or Test result is considered to be an adverse event by the Investigator

9.1.2 Adverse Events of Special Interest

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

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

9.1.3 Serious Adverse Events (SAE)

A serious adverse event (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 (i.e., immediate risk of death from the reaction as it occurred).
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a
- 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned)
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions
- Results in a congenital anomaly or birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

Events **not** considered to be SAEs are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care or social admissions

9.1.4 Expectedness

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

Unexpected, as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of

drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. Such events would be considered unexpected until they have been observed with the drug under investigation.

9.1.5 Attribution

A suspected adverse reaction means any adverse event for which there is reasonable possibility that the study drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event.

The Investigator will assign attribution of the possible association of the event with the study drug using the following definitions:

- **Unrelated to study drug**: The adverse event is *clearly not related* or is *doubtfully related* to the study drug
- **Related to study drug**: The adverse event *may be related,* is *likely related*, or is *clearly related* to the study drug

9.1.6 Severity

Signs or symptoms should be graded and recorded by the Investigator according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (Appendix 4). When specific adverse events are not listed in the CTCAE, they are to be graded as mild, moderate, severe, or life-threatening according to the following grades and definitions:

Table 2 AE Severity Grading

Severity (Toxicity Grade)	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental activities of daily living (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

9.1.7 Individual Case Safety Report (ICSR)

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

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

The minimum information required is:

1. suspected Janssen medicinal product (doses, indication)
2. date of therapy (start and end date, if available)
3. batch or lot number, if available
4. subject details (subject ID and country)
5. gender
6. age at AE onset
7. reporter ID
8. adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
9. protocol ID

9.1.8 Special Reporting Situations

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

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product

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

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

9.1.9 Pregnancy

Because the Janssen medicinal product may have an effect on sperm, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the Principal Investigator **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form."

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

9.2 ADVERSE EVENTS MONITORING

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board (IRB); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

For a detailed description of the Data and Safety Monitoring Plan for a Multicenter Phase 2 or 3 Institutional Study at the Helen Diller Comprehensive Cancer Center please refer to Appendix 6 Multicenter Institutional Studies.

9.3 REPORTING REQUIREMENTS

All AEs and SAEs whether reported by the patient, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the patient's medical record and on the appropriate study-specific CRFs.

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.03 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events, see Appendix 4.

The Sponsor-Investigator at the UCSF Coordinating Center will hold the role of Study Chair (Dr. Rahul Aggarwal). The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites.

Anticipated events will be recorded and reported as described in Section 9.3.3.

9.3.1 SAE Reporting to the Sponsor-Investigator and Janssen

All participating sites will report SAEs to the Sponsor-Investigator within 24 hours of knowledge of the event. The Sponsor-Investigator will report to Janssen within 24 hours of being notified of the event, using MedWatch forms, as outlined below:

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

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

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

SAEs and Special Reporting Situations

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

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

All participating sites will report all SAEs and special situations following exposure to a Janssen product under study to the Sponsor-Investigator within 24 hours of knowledge of the event, using MedWatch forms. UCSF and the Sponsor-Investigator will transmit all SAEs and special situations following exposure to a Janssen product under study using MedWatch form **within 24-hours of becoming aware of the event(s).**

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported by participating sites to the Sponsor-Investigator **within 24 hours of knowledge of the event.** SAE follow-up information will be reported directly to Janssen by the Sponsor-Investigator, **within 24 hours becoming aware**, using the MedWatch form. The Sponsor-Investigator will also notify the UCSF DSMC of any SAEs.

Reporting Deaths: Regardless of relationship to study drug, all deaths on study should be reported to Janssen through and including 30 days after the last dose of study. Deaths occurring after the safety follow-up period do not have to be reported as SAEs unless considered related to study drug. All study drug related deaths should be reported to the UCSF DSMC within 1 business day of becoming aware. All deaths will be reviewed by the UCSF DSMC.

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

- For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor-Investigator and Janssen in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE CRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality.

- Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor-Investigator or designated representative and Janssen.

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

All events should be followed to their resolution, until the Investigator assesses them as stable, irreversible, or until the patient is lost to follow-up, whichever comes first. Any SAEs occurring any time after the reporting period must be promptly reported if a causal relationship to apalutamide is suspected.

Copies of SAE Reporting to Regulatory Authorities to Janssen within 24 hours:

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

Product Quality Complaint (PQC) Handling:

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

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product

- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules

- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe

- Suspected Contamination

- Suspected Counterfeit

PQC Reporting:

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen, and are mandated by regulatory agencies worldwide. Janssen has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be

collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported by participating sites to the Sponsor-Investigator **within 24 hours of knowledge of the event**. The Sponsor-Investigator will report all initial PQCs to Janssen **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the Sponsor-Investigator must report the PQC to Janssen and the UCSF coordinating center according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen.

Transmission Methods:

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

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

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

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

9.3.2 Non-Serious AE Reporting

Adverse events should be recorded on the AE CRF from the time the patient has signed the informed consent at screening (see Section 8.2) until 30 days after the last dose of study drug. All events should be followed to their resolution, until the Investigator assesses them as stable, irreversible, or until the patient is lost to follow-up, whichever comes first. If a patient begins a new systemic anti-cancer therapy, the AE reporting period for non-SAEs ends at the time the new treatment is started.

All non-serious adverse events should be reported to the Sponsor-Investigator and UCSF, who will report this to Janssen.

9.3.3 UCSF Sponsor-Investigator Reporting Requirements to Regulatory Authorities

Adverse events reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations. The Sponsor-Investigator or its designee will be responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting.

For anticipated events reported as individual serious adverse events Janssen will make a determination of relatedness in addition to and independent of the investigator's assessment. Janssen will periodically evaluate the accumulating data and, when there is sufficient evidence and Janssen has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators and the Study Chair.

Reporting to the UCSF Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the Sponsor-Investigator, who will then notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to the UCSF Institutional Review Board

The Sponsor-Investigator must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 5 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

The Sponsor-Investigator or its designee will be responsible for reporting relevant SAEs to the FDA.

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Provide Copies SAE Reporting to Regulatory Authorities to Janssen

Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with

the Janssen Product under study, are to be provided to Janssen **within 24 hours of such report or correspondence being sent to applicable regulatory authorities.**

10 END OF TREATMENT

A patient may be discontinued from study treatment at any time if the patient or the Investigator feels that it is not in the patient's best interest to continue on study. If a patient's study treatment must be discontinued, this will not result in automatic withdrawal of the patient from the study.

Study treatment with apalutamide will be discontinued for the following reasons, whichever occurs first:

- Disease progression by PCWG criteria. PSA progression is defined as increase of at least 2 ng/mL and 25% above the nadir or baseline on study, whichever is lower, confirmed on repeat measurement at least two weeks later.
- Completion of 13 cycles of study therapy (52 weeks)
- Any episode of seizure
- Any other adverse event that cannot be adequately managed with dose modifications, including dose interruption for treatment-related adverse events that do not improve to Grade 1 or baseline within 14 days, will require study drug discontinuation
- Protocol violation requiring discontinuation of study treatment
- Patient is not compliant with study procedures
- Lost to follow-up
- Patient withdrawal of consent
- Janssen's request for early termination of study

All patients discontinuing study treatment in the absence of disease progression will enter the Post-Treatment Period for PSA monitoring until the time of confirmed PSA progression.

Follow up on study will continue at least the first occurrence of one of the following:

- Disease progression by PCWG criteria.
- Protocol violation requiring discontinuation of study treatment
- Patient is not compliant with study procedures
- Lost to follow-up
- Patient withdrawal of consent
- Janssen's request for early termination of study

If a patient is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

11 PROTOCOL VIOLATIONS

A protocol violation occurs when the patient or Investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, patient safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria [no waivers will be granted to meet the eligibility criteria]
- Use of a prohibited concomitant medication
- Dose modifications that are not within the protocol specifications
- Any other deviation that presents significant risk or safety concerns to the patient

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor-Investigator will determine if a protocol violation should result in withdrawal of a patient.

12 STATISTICAL METHODS AND CONSIDERATIONS

12.1 ANALYSIS POPULATIONS

Safety Analysis Population [SAFETY]: All patients who receive at least one dose of study drug, with treatment assignments designated according to actual study treatment received will be the primary population for evaluating safety and treatment compliance and administration.

12.2 ANALYTIC PLAN

12.2.1 Analysis of Primary Endpoint

The primary endpoint for the study is the proportion of patients with undetectable serum PSA (< 0.2 ng/mL) at 6 months following completion of apalutamide therapy (18 months from date of randomization). Fisher's exact test will be used to compare the proportion in the two treatment arms. Patients who discontinue apalutamide prior to completion of 12 months of therapy for reasons other than disease progression by PCWG criteria, as well as patients who withdraw or are lost to follow up, will be considered inevaluable for this analysis. Patients who discontinue treatment for radiographic or clinical progression, even if occurring prior to receipt of SBRT in the experimental arm), would be evaluable for analysis of the primary endpoint.

12.2.2 Analyses of Secondary Endpoints

Comparison of time to PSA progression will be performed using a two-sided log-rank test. Kaplan-Meier methods will be used to estimate medians for each treatment arm. Cox proportional-hazard models, including the same factors as above, will be used to estimate the hazard ratio and its 95% confidence interval (CI).

Adverse events (AEs) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. All AEs reported from the first dose of study drug until 30 days after the last dose of study drug will be considered as treatment-emergent AEs and will be summarized by treatment arm. For each treatment arm, adverse event incidence rates will be summarized with frequency and percentage, with all patients treated in that treatment arm as the denominator, unless otherwise specified. In addition, AE incidence rates will also be summarized by severity and relationship to study drug. Treatment-related AEs are those judged by the Investigator to be at least possibly related to the study treatment. Adverse events with missing severity or relationship to study drug will be classified as severe and treatment-related, respectively.

12.2.3 Analysis of Exploratory Endpoints

The number and distribution of lesions detected on PSMA PET scan at baseline and at the time of PSA progression will be summarized using descriptive statistics for each treatment arm.

To determine the genomic factors associated with the development of oligometastatic disease, patient tumor biopsies will be compared to independent datasets of RNA/DNA sequencing from tumors obtained from patients with localized prostate cancer as well as those with more widespread castration-resistant prostate cancer. These analyses will be largely descriptive in nature.

Gene expression levels and genomic alterations (single nucleotide variants and/or copy number changes) in metastatic tumor biopsies and in germline DNA will be investigated for an association with efficacy outcomes using appropriate statistical methods (e.g. categorical or survival models), depending on the endpoints. Analyses may be performed within and between each treatment group. Other clinical covariates (such as baseline clinical disease characteristics and patient 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 to identify "high-risk" biomarker profiles that are correlated with poor outcome.

Note: The italicized endpoints above were discontinued in Protocol v. 8.0. See Section 7.3 for additional information.

Whenever available, archival primary prostate cancer tissue for patients enrolled on the current study will be analyzed for gene expression patterns and compared to the patterns of gene expression observed in the baseline and progression tumor biopsies obtained at from an oligometastatic site of disease.

The number and site of oligometastatic sites of disease on baseline PSMA PET scan, as well as the PSMA avidity (SUVmax) for each lesion will be descriptively reported. Intra- and inter-lesional heterogeneity of uptake will be characterized using descriptive statistics. The association between patterns of uptake on baseline PSMA PET with outcomes on study will be investigated using appropriate statistical methods (e.g. categorical or survival models) as appropriate, within and across treatment groups.

12.2.4 Interim Analysis

No interim analysis will be performed, as the primary endpoint (PSA undetectable rate 6 months following completion of protocol treatment) will not be evaluable until after all patients have been accrued on study.

12.2.5 Determination of Sample Size

The sample size is based upon the primary endpoint of the study, the proportion of patients with an undetectable serum PSA (< 0.2 ng/mL) 6 months following completion of protocol therapy with apalutamide. Assuming a 10% inevaluable/drop-out rate per treatment arm, a sample size of 60 patients (30 patients/arm) provides 84% power to detect a difference in proportion of patients with undetectable PSA of 25% in the apalutamide + SBRT arm vs. 2.5 % in the apalutamide without SBRT treatment arm, with a unidirectional level of significance of 0.10 using Fisher's exact test.

13 STUDY MANAGEMENT

13.1 INVESTIGATOR RESPONSIBILITIES

The investigator is responsible for ensuring that the study is performed in accordance with current 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 subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of the study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

13.2 PRE-STUDY DOCUMENTATION

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

13.3 INSTITUTIONAL REVIEW BOARD APPROVAL

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the UCSF Institutional Review Board or the IRB of the participating site. For UCSF, prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by each respective IRB prior to implementation.

13.4 INFORMED CONSENT

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any

study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.5 CHANGES IN THE PROTOCOL

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation.

The Study Chair and the UCSF study team will be responsible for updating any participating sites.

13.6 HANDLING AND DOCUMENTATION OF CLINICAL SUPPLIES

The UCSF Principal Investigator (Sponsor-Investigator) and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

13.7 CASE REPORT FORMS (CRFs)

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after

that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

Each participating site will complete study specific CRFs for safety monitoring and data analysis. Each site will enter the study data into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The participating site's Clinical Research Coordinator (CRC) will complete the CRFs; the Investigator will review and approve the completed CRFs – this process must be completed within 3 business days of the visit. Study data from the participating site will be reported and reviewed in aggregate with data from patients enrolled at the coordinating center, UCSF. All source documentation and CTMS data will be available for review/monitoring as needed.

13.8 OVERSIGHT AND MONITORING PLAN

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 6 Data and Safety Monitoring Plan for a Phase 2 or 3 Multicenter Institutional Study, for additional information.

13.9 MULTICENTER COMMUNICATION

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, quarterly conference calls with the participating sites or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse events (i.e., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

13.10 RECORD KEEPING AND RECORD RETENTION

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and medical records, such as progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

13.11 REGULATORY DOCUMENTATION

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF IRB. Prior to implementing this protocol at the participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form, and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals.

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

14 PROTECTION OF HUMAN SUBJECTS

14.1 PROTECTION FROM UNNECESSARY HARM

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

14.2 PROTECTION OF PRIVACY

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

In order to maintain patient confidentiality, only a site number and patient number will identify all study patients on blood samples and tumor specimens.

Long-term Storage of Samples for Future Research

Samples collected for biomarker assessments are planned to be stored until testing and for up to 5 years after the end of the study at the Feng laboratory at UCSF. All samples will be labeled with unique study ID number, and no personal identifying information will be attached to the sample.

15 REFERENCES

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APPENDIX 1: SCHEDULE OF ACTIVITIES

	Screening	Treatment Phase			Post treatment		
Activities and Forms to be Completed	**≤42 Days Prior to Randomization**	**Cycle 1 Day 1**	**D1 C2-C4, D1 of every 2 cycles starting at C5 to C13 (+/- 7 days)**	**Every 16 weeks (Starting on C1D1)**	**End-of-Treatment**	**Safety Follow-up**	**At PSA PD by PCWG (+ 28 days)**
Screening							
Informed Consent	X						
Medical/Oncological History [3]	X						
Inclusion/Exclusion Criteria	X						
Randomization [4]	X						
Study Treatment Administration							
Apalutamide Administration [5]		240 mg per day taken orally					
SBRT [6]			X				
Assess Study Drug Compliance			X		X		
Laboratory Studies							
Hematology [7]	X	X	X		X		
Blood Chemistry [7]	X	X	X		X		
Serum Albumin	X						
PSA [8]	X	X	X		X	X	
Testosterone	X						
Thyroid-Stimulating Hormone [9]	X	X		X	X		
Efficacy							
ECOG Performance Status	X	X	X		X		X
PSMA PET Scan [10]	X						X

	Screening	Treatment Phase			Posttreatment		
Activities and Forms to be Completed	**≤42 Days Prior to Randomization**	**Cycle 1 Day 1**	**D1 C2-C4, D1 of every 2 cycles starting at C5 to C13, (+/- 7 days)**	**Every 16 weeks (Starting on C1D1)**	**End-of-Treatment [1]**	**Safety Follow-up [2]**	**At PSA PD by PCWG (+ 28 days)**
Safety							
Physical Examination [12]	X	X	X		X		
Vital Signs (BP and heart rate)	X	X	X		X		
DXA Bone density test (femoral neck and lumbar spine)	X						
Adverse Events		Continuous until 30 days after the last dose of study drug					
Concomitant Medications	Continuous until 30 days after the last dose of study drugs						
Exploratory Biomarkers							
Archival FFPE blocks/slides [11]	X						

C1D1=Cycle 1 Day 1; BICR=blinded independent central review; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EQ-5D=Euro QoL; FACT-P=functional assessment of cancer therapy-prostate; FFPE=formalin-fixed paraffin-embedded; PSA=prostate specific antigen

Footnotes

1. **End-of-Treatment:** These assessments do not need to be completed if they have been performed within 1 week of the last dose of study drug
2. **Safety Follow-Up:** Patients should be evaluated for safety up to 30 days after the last dose of study drug. All AEs should be followed to their resolution, until the Investigator assesses them as stable, irreversible, or until the patient is lost to follow-up, whichever comes first. If a patient begins a new systemic anti-cancer therapy, the AE reporting period for non-SAEs ends at the time the new treatment is started.
3. **Medical/Oncological History:** Includes oncologic history, demographics, history of other disease processes (active or resolved) and concomitant illnesses.
4. **Study Randomization:** The Cycle 1 Day 1 visit can occur on the same day or within 7 days after randomization.
5. **Apalutamide:** Patients in both treatment arms will receive oral daily apalutamide continuously, starting on Cycle 1 Day 1. One cycle consists of 28 days.
6. **Stereotactic body radiation therapy (SBRT):** Patients randomized to SBRT arm must begin treatment within 90 days following initiation of apalutamide therapy.
7. **Samples for Hematology, Blood Chemistry:** All laboratory assessments will be performed by local laboratory. On Cycle 1 Day 1 only, clinical laboratory tests do not need to be repeated if the Screening tests were done within 4 days of Cycle 1 Day 1. See Appendix 2 for complete list of hematology and blood chemistry tests.
8. **Samples for PSA:** PSA evaluations will be performed by local laboratories. On Cycle 1 Day 1 only, the PSA evaluation does not need to be repeated if the Screening tests were done within 4 days of Cycle 1 Day 1. During the treatment period, PSA will be measured on Day 1 of every cycle (+/- 7 days). During the post-treatment period PSA will be measured every 28 days (+/- 7 days).
9. **TSH:** TSH will be completed during Screening and Day 1 of each cycle for the first four cycles, then every 4 cycles starting at Cycle 5
10. **PSMA PET imaging:** Whole body (vertex to toes) PSMA PET imaging will be performed during Screening (within 12 weeks of randomization). At the time of PSA progression by PCWG criteria there is optional follow up PSMA PET scan. PSMA PET imaging may use Ga-PSMA-11 or other PSMA PET tracer. Either PET/MR or PET/CT may be performed.
11. **Collection of archival primary prostate cancer tissue (optional):** Archival tumor specimens will be collected whenever available.

12. Physical exams may be performed via a telemedicine visit. Vital signs (BP and heart rate) will be self-reported by the patient if the physical exam visit is through telemedicine.

APPENDIX 2: REQUIRED LABORATORY TESTS

Hematology (See Appendix 1 for timing)	Chemistry and PSA (See Appendix 1 for	Other
Hemoglobin	Total bilirubin (Note: if	
Platelet count	> 1.5 x ULN, include analysis of	Thyroid stimulating hormone
Red blood cell count	direct and indirect bilirubin)	(TSH); See Appendix 1
White blood cell count	Alanine transaminase (ALT)	
White blood cell differential	Aspartate transaminase (AST)	
	Alkaline phosphatase	
	Blood urea nitrogen (BUN) or	
	Creatinine	
	Prostate specific antigen (PSA)	
	Lactate dehydrogenase	

APPENDIX 3: ECOG PERFORMANCE STATUS GRADES

0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX 4: NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

The NCI CTCAE (Version 4.03) may be reviewed on-line at the following NCI website:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

APPENDIX 5: PROHIBITED OR RESTRICTED MEDICATIONS OR SUPPLEMENTS WHILE ON STUDY

Medications that are PROHIBITED while on study:

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

Supplements that are RESTRICTED while on study:

- Pomegranate

Medications that are RESTRICTED while on study:

Investigators should refer to the apalutamide Investigator's Brochure (Sections 4.3.3.3 and 5.10) and associated addenda for complete details on the drug interaction potential of apalutamide. Highlights of drug interaction are summarized below.

- Strong CYP3A4 inducers: the potential for drug-drug interactions with apalutamide has not been tested clinically. Strong inducers of CYP3A4 (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, efavirenz, tipranavir, St. John's wort) should be avoided as much as possible.
- Apalutamide may also induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have narrow therapeutic index
- Strong CYP2C8 inhibitors (eg, gemfibrozil) should be used with caution with apalutamide
- The potential for drug-drug interaction between apalutamide and warfarin (e.g., Coumadin) is unknown at present. If a patient is taking warfarin, re-assess (prothrombin) PT/(international normalized ratio) INR as clinically indicated and adjust the dose of warfarin accordingly.
- Corticosteroids (Oral, IV, or IM): due to possible resistance mechanisms, which may be contributed by glucocorticoid receptor signaling, concurrent use of corticosteroids during the study should be avoided whenever possible; short term use (≤ 4 weeks) will be allowed if clinically indicated, however, its use must be tapered off as soon as possible.

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

APPENDIX 6: DATA AND SAFETY MONITORING PLAN

Data and Safety Monitoring Plan for a Multicenter Study Phase II or III Trial

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Semiannual auditing (depending on accrual).
- Review of serious adverse events.
- Minimum of a biennial regulatory auditing visit.

2. Monitoring and Reporting Guidelines

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the trial and for auditing its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and participant safety at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

All institutional Phase II or III therapeutic trials are designated with a moderate risk assessment. The data is audited by a DSMC Monitor/Auditor on a semiannual basis with a random selection of twenty percent of the participants (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for review or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than 10 total participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

The participating site's source documents are audited remotely via either review of redacted source documents downloaded by the site into the CRA console of OnCore and/or via access to the site's electronic medical records. The DSMC Monitor/Auditor will audit no more than three participant charts at each participating site during the course of auditing this trial.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV)

reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

Multicenter communication

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.
- Adverse events (i.e., new adverse events and updates on unresolved adverse events and new safety information).
- Protocol Violations.
- Other issues affecting the conduct of the study.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the remote monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and applicable FDA regulations.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), regardless of being unexpected or considered to be associated with the use of the study drug will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

- Definite – The adverse event is clearly related to the investigational agent(s) or study procedure.
- Probable – The adverse event is likely related to the investigational agent(s) or study procedure.
- Possible – The adverse event may be related to the investigational agent(s) or study procedure.
- Unrelated – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center Site Committee meetings. All grade 3-5 adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled monthly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment from the UCSF Coordinating Center and the participating sites.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All Serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within one business days of becoming aware of the event. The SAEs are reviewed and audited by the UCSF Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or Vice Chair and the DSMC Director within 1 business day of this notification.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC Chair (or Vice Chair) and the DSMC Director at the time the increased rate is identified via a report. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified within their reporting guidelines.

Data and Safety Monitoring Committee Contacts:

Katie Kelley, MD (DSMC Chair)
[redacted]
UCSF HDFCCC
[redacted]
John McAdams (DSMC Director)
[redacted]
UCSF HDFCCC
San Francisco, CA 94143