Title Page

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF MEVROMETOSTAT (PF-06821497) WITH ENZALUTAMIDE IN METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER (MEVPRO-3)

Study Intervention Number:	PF-06821497
Study Intervention Name:	Mevrometostat
US IND Number:	134135
EU CT Number:	2024-519369-24-00
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number	Not available
Protocol Number:	C2321008
Phase:	3
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001 United States

Brief Title:

A Study to Learn About the Investigational Medicine Called Mevrometostat (PF-06821497) in Men With Metastatic Castration-Sensitive Prostate Cancer Who Have Not Tried Novel Hormonal Therapy or Chemotherapy for Metastatic Prostate Cancer (MEVPRO-3)

Document History

Document	Version Date
Original protocol	07 February 2025
Amendment 1	16 June 2025

This amendment incorporates all revisions to date.

Protocol Amendment Summary of Changes Table

Amendment 1 (16 June 2025)

Overall Rationale for the Amendment: The purpose of this amendment was to provide updated clinical risks for mevrometostat and enzalutamide, clarify reporting requirements for second primary malignancies, and clarify inclusion/exclusion criteria. Updates were made to align enzalutamide supply with local requirements.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Updated potential risks of clinical significance	To provide additional information on second primary malignancies and updated potential risks of clinical significance for enzalutamide based on the XTANDI IB update (ed 15.0; Apr 2025)	Section 2.3.1 Risk Assessment
Specified that any diagnosis of a second primary malignancy is to be reported as an SAE	To provide clarity on second primary malignancy reporting requirements	Section 8.4.1.2 Reporting Second Primary Malignancies
Specified that use of 5-alpha reductase inhibitors is prohibited within 28 days prior to randomization	To provide clarity on prohibited prior and concomitant therapy	Section 5.2 Exclusion Criteria (#6)
Specified that radiotherapy, including concurrent radiotherapy, is not allowed during study	To provide clarity on prohibited modalities of radiotherapy	Section 5.1 Inclusion Criteria (#5)
Updated parameters for exclusionary hepatic dysfunction	To provide clarity on exclusion criteria	Section 5.2 Exclusion Criteria (#10)

Description of Change	Brief Rationale	Section # and Name
Added exclusion for prior surgery from which the participant has not fully recovered at least 28 days prior to randomization	To provide clarity on exclusion criteria	Section 5.2 Exclusion Criteria (#14)
Specified that rising PSA levels are exclusionary if they are indicative of disease progression	To provide clarity on inclusion criteria	Section 1.1 Synopsis; Section 5.1 Inclusion Criteria (#5)
Time frame for exclusionary suicidal behavior (5 years) was added	To provide clarity on exclusion criteria	Section 5.2 Exclusion Criteria (#1)
Non-Substantial Modification(s)		
Streamlined guidance for potential cases of acute kidney injury	To clarify guidance for investigators and to align with the current Pfizer protocol template	Section 7.1.1 Potential Cases of Acute Kidney Injury; Table 6 Core Lab Tests; Section 10.7 Kidney Safety: Monitoring Guidelines; Section 10.7.2 Kidney Function Calculations
Added Neutrophils and eGFR as core lab tests; streamlined guidance for clinical laboratory tests	To align with the current Pfizer template	Section 10.2 Appendix 2: Clinical Laboratory Tests; Table 6 Core Lab Tests
Updated dose formulation of enzalutamide based on local availability	To facilitate the use of local enzalutamide formulations	Section 6.1 Study Intervention(s) Administered; Section 6.1.1.2 Enzalutamide; Section 6.2.1.1 Mevrometostat/Placebo and Enzalutamide
Specified hormonal therapies prohibited during the study as referenced in the Inclusion/Exclusion criteria	For consistency within the protocol	Section 6.9.1 Prohibited During the Study
Updated reporting requirements for disease-related events and deleted the Lack of Efficacy section	To align with the current Pfizer protocol template	Section 8.4.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or

Description of Change	Brief Rationale	Section # and Name
		SAEs; Section 10.3.1 Definition of an AE; formerly Section 8.4.8.1
Added guidance for providing AE outcome assessments	To align with the current Pfizer protocol template	Section 10.3.3 Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period
Language clarified to highlight anchor timepoint for LTFU activities	To provide clarity on when LTFU activities should occur	Table 1 Schedule of Activities; Section 7.1 Discontinuation of Study Intervention
Specified timing of potential EDP exposure	To align with the current Pfizer protocol template	Section 8.4.5.1 Exposure During Pregnancy
Language added to clarify EOT occurrence and timing of EOT assessments	To provide clarity on when EOT activities should occur	Table 1 Schedule of Activities; Section 7.1 Discontinuation of Study Intervention
Updated safety follow-up description	To differentiate between timing of last dose and permanent discontinuation	Table 1 Schedule of Activities; Section 4.1 Overall Design
Clarified hematologic abnormality exclusion criteria	To provide clarity on exclusion criteria	Section 5.2 Exclusion Criteria (#11)
Clarified that obtaining consent may not be delegated to a local healthcare professional	To align with the current Pfizer protocol template	Section 10.1.3 Informed Consent Process
Added that temporary or permanent treatment discontinuation should be discussed with the medical monitor.	To align with the current Pfizer protocol template.	Section 7.1 Discontinuation of Study Intervention
Specified that medical records may be requested to facilitate assessment of medical history	To align with the current Pfizer protocol template	Section 8.1.1.2 Medical History
Provided guidance for reporting SAEs via paper	To align with the current Pfizer protocol template	Section 10.3.3 Recording/Reporting and

Description of Change	Brief Rationale	Section # and Name
		Follow-Up of AEs and/or SAEs During the Active Collection Period
Specified that PRO data will not be utilized for AE/SAE reporting	To align with the current Pfizer protocol template	Section 8.2.4 Patient-Reported Outcomes Assessments
Clarified ECG guidance	To align with the current Pfizer protocol template	Section 8.3.3 Electrocardiograms
Specified that laboratory test results will be graded according to NCI CTCAE	To align with the current Pfizer protocol template	Section 8.3.4 Clinical Safety Laboratory Assessments
Updated enrollment for Study 1001 and clinical results for Study C2321001 Part 2B (expansion cohort)	To provide the most recently published clinical information on mevrometostat	Section 2.2.1 Clinical Overview
Updated timeline description for missed retained research samples for genetics	To provide clarity on when to collect missed sample	Table 1 Schedule of Activities
Combined Contraception counseling and Germ cell cryopreservation counseling rows	To align with the current Pfizer protocol template	Table 1 Schedule of Activities
Generalized procedures for reporting AEs and SAEs	To align with the current Pfizer template	Section 10.3.3 Recording/Reporting and Follow-Up of AEs and/or SAEs during the Active Collection Period; Section 10.3.4 Reporting of SAEs
Removed section detailing electronic consent process	Electronic consent is not being used in this study	Previously Section 10.1.3.1 Electronic Consent
Updated description of contraception options	To align with the current Pfizer template	Section 10.4.1 Male Participant Reproductive Inclusion Criteria; Section 10.4.2 Contraception Methods
Added description of planned sensitivity analysis that counts all disease progressions and deaths as	To provide clarity on planned analyses	Section 9.3.2 Primary Endpoint/Estimand/Analysis

Description of Change	Brief Rationale	Section # and Name
events, regardless of timing or missing tumor assessments		
Updated safety reporting requirements for EU Member States	To align with the current Pfizer protocol template	Section 10.9.1 European Union
Added safety reporting requirements for Switzerland	To align with the current Pfizer protocol template	Section 10.9.5 Switzerland
General editorial changes	To correct minor errors, to maintain consistency, to align with the current Pfizer protocol template, and/or to increase clarity	Throughout protocol

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Mevrometostat (PF-06821497) With Enzalutamide in Metastatic Castration-Sensitive Prostate Cancer (MEVPRO-3)

Brief Title: A Study to Learn About the Investigational Medicine Called Mevrometostat (PF-06821497) in Men With Metastatic Castration-Sensitive Prostate Cancer Who Have Not Tried Novel Hormonal Therapy or Chemotherapy for Metastatic Prostate Cancer (MEVPRO-3)

Regulatory Agency Identification Number(s):

US IND Number:	134135
EU Clinical Trial (CT) Number:	2024-519369-24-00
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	Not Available
Protocol Number:	C2321008
Phase:	3

Study Rationale:

The rationale for this study is to evaluate whether the addition of enhancer of zeste homolog 2 (EZH2) inhibition to enzalutamide can delay or prevent antiandrogen resistance, thereby increasing the duration of clinical benefit of enzalutamide in participants who are treatment naïve to androgen receptor pathway inhibitors (ARPIs) and have not yet received chemotherapy in the metastatic castration-sensitive prostate cancer (mCSPC) setting. This Phase 3 randomized study (C2321008, hereafter referred to as MEVPRO-3) is designed to demonstrate that mevrometostat + enzalutamide provides superior clinical benefit compared to placebo + enzalutamide in participants with mCSPC.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To demonstrate that mevrometostat in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging blinded independent central review (BICR)-assessed radiologic progression-free survival (rPFS)	• BICR assessed rPFS per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 (soft tissue disease) and Prostate Cancer Working Group 3 (PCWG3) (bone disease)
Secondary:	**Secondary:**
• To demonstrate that mevrometostat in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging overall survival (OS)	• OS (alpha protected)
• To compare anti-tumor activity between mevrometostat in combination with enzalutamide and placebo in combination with enzalutamide	• Proportion of participants with measurable soft tissue disease at baseline with an objective response per RECIST 1.1 (assessed by BICR and investigator) • Duration of soft tissue response per RECIST 1.1 (assessed by BICR and investigator) • Proportion of participants with prostate-specific antigen (PSA) response ≥50% in participants with detectable PSA values at baseline • Time to PSA progression • Time to initiation of antineoplastic therapy • Time to first symptomatic skeletal event • Time from randomization to castration-resistant prostate cancer (CRPC)
• To compare safety and tolerability between mevrometostat in combination with enzalutamide and placebo in combination with enzalutamide	• Type, incidence, severity (as graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0), seriousness and relationship to study medications of adverse events (AEs) and any laboratory test and electrocardiogram (ECG) abnormalities
• To evaluate the pharmacokinetics (PK) of mevrometostat when dosed in combination with enzalutamide	• PK characterized by pre-dose trough and post-dose plasma concentrations of mevrometostat at selected visits
• To compare patient-reported outcomes (PROs) between mevrometostat in combination with enzalutamide and placebo in combination with enzalutamide	• Change from baseline and time to confirmed deterioration in participant-reported worst pain symptoms per Brief Pain Inventory – Short Form (BPI-SF) • Change from baseline in health-related quality of life (HRQoL), functioning, and symptoms and time to definitive deterioration per Functional Assessment of Cancer Therapy – Prostate (FACT-P) • Change from baseline and time to definitive deterioration in participant-reported prostate cancer specific functioning and symptoms per European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer 25 (EORTC QLQ-PR25)

Objectives	Endpoints
	• Change from baseline and time to confirmed deterioration in participant-reported fatigue symptoms per Brief Fatigue Inventory (BFI) • Change from baseline in participant-reported general health status per European Quality of Life 5-Dimensions 5-Level (EQ-5D-5L)
• To assess the relationship between circulating tumor DNA (ctDNA) burden and outcome	• ctDNA burden at baseline and on study

Overall Design

This is a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study evaluating mevrometostat in combination with enzalutamide versus placebo in combination with enzalutamide in participants with mCSPC who have not received systemic anticancer treatments with the exception of androgen-deprivation therapy (ADT) and first-generation antiandrogen agents. Prior therapy with up to 3 months of ADT (chemical or surgical) is allowed, with no radiographic evidence of disease progression or rising PSA levels indicative of disease progression prior to Day 1.

Approximately 1000 participants will be randomly assigned on a 1:1 basis to:

- Investigational Arm A: Mevrometostat 875 mg twice daily (BID) + enzalutamide 160 mg once daily (QD)
- Comparator Arm B: Placebo BID + enzalutamide 160 mg QD

Randomization will be stratified by:

- Disease volume (low vs high). High volume of disease is defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis
- De novo vs relapsed mCSPC

Randomized participants will receive treatment as per assigned treatment arm continuing until study intervention discontinuation criteria are met.

Disease status will be assessed at screening and at regular intervals during the study by computed tomography (CT) of the chest and CT/magnetic resonance imaging (MRI) of abdomen and pelvis for assessment of soft tissue/visceral disease, technetium-99m (^{99m}Tc)-methylene diphosphonate radionuclide bone scintigraphy for bone metastases, PSA measurements, and PRO assessments. A third-party core imaging laboratory will perform BICR assessment of rPFS data. BICR review of radiographic assessments ends following BICR-determined radiographic progression.

Treatment with study intervention will continue until BICR-determined radiographic disease progression, participant refusal, or unacceptable toxicity occurs, or other discontinuation of study intervention criteria are met. Participants will enter the Long-Term Follow-Up (LTFU) period after Safety Follow-Up. If the participant has not discontinued from study procedures and/or post-treatment study follow-up, LTFU will continue until the end of the study. It is recommended that participants remain on study treatment until BICR confirmed radiographic progression. Participants who discontinue treatment and do not have radiologic disease progression will continue radiographic imaging and PSA assessments and serum testosterone assessments until they progress radiographically as determined by BICR (regardless of the initiation of a new antineoplastic therapy) or death. After confirmation of radiographic progression by BICR, further radiographic imaging and PSA assessments will continue as per local clinical practice until the next report of progression after the start of subsequent antineoplastic therapy.

An independent external data monitoring committee (E-DMC) will monitor the safety of the participants on a periodic basis.

Number of Participants

Approximately 1000 participants will be enrolled in the study.

Note: "Enrolled" means a participant's agreement to participate in this clinical study following completion of the informed consent process and randomization to study intervention.

A total of 227 rPFS events will provide approximately 90% power to detect a target hazard ratio (HR) of 0.65 using a 2-sided log-rank test with a 5% level of significance.

For OS, a total of 252 events will provide approximately 80% power to detect a target HR of 0.70 using a 2-sided log-rank test with a 5% level of significance and a 3-look group sequential-design.

Study Population

Eligible participants include adult men (age ≥18 years) with histologically or cytologically confirmed adenocarcinoma of the prostate, surgical or medical castration, and documented progression of metastatic disease. Participants must have an ECOG performance status of 0 or 1 with no medical or psychiatric condition or laboratory abnormality that may increase the risk of participation. Participants must be treatment naïve at the mCSPC stage (eg, participants cannot have received any cytotoxic chemotherapy [includes but not limited to docetaxel], prior androgen receptor pathway inhibitor [ARPI; enzalutamide, apalutamide, darolutamide], abiraterone acetate, or other systemic treatment) with some exceptions.

Study Arms and Duration:

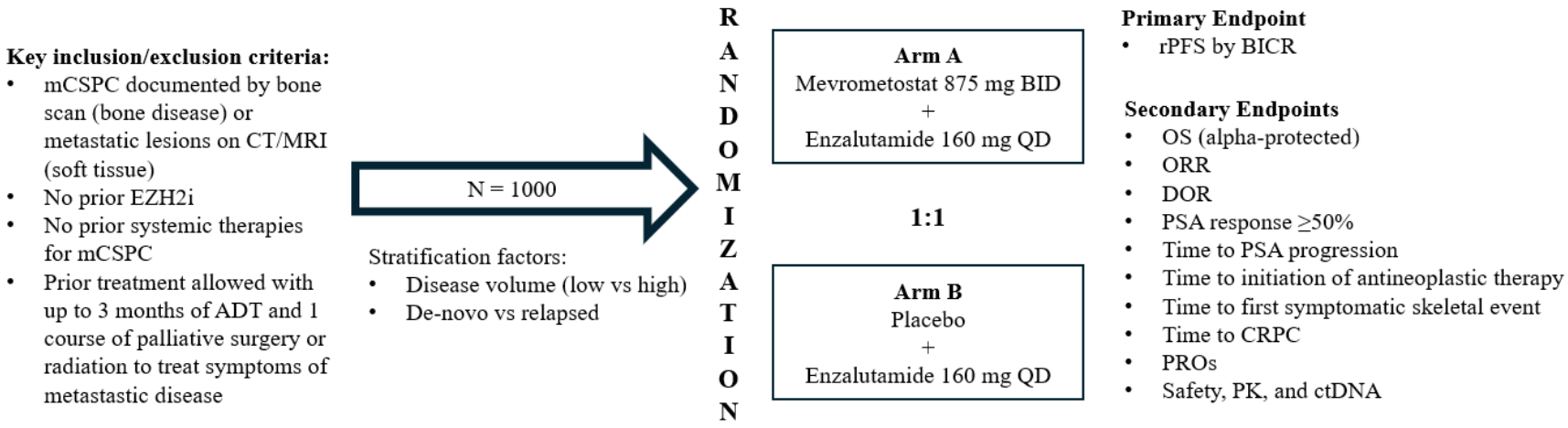
Study Arm(s)		
Arm Title	**Arm A**	**Arm B**
Arm Description	Mevrometostat dosed 875 mg BID + enzalutamide 160 mg QD. Treatment will be administered until confirmed disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, or study termination.	Placebo BID + enzalutamide 160 mg QD. Treatment will be administered until confirmed disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, or study termination.

Ethical Considerations:

The results of an ongoing Phase 1 study of mevrometostat, C2321001, either as monotherapy in participants with solid tumors or in combination with enzalutamide in participants with prostate cancer, support this investigation of mevrometostat plus enzalutamide for participants with mCSPC. Taking into account the measures to minimize risk to participants, the potential risks associated with mevrometostat plus enzalutamide are justified by the potential benefits that may be afforded to participants with mCSPC. Therefore, the Phase 1 results suggest a favorable benefit-risk profile to support the study rationale.

Participants may experience delayed progression of disease and clinical benefit with maintained quality of life from the combination of mevrometostat plus enzalutamide. Study participants may also benefit from more intense monitoring and more frequent assessments. Based on the Phase 1 clinical data for participants with prostate cancer, the most frequently reported all-causality adverse events (≥10%) occurring with the combination of mevrometostat + enzalutamide include diarrhea, decreased appetite, nausea, fatigue, dysgeusia, asthenia, edema peripheral, vomiting, weight decreased, alopecia, hypokalemia, hypocalcemia, anemia, thrombocytopenia, and neutropenia. Study safety data will be monitored on a regular basis by the sponsor, as well as by an independent external data monitoring committee E-DMC (external data monitoring committee). Participants will be notified to seek advice regarding sperm cryopreservation due to the possibility of reduced sperm counts during treatment.

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Abbreviations used in the SoA table are provided in Appendix 12.

Table 1. Study Schedule of Activities

Visit Identifier	Screening	Treatment Period										Follow-up		Notes
Study Week		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29+**	**37+**	**EOT**	**Safety**	**LTFU**	All screening should be done ≤28 days before first dose **Week 29+**: Activities every 4 weeks until C14D1, then every 8 weeks thereafter **Week 37+** : Activities every 12 weeks **EOT**: Occurs following discontinuation of study intervention and should be no more than 1 week after the discontinuation of all study intervention. If EOT visit coincides with a regular study visit, EOT activities will supersede those of the scheduled visit. **Safety**: Approx 28-35 days after last dose of study intervention or before initiation of subsequent therapy, whichever occurs first. **LTFU**: Activities every 8 weeks until Week 25, then every 12 weeks thereafter, continuing the assessment schedule established at randomization.
Cycle 1 cycle = 28 days		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**		**Scans, sT, and PSA**				
Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
Informed consent	X													Informed consent must be obtained prior to any study-specific procedures or enrollment process.
Screen for inclusion/ exclusion criteria	X													See Section 5.1 and Section 5.2.
Demographics	X													See Section 8.1.1.1.
Randomization	X													After participant is deemed eligible for the study; the participant enrollment number and Treatment Arm are assigned at randomization. Participants must start treatment within 3 days after randomization. See Section 6.3.
Medical history and PE														
Medical history	X													Relevant medical and surgical history and current illnesses. See Section 8.1.1.2.

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Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
Prior treatment for prostate cancer	X													Section 8.1.1.2.
Screening tumor biopsy	X													Local assessment of tumor histopathology. Biopsy is only required if no prior histological or cytological confirmation of prostate adenocarcinoma is available.
Physical exam	X	X	X	X	X	X	X	X	X		X	X		Physical examinations to be completed before administration of study intervention. See Section 8.3.1.
ECOG performance status	X	X	X	X	X	X	X	X	X		X	X		See Section 8.3.2.1 and (Appendix 11).
Vital signs, height, weight	X	X	X	X	X	X	X	X	X		X	X		Measure blood pressure, heart rate, temperature (C), height (cm), and weight (kg). Height is only required to be collected at screening. See Section 8.3.2.

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Visit Identifier	Screening	Treatment Period										Follow-up		Notes
Study Week		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29+**	**37+**	**EOT**	**Safety**	**LTFU**	All screening should be done ≤28 days before first dose **Week 29+**: Activities every 4 weeks until C14D1, then every 8 weeks thereafter **Week 37+** : Activities every 12 weeks **EOT**: Occurs following discontinuation of study intervention and should be no more than 1 week after the discontinuation of all study intervention. If EOT visit coincides with a regular study visit, EOT activities will supersede those of the scheduled visit. **Safety**: Approx 28-35 days after last dose of study intervention or before initiation of subsequent therapy, whichever occurs first. **LTFU**: Activities every 8 weeks until Week 25, then every 12 weeks thereafter, continuing the assessment schedule established at randomization.
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Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
12-lead ECG (single)	X										X	X		Management of signs or symptoms of ischemic heart disease is to be per general clinical practice and local guidelines, including QTcF interval (machine reported or manually). See Section 8.3.3 and Appendix 8.
Contraception counseling	X													See Section 5.3.1 and Appendix 4. Counseling to seek advice about donation and cryopreservation of germ cells prior to start of study intervention due to the possibility of reduced sperm counts during treatment. See Section 5.3.1.
Contraception check	X	X												If risk of pregnancy has changed, contraception counseling should be provided.
Serious / nonserious AE monitoring	X													Report serious and nonserious adverse event information from time informed consent is signed through screen failure or through a minimum of 28 days after the last dose of study intervention. See Section 8.4 and Appendix 3.

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Visit Identifier	Screening	Treatment Period										Follow-up		Notes
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Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
Prior / concomitant treatment(s)	X													Continuous ADT must be administered during the Treatment Period. See Section 6.9.
Symptomatic skeletal events		X	X	X	X	X	X	X	X		X	X	X	See Section 8.3.5.
Laboratory assessments See Appendix 2 for a list of clinical laboratory tests to be done. For laboratory collection volumes, see the laboratory manual.														
Hematology, CD4* (pre-dose)	X	X	X	X	X	X	X	X	X		X	X		If screening laboratory assessments are performed within 7 days of the C1D1 visit, laboratory assessments do not need to be repeated at C1D1. Samples may be collected up to 3 days prior to the visit to guide decision making. *Consider obtaining CD4 count if lymphocyte count is <500/µL. See Section 8.3.4 and Appendix 2.

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Visit Identifier	Screening	Treatment Period										Follow-up		Notes
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Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
Blood chemistry (pre-dose)	X	X	X	X	X	X	X	X	X		X	X		If screening laboratory assessments are performed within 7 days of the C1D1 visit, laboratory assessments do not need to be repeated at C1D1. Samples may be collected up to 3 days prior to the visit to guide decision making. See Section 8.3.4 and Appendix 2.
Serum testosterone (sT)	X	X		X		X		X		X	X	X	X	sT is collected at screening and every 8 weeks (at Week 1, 9, 17, 25), then every 12 weeks (at Week 37, 49, 61, etc), EOT and at the Safety Follow-up visit. sT is collected during LTFU, regardless of investigator assessment of progression until BICR confirmed progression.
PSA (pre-dose)	X	X		X		X		X		X	X	X	X	PSA collected at screening and every 8 weeks (at Week 1, 9, 17, 25), then every 12 weeks (at Week 37, 49, 61, etc), EOT and at the Safety Follow-up Visit. PSA is collected during LTFU, regardless of investigator assessment of progression until BICR confirmed progression. See Section 8.3.4 and Appendix 2.

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Visit Identifier	Screening	Treatment Period										Follow-up		Notes
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Cycle 1 cycle = 28 days		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**		**Scans, sT, and PSA**				
Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
Radiographic assessments Imaging assessments are to be scheduled using the randomization date as the reference date for all time points. All radiographic assessments must be forwarded to BICR; the same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Radiographic assessments continue for all participants until blinded independent central confirmation of radiographic progression. Radiographic assessments continue as scheduled regardless of dosing delays. See Section 8.2.2. Tumor assessments are to be performed during the EOT visit if the reason for study treatment discontinuation was anything other than central radiographically confirmed disease progression and it has been ≥8 weeks since the last assessment. Tumor assessments should continue during follow-up if the participant discontinues treatment for reasons other than BICR confirmed radiographic disease progression.														
CT scan of chest; CT or MRI of abdomen and pelvis	X			X		X		X		X	X		X	Screening/baseline scans obtained within -42 days of randomization will be accepted. Scans will be performed every 8 weeks (at Week 9, 17, 25), then every 12 weeks (at Week 37, 49, 61, etc). See Section 8.1, Section 8.2.2, and Appendix 10 Sections 10.10.1 and 10.10.2.2.

Table 1. Study Schedule of Activities

Visit Identifier	Screening	Treatment Period										Follow-up		Notes
Study Week		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29+**	**37+**	**EOT**	**Safety**	**LTFU**	All screening should be done ≤28 days before first dose **Week 29+**: Activities every 4 weeks until C14D1, then every 8 weeks thereafter **Week 37+** : Activities every 12 weeks **EOT**: Occurs following discontinuation of study intervention and should be no more than 1 week after the discontinuation of all study intervention. If EOT visit coincides with a regular study visit, EOT activities will supersede those of the scheduled visit. **Safety**: Approx 28-35 days after last dose of study intervention or before initiation of subsequent therapy, whichever occurs first. **LTFU**: Activities every 8 weeks until Week 25, then every 12 weeks thereafter, continuing the assessment schedule established at randomization.
Cycle 1 cycle = 28 days		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**		**Scans, sT, and PSA**				
Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
Whole body bone scan: Tc-99m Bone Scintigraphy	X			X		X		X		X	X		X	Screening/baseline scans obtained within -42 days will be accepted. Scans will be performed every 8 weeks (at Week 9, 17, 25), then every 12 weeks (at Week 37, 49, 61, etc). See Section 8.1, Section 8.2.2, and Appendix 10 Sections 10.10.1 and 10.10.2.2
PRO assessments														
FACT-P		X	X	X	X	X	X	X	X		X	X	X	Questionnaires should be completed alone before the first dose of study treatment on C1D1. At all subsequent visits, questionnaires should be completed alone in the same order and before any other study activities. See Section 8.2.4.
EORTC QLQ-PR25		X	X	X	X	X	X	X	X		X	X	X	
BFI		X	X	X	X	X	X	X	X		X	X	X	
EQ-5D-5L		X	X	X	X	X	X	X	X		X	X	X	
BPI-SF		X	X	X	X	X	X	X	X		X	X	X	

Table 1. Study Schedule of Activities

Visit Identifier	Screening	Treatment Period										Follow-up		Notes
Study Week		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29+**	**37+**	**EOT**	**Safety**	**LTFU**	All screening should be done ≤28 days before first dose **Week 29+**: Activities every 4 weeks until C14D1, then every 8 weeks thereafter **Week 37+** : Activities every 12 weeks **EOT**: Occurs following discontinuation of study intervention and should be no more than 1 week after the discontinuation of all study intervention. If EOT visit coincides with a regular study visit, EOT activities will supersede those of the scheduled visit. **Safety**: Approx 28-35 days after last dose of study intervention or before initiation of subsequent therapy, whichever occurs first. **LTFU**: Activities every 8 weeks until Week 25, then every 12 weeks thereafter, continuing the assessment schedule established at randomization.
Cycle 1 cycle = 28 days		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**		**Scans, sT, and PSA**				
Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
Study intervention and other treatments														
Study intervention dispensation (mevrometostat / placebo and enzalutamide)		X	X	X	X	X	X	X	X					
Study intervention accountability			X	X	X	X	X	X	X					

Table 1. Study Schedule of Activities

Visit Identifier	Screening	Treatment Period										Follow-up		Notes
Study Week		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29+**	**37+**	**EOT**	**Safety**	**LTFU**	All screening should be done ≤28 days before first dose **Week 29+**: Activities every 4 weeks until C14D1, then every 8 weeks thereafter **Week 37+** : Activities every 12 weeks **EOT**: Occurs following discontinuation of study intervention and should be no more than 1 week after the discontinuation of all study intervention. If EOT visit coincides with a regular study visit, EOT activities will supersede those of the scheduled visit. **Safety**: Approx 28-35 days after last dose of study intervention or before initiation of subsequent therapy, whichever occurs first. **LTFU**: Activities every 8 weeks until Week 25, then every 12 weeks thereafter, continuing the assessment schedule established at randomization.
Cycle 1 cycle = 28 days		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**		**Scans, sT, and PSA**				
Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
Blood sample for PK				X Pre- and post-dose	X Pre- and post-dose	X Pre-dose only								Collect blood samples for PK pre-dose (within 1 hr prior to morning dose of mevrometostat) and 3 hrs (± 1 hr) post dose on Weeks 9 (C3D1) and 13 (C4D1) and pre-dose (within 1 hr prior to morning dose of mevrometostat) on Week 17 (C5D1). The morning dose must be taken in clinic on PK days (not at home). Record the dose and timing on both the day of, and the day before PK sampling. Food must be consumed within 1 hr prior to dosing where post dose sample is collected (i.e. Weeks 9 and 13).
Biomarker assessments See laboratory manual.														
Tumor tissue (de novo or archival)		X									X (optional)			Provision of available tumor tissue (de novo or archived) for retrospective molecular profiling analysis. Biopsy at EOT is optional.

Table 1. Study Schedule of Activities

Visit Identifier	Screening	Treatment Period										Follow-up		Notes
Study Week		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29+**	**37+ Scans, sT, and PSA**	**EOT**	**Safety**	**LTFU**	All screening should be done ≤28 days before first dose **Week 29+**: Activities every 4 weeks until C14D1, then every 8 weeks thereafter **Week 37+** : Activities every 12 weeks **EOT**: Occurs following discontinuation of study intervention and should be no more than 1 week after the discontinuation of all study intervention. If EOT visit coincides with a regular study visit, EOT activities will supersede those of the scheduled visit. **Safety**: Approx 28-35 days after last dose of study intervention or before initiation of subsequent therapy, whichever occurs first. **LTFU**: Activities every 8 weeks until Week 25, then every 12 weeks thereafter, continuing the assessment schedule established at randomization.
Cycle 1 cycle = 28 days		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**						
Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
Blood sample for cf nucleic acid analyses (pre-dose)		X		X				X			X			
Retained research sample for genetics (pre-dose) (Prep D1)		X												If not collected at designated timepoint, collect at next biospecimen collection timepoint.

LTFU
Long-term follow-up begins after safety follow-up and may be conducted by telephone unless imaging is required. Follow-up frequency is per the radiographic imaging schedule for every 8 weeks through Week 25 of the study, then every 12 weeks thereafter (continuing the assessment schedule established at randomization) until the participant dies or withdraws consent for follow-up, or the study is terminated by the sponsor.

Table 1. Study Schedule of Activities

Visit Identifier	Screening	Treatment Period									Follow-up		Notes
Study Week		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29+**	**37+**	**EOT**	**Safety**	**LTFU**	All screening should be done ≤28 days before first dose **Week 29+**: Activities every 4 weeks until C14D1, then every 8 weeks thereafter **Week 37+** : Activities every 12 weeks **EOT**: Occurs following discontinuation of study intervention and should be no more than 1 week after the discontinuation of all study intervention. If EOT visit coincides with a regular study visit, EOT activities will supersede those of the scheduled visit. **Safety**: Approx 28-35 days after last dose of study intervention or before initiation of subsequent therapy, whichever occurs first. **LTFU**: Activities every 8 weeks until Week 25, then every 12 weeks thereafter, continuing the assessment schedule established at randomization.
Cycle 1 cycle = 28 days		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**		**Scans, sT, and PSA**				
Visit Window	**Day -28 to Day -1**	**± 3 days (± 7 days for scans)**									**± 7 days**	**+ 7 days**	**± 7 days**	Screening period is relative to the start of study intervention (Day 1). Study drug supplies must be taken into account when scheduling visits during the visit windows.
Collection of new antineoplastic / investigational therapy		X												Record all subsequent antineoplastic treatments systemic or localized (ie, radiotherapy, surgery) for participants starting a new antineoplastic or investigational therapy. See Section 7.1. Visit may be completed via phone. See Section 8.1.1.3.
Diagnosis of second primary malignancy		X												Record any second primary malignancy (including MDS, T-LBL, and AML) and report as an SAE. See Section 8.4.1.2.
Survival status													X	Post-treatment survival status will be collected during LTFU. Obtain survival status by telephone, clinic visit, chart review, or by communicating with an individual (eg, email, family, friend, or referring health care provider) who is knowledgeable of the participant's survival status. Publicly available information may be used to determine survival status only as appropriately directed in accordance with local law. See Section 7.1.

2. INTRODUCTION

Mevrometostat (PF-06821497) is a potent and selective inhibitor of EZH2 enzymatic activity. In vivo, mevrometostat showed robust TGI and induced durable tumor regressions, including in a prostate xenograft model, in combination with enzalutamide, and anti-tumor activity in an enzalutamide-resistant prostate cancer tumor model. Preliminary data indicate that mevrometostat, as monotherapy and in combination with enzalutamide, has been well tolerated and demonstrated encouraging anti-tumor activity in mCRPC suggesting potential delay and reversal of AR pathway resistance.

2.1. Study Rationale

The rationale for this study is to evaluate whether the addition of EZH2 inhibition to enzalutamide can delay or prevent antiandrogen resistance, thereby increasing the duration of clinical benefit of enzalutamide in participants who are treatment naïve to ARPIs and have not yet received chemotherapy in the mCSPC setting. This Phase 3 randomized study (C2321008, hereafter referred to as MEVPRO-3) is designed to demonstrate that mevrometostat + enzalutamide provides superior clinical benefit compared to placebo + enzalutamide in participants with mCSPC.

2.2. Background

Prostate cancer is the second leading cause of cancer-related death among men in the US, and the third leading cause in Europe (Malvezzi et al, 2019; Siegel et al, 2020). Prostate cancer is mainly diagnosed in men aged ≥65 years with a mean age at diagnosis of 67 years (American Cancer Society; National Cancer Institute Surveillance).

Prostate cancer progresses through a series of characteristic clinical states that represent both the natural history of the disease and response to treatment. Prostate cancer may present as localized disease, locally advanced disease, or metastatic disease at initial diagnosis.

While localized disease may be amenable to curative primary intervention such as surgery or radiation therapy, in some patients the disease will recur and/or progress (Kupelian et al, 2002; Freedland et al, 2005; Shore et al, 2024). Early in the disease, prostate cancers need normal levels of androgens to survive. Such prostate cancers are referred to as androgen-dependent HSPC or CSPC; therefore, treatments that decrease androgen levels or block androgen activity can inhibit the growth of prostate cancer. ADT is often initiated in men who experience recurrence or progression of their disease. While ADT has been a standard therapy generally leading to an initial positive response, nearly all patients eventually progress to CRPC, defined as disease progression despite castrate hormone levels (testosterone ≤50 ng/dL). In addition, the development of metastatic disease, regardless of the hormone-sensitivity of the cancer, is associated with a much poorer prognosis (5-year survival rate [OS] rate] of 30%) (Siegel et al, 2021; Sayegh et al, 2022).

mCSPC can be diagnosed either de novo or following relapse after local treatment. Overall, mCSPC accounts for up to 5% of the annual prostate cancer incidence globally (Armstrong et al, 2019). Historically, mCSPC was treated with ADT alone; however, despite initial response, most patients will progress, within several years, to mCRPC (Kyriakopoulos et al,

2018; Chi et al, 2021; Freedland et al, 2021; Armstrong et al, 2022). Recently, novel intensification strategies combining ADT with ARPIs (abiraterone, apalutamide, darolutamide, and enzalutamide) +/- docetaxel have emerged based on positive data from several contemporary and pivotal Phase 3 studies demonstrating delay in progression to mCRPC and improvement in PFS and OS (James et al, 2017; Armstrong et al, 2019; Chi et al, 2019; Davis et al, 2019; Fizazi et al, 2022; Smith et al, 2022; Saad et al, 2024).

Despite these advancements, there remains a clinical unmet need for patients with mCSPC as these treatment regimens remain suboptimal, are contraindicated for many patients, and resistance inevitably occurs. AR signaling remains a key oncogenic driver with continued focus on understanding the mechanisms of resistance to ARPIs. Thus, a focus in the management of mCSPC in prolonging survival with an increased QoL by delaying the onset of castration-resistant disease and its comorbidities is needed.

2.2.1. Clinical Overview

The safety, tolerability, PK, PD, and anti-tumor activity of mevrometostat were evaluated in Study C2321001 (hereafter referred to as Study 1001), a Phase 1, FIH, open-label, multicenter study in participants with advanced solid tumors including CRPC. As of 10 December 2024, 276 participants have been enrolled in Study C2321001, including11 participants with SCLC, FL and CRPC in Part 1A, 14 participants with FL in Part 1B, 29 participants with SCLC in Part 2A, 85 participants with CRPC in Part 2A (47 participants were dosed on an empty stomach and 38 participants were dosed with food), 9 participants with CRPC in the China monotherapy cohort, 6 participants with CRPC in the Japan monotherapy cohort, 81 participants with mCRPC in Part 2B, 27 participants with mCRPC in Part 1C and 14 participants (dosed with food) with mCRPC in Part 2C. Participants were dosed on an empty stomach unless otherwise indicated.

Mevrometostat exhibited PD activity in blood and tumor tissue: A ≥70% maximal decrease in H3K27Me3 marker level from baseline was observed in granulocytes from participants treated with mevrometostat monotherapy at ≥75 mg BID (up to 500 mg BID) and from participants with mCRPC treated with mevrometostat at doses ≥375 mg BID in combination with enzalutamide. Further, mevrometostat in combination with enzalutamide reduced tumor H3K27Me3 PD marker more effectively at 1250 mg BID than at 500 mg BID.

As of November 2, 2023, 47 participants in Study 1001 Part 2A (dose escalation) had been treated with mevrometostat, and median (interquartile range) duration of follow-up was 9.7 (2.0, 22.8) months (Schweizer et al, 2024). Median (95% CI) rPFS was 17.0 (6.3, NE) months, and overall there had been 14 progression events and 4 deaths. Among 22 participants with measurable disease at baseline there were 5 reported partial responses and 1 reported complete response, and the ORR (95% CI) was 27.3% (10.7, 50.2). Diarrhea (42.6%), dysgeusia (42.6%), and anemia (36.2%) were the most common TEAEs considered related to mevrometostat. Grade 3 TEAEs considered mevrometostat-related were reported in 17.0% of participants. Serious TEAEs related to mevrometostat were reported in 6.4% of participants. Treatment discontinuations due to AEs were reported in 9 (19.1%) participants. There were no treatment-related deaths reported.

As of September 2, 2024, there were 81 participants in Study 1001 Part 2B (randomized, dose expansion): 41 participants received mevrometostat in combination with enzalutamide and 40 participants received enzalutamide (Schweizer et al, 2025). Median (95% CI) rPFS was 14.3 (7.5, not estimable) months in the mevrometostat + enzalutamide arm and 6.2 (4.1, 13.9) months in the enzalutamide arm (HR=0.51; 90% CI 0.28, 0.95). In participants with measurable disease at baseline (n=15 in the mevrometostat + enzalutamide arm and n=14 in the enzalutamide arm), the ORR (95% CI) was 26.7% (7.8, 55.1) in the mevrometostat + enzalutamide arm (4 PRs) and 14.3% (1.8, 42.8) for the enzalutamide arm (2 PRs). Confirmed PSA50 (95% CI) was reported in 34.1% (20.1, 50.6) of participants in the mevrometostat + enzalutamide arm and 15.4% (6.0, 31.3) of participants in the enzalutamide arm. No treatment-related deaths were reported. The most common TEAEs were diarrhea (78.0%), decreased appetite (58.5%), and dysgeusia (58.5%) in the mevrometostat + enzalutamide arm, and asthenic conditions (42.5%), nausea (25.0%), and anemia (22.5%) in the enzalutamide arm. Grade ≥3 TEAEs were reported in 53.7% of participants in the mevrometostat + enzalutamide arm (the most common were diarrhea, neutropenia, and sepsis) and 42.5% of participants in the enzalutamide arm.

2.2.1.1. Drug Mechanism of Action

Mevrometostat is a potent and selective inhibitor of EZH2 enzymatic activity, which inhibits WT and EZH2 Y641N mutant enzymes. Mevrometostat is a competitive inhibitor with respect to S-adenosyl-L-methionine substrate and shows strong reduction of H3K27Me3 levels (the canonical enzymatic target PD marker of EZH2) both preclinically and in both periphery granulocytes and tumor biopsies from patients within the current FIH Study 1001. EZH2 is overexpressed in prostate cancer, where its expression level has been shown to be an independent prognostic indicator of disease (Varambally et al, 2002; van Leenders et al, 2007). EZH2 has been shown to cooperate with AR to drive prostate cancer progression through both polycomb-dependent and independent mechanisms including epigenetic silencing via H3K27Me3 of genes including tumor suppressors and developmental regulators (Zhao et al, 2012; Yang & Yu, 2013; Fong et al, 2017), PRC2-independent methylation and activation of the transcription factors AR and FOXA1 (Xu et al, 2012; Kim et al, 2018; Park et al, 2021), and induction of neuroendocrine differentiation that is associated with AR independence and poor prognosis (Dardenne et al, 2016; Ku et al, 2017). EZH2i have been shown to work synergistically with enzalutamide to inhibit CRPC tumor growth (Kim et al, 2018; Shankar et al, 2020) and overcome resistance to SOC mCRPC treatments including enzalutamide (Ku et al, 2017). In addition to its oncogenic role in AR-dependent disease, EZH2 has been shown to promote transition of prostate cancer to an NEPC state. EZH2 inhibition has been shown to reverse the reprogramming of these tumors back to a luminal state, resensitizing them to ARPIs, including enzalutamide (Ku et al, 2017).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of mevrometostat may be found in the IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs, including SRSDs for enzalutamide.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Mevrometostat		
Hepatic toxicity (hepatic failure, important potential risk)	One death due to hepatic failure was reported in a participant with CRPC enrolled in the Phase 1 Study 1001 treated with 150 mg BID single agent mevrometostat. Details of this case are available in the IB.	Participants with moderate/severe hepatic impairment are excluded. Specific dosing interruptions are to be implemented in case of suspected drug-induced liver toxicity. Rules for temporary and permanent discontinuation are described in Section 6.6.3.
GI toxicity (diarrhea)	EZH2 has a role in maintaining the intestinal epithelial integrity and homeostasis under inflammatory conditions, and its inhibition may cause disruption of intestinal homeostasis. Diarrhea is a frequently observed AE with mevrometostat and is one of the most common TEAEs across all tumor types in monotherapy and in combination with SOC. The cases are predominantly low grade.	Diarrhea will be managed within current protocol guidance providing detail on the mitigation of diarrhea. Reference guidelines for the management of diarrhea dose modifications are in Section 6.6.4 and Section 6.9.6.
Opportunistic infections and myelosuppression/cytopenia	Non-clinical findings indicate a potential role for EZH2i in T-cell function	Regular monitoring of lymphocyte counts and CBC are to be performed, and implementation of additional tests and prophylaxis as needed. An appropriate prophylactic treatment including standard pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered. See Section 6.6.4 for dose modification guidance.
Secondary malignancies	Secondary malignancies have been reported as important risks for tazemetostat and enzalutamide in clinical studies. Since mevrometostat is within the same drug class as tazemetostat (ie, EZH2i), secondary malignancies are categorized as an important potential risk. Details for potential	Monitoring and reporting of all occurrences of secondary malignancies as SAEs is required, regardless of severity grade or causality attribution. Please refer to Section 8.4.1.2 for additional details.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	second primary malignancies in adult participants receiving mevrometostat in the Phase 1 study (Study 1001) are available in the IB. Mevrometostat was not found to be genotoxic in preclinical assessments.	
Sun exposure	Mevrometostat has the potential to be phototoxic based on preclinical data.	Participants will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect by minimizing the participants' exposure to light, including high intensity UVB light sources such as tanning beds, tanning booths, and sunlamps. Participants should be encouraged to apply sunscreen/sunblock daily.
Embryo-fetal toxicity	Pharmacology-based risk of fetal harm and infertility; mevrometostat has the potential to cause embryo-fetal toxicity. The tazemetostat prescribing information indicates fetal skeletal malformations and variations in EFD studies in rats and rabbits.	All participants will be required to use effective contraception methods; contraception use will be monitored throughout the study.
Study Intervention(s) Enzalutamide		
Seizure	In 8 RCTs (of participants receiving enzalutamide), 0.6% of participants treated with enzalutamide experienced a seizure.	Participants with a history of seizure or any condition that may predispose to seizure will be excluded.
PRES	There have been rare reports of PRES in participants receiving enzalutamide during post-approval use.	Permanently discontinue enzalutamide in participants who develop PRES.
Cardiovascular disease	In the combined data of 5 RCTs (AFFIRM, PROSPER, PREVAIL, ARCHES, and EMBARK), IHD occurred in 3.5% of participants in the enzalutamide arm.	Participants with clinically significant cardiovascular disease will be excluded.
Hypersensitivity	Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in 8 RCTs.	In accordance with the local label, participants who experience any symptoms of hypersensitivity should temporarily discontinue enzalutamide and promptly seek medical care. Permanently

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		discontinue enzalutamide for serious hypersensitivity reactions.
Falls and Fractures	In the combined data of 5 RCTs, falls occurred in 12% of participants treated with enzalutamide compared to 6% treated with placebo. Fractures occurred in 13% of participants treated with enzalutamide and 6% of participants treated with placebo.	Further details and guidelines for safety monitoring of enzalutamide are according to the IB and local prescribing information.
Dysphagia	Severe dysphagia or choking, including events that could be life-threatening requiring medical intervention or fatal, can occur due to enzalutamide product size.	Discontinue enzalutamide for patients who cannot swallow capsules.
Embryo-fetal toxicity	Based on embryo-fetal toxicity study and the known reproductive and developmental toxicity of other antiandrogens, it is assumed that enzalutamide may cause fetal harm and is thus contraindicated in pregnant women.	All participants will be required to use effective contraception methods; contraception use will be monitored throughout the study.
Study Procedures		
Participants will have CT/MRI scans and bone scans during study participation	CT scans expose participants to a small dose of radiation. Contrast dye used for CT scans may cause pain or burning upon injection, may worsen kidney function in participants with kidney disease, and may cause allergic reactions that could be severe and life-threatening. Radioactive material for bone scan may cause discomfort or burning upon injection.	Radiation exposure during the study is not expected to exceed what a participant would receive under SOC and should not create a significant risk to health. Participants with renal function impairment are excluded from participation in the study. CT scans will be conducted at facilities prepared for adverse reactions to the contrast dye. Hydration and/or premedication prior to contrast media administration, or steroids administration in case of allergic reaction, may be instituted as per local standard practice.
In the event that a participant is not able to visit the prespecified laboratory, protocol-specified safety laboratory evaluations or ECGs may be conducted at a different local laboratory once it is approved by the investigator and the sponsor.	Participant safety may be jeopardized if safety assessments are not correctly performed and/or investigator is not made aware of abnormal findings in a timely manner.	Only routine safety assessments will be performed by alternative facilities. Test results must be provided to qualified site staff as soon as possible.

2.3.2. Benefit Assessment

The results of the ongoing Phase 1 Study 1001 of mevrometostat, either as monotherapy in participants with solid tumors or in combination with enzalutamide, in participants with prostate cancer support this investigation of mevrometostat plus enzalutamide for participants with mCSPC. Taking into account the measures to minimize risk to participants, the potential risks associated with mevrometostat plus enzalutamide are justified by the potential benefits that may be afforded to participants with mCSPC. Therefore, the Phase 1 results suggest a favorable benefit-risk profile to support the study rationale.

Participants may experience delayed progression of disease and clinical benefit with maintained quality of life from the combination of mevrometostat plus enzalutamide. Study participants may also benefit from more intense monitoring and more frequent assessments.

Based on the phase 1 clinical data for participants with prostate cancer, the most frequent all-causality adverse events (≥10%) occurring with the combination of mevrometostat plus enzalutamide include diarrhea, decreased appetite, nausea, fatigue, dysgeusia, asthenia, edema peripheral, vomiting, weight decreased, alopecia, hypokalemia, hypocalcemia, anemia, thrombocytopenia, and neutropenia. Study safety data will be monitored on a regular basis by the sponsor as well as an independent E-DMC.

With the encouraging anti-tumor activity and favorable safety profile, there is strong rationale to evaluate mevrometostat with enzalutamide in participants with mCSPC. The available safety and efficacy data suggest that participants who participate in this trial are not placed at undue risk.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with mevrometostat are justified by the anticipated benefits that may be afforded to participants with mCSPC.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To demonstrate that mevrometostat in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging BICR assessed rPFS	• BICR assessed rPFS per RECIST 1.1 (soft tissue disease) and PCWG3 (bone disease)	• Section 9.1.1.1
Secondary:	**Secondary:**	**Secondary:**
• To demonstrate that mevrometostat in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging OS	• OS (alpha protected)	• Section 9.1.1.2

Objectives	Endpoints	Estimands
• To compare anti-tumor activity between mevrometostat in combination with enzalutamide and placebo in combination with enzalutamide	• Proportion of participants with measurable soft tissue disease at baseline with an objective response per RECIST 1.1 (assessed by BICR and investigator) • Duration of soft tissue response per RECIST 1.1 (assessed by BICR and investigator) • Proportion of participants with PSA response ≥50% in participants with detectable PSA values at baseline • Time to PSA progression • Time to initiation of antineoplastic therapy • Time to first symptomatic skeletal event • Time from randomization to CRPC	• Not applicable
• To compare safety and tolerability between mevrometostat in combination with enzalutamide and placebo in combination with enzalutamide	• Type, incidence, severity (as graded by the NCI CTCAE v5.0), seriousness and relationship to study medications of AEs and any laboratory test and ECG abnormalities	• Not applicable
• To evaluate the PK of mevrometostat when dosed in combination with enzalutamide	• PK characterized by pre-dose trough and post-dose plasma concentrations of mevrometostat at selected visits	• Not applicable
• To compare PROs between mevrometostat in combination with enzalutamide and placebo in combination with enzalutamide	• Change from baseline and time to confirmed deterioration in participant-reported worst pain symptoms per BPI-SF • Change from baseline in HRQoL, functioning, and symptoms and time to definitive deterioration per FACT-P • Change from baseline and time to definitive deterioration in participant-reported prostate cancer specific functioning, and symptoms per EORTC QLQ-PR25 • Change from baseline and time to confirmed deterioration in participant-reported fatigue symptoms per BFI • Change from baseline in participant-reported general health status per EQ-5D-5L	• Not applicable
• To assess the relationship between ctDNA burden and outcome	• ctDNA burden at baseline and on study	• Not applicable
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To compare PFS2 between mevrometostat in combination with enzalutamide and placebo in combination with enzalutamide	• PFS2 based on investigator assessment	• Not applicable
• To understand the relationship between the therapeutic intervention(s) being studied and the biology of the participant's disease	• Measurements of biomarkers, which may consist of DNA, RNA, protein or defined cell types, resulting from analyses of peripheral blood and/or tumor tissue biospecimens obtained at baseline, on treatment and/or at EOT	• Not applicable
• To compare time to initiation of opioids between mevrometostat in combination with enzalutamide and	• Time to initiation of opioids	• Not applicable

Objectives	Endpoints	Estimands
placebo in combination with enzalutamide		

4. STUDY DESIGN

4.1. Overall Design

This is a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study evaluating mevrometostat in combination with enzalutamide versus placebo in combination with enzalutamide in participants with mCSPC who have not received systemic anticancer treatments with the exception of ADT and first-generation antiandrogen agents. Prior therapy with up to 3 months of ADT (chemical or surgical) is allowed, if required prior to randomization, with no radiographic evidence of disease progression or rising PSA levels indicative of disease progression prior to Day 1.

Approximately 1000 participants will be randomly assigned on a 1:1 basis to:

- Investigational Arm A: Mevrometostat 875 mg BID + enzalutamide 160 mg QD
- Comparator Arm B: Placebo BID + enzalutamide 160 mg QD

Randomization will be stratified by:

- Disease volume (low vs high). High volume of disease is defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis
- De novo vs relapsed mCSPC

Randomized participants will receive protocol-assigned treatment as per assigned treatment arm continuing until study intervention discontinuation criteria (Section 7.1) are met. Participants should start treatment within 3 days after randomization.

Participants will undergo study-related safety and efficacy assessments, as outlined in the SoA.

Disease status will be assessed at screening and at regular intervals during the study by CT of the chest and CT/MRI of abdomen and pelvis for assessment of soft tissue/visceral disease, ^{99m}Tc-methylene diphosphonate radionuclide bone scintigraphy for bone metastases, PSA measurements, and PRO assessments. The primary endpoint of this study will be rPFS assessed via bone scan for bone metastases according to PCWG3 (Scher et al, 2016) criteria and CT of the chest and CT/MRI of abdomen and pelvis for assessment of soft tissue/visceral disease based on RECIST v1.1 criteria (Appendix 10) (Eisenhauer et al, 2009). A third-party core imaging laboratory will perform BICR assessment of rPFS data. All radiographic assessments must be forwarded to the independent core imaging laboratory as requested by

the sponsor. BICR review of radiographic assessments ends following BICR-determined radiographic progression.

Safety will be assessed by AEs, physical examinations, vital signs, and clinical laboratory tests. An independent E-DMC will monitor the safety of the participants on a periodic basis (Appendix 10 Section 10.1.5.1).

Pharmacokinetics is a secondary endpoint for the study. Collection of PK samples enables population PK analyses to understand the effect of participant characteristics (body weight, age, race and ethnicity, sex, or organ impairment) on mevrometostat. Refer to Section 9.3.6 and SoA for further detail.

The biomarker analysis included in this study will be used to help understand the disease and mechanism of action of the agent(s) studied as well as potential mechanisms of resistance. This analysis may help in the future development of mevrometostat as a single agent, or in combination with other compounds, and may provide information on tumor subtypes that may respond to the study intervention.

Tumor tissue and blood samples will be collected to evaluate biomarkers (genes and proteins) involved in the biology of the participant's disease to understand the relationship between the therapeutic interventions being studied and the biology of the participant's disease. The measurement of the biomarkers may consist of DNA, RNA, protein or defined cell types resulting from analyses of peripheral blood and/or tumor tissue biospecimens obtained at baseline, on treatment, and/or at EOT. Assessment of the relationship between ctDNA burden and outcome is a secondary objective of this study. Unless prohibited by local regulation or ethics committee decision, a retained research sample for research analyses related to the study intervention(s) and prostate cancer will be obtained. Refer to Section 8.6.2 and SoA for further detail.

The overall study design is described in Section 1.2. The study endpoints are defined in Section 3.

Treatment with study intervention will continue until BICR-determined radiographic disease progression, participant refusal, or unacceptable toxicity occurs, or other discontinuation of study intervention criteria are met (Section 7.1). Participants discontinuing the Treatment Phase will continue to the EOT Visit and Safety Follow-up (approximately 28-35 days after last dose of study intervention or before initiation of a new antineoplastic or investigational therapy, whichever occurs first). Refer to Section 7.1 for further detail.

Participants enter the LTFU period after Safety Follow-up. If the participant has not discontinued from study procedures and/or post-treatment study follow-up, LTFU will continue until the end of the study. Data collected during the LTFU period may include evaluation for symptomatic skeletal events and ePRO assessments.

Participants who discontinue treatment and do not have radiologic disease progression will continue radiographic imaging, PSA, and serum testosterone assessments (per SoA) until they progress radiographically as determined by BICR (regardless of the initiation of a new

antineoplastic therapy) or death. After confirmation of radiographic progression by BICR, further radiographic imaging and PSA assessments will continue as per local clinical practice until the next report of progression after the start of subsequent antineoplastic therapy. Crossover will not be allowed in the trial.

For all participants in the LTFU period, survival status, initiation of new antineoplastic therapy, diagnosis of MDS, T-LBL, and AML or second primary malignancy will be monitored and collected every 12 weeks from the last dose of study intervention until the participant dies or withdraws consent for follow-up, or the study is terminated by the sponsor. LTFU will no longer be required after the desired number of OS events has been achieved.

Once communication is sent to the investigational sites that the OS PCD has been reached, participants who are still on study treatment will follow a reduced study schedule. OS PCD is expected to occur at the time the number of OS events have been achieved for the secondary endpoint analysis (Section 9.3.2).

4.2. Scientific Rationale for Study Design

4.2.1. Participant Input Into Design

Patients with prostate cancer shared insights during a series of several meetings, including a meeting specific to the current study. No significant insights were identified that would impact study participation based on the study design and schedule of activities.

4.2.2. Diversity of Study Population

Reasonable attempts will be made to enroll participants with different characteristics to ensure the study population is representative of the patient population that will use the study intervention in clinical practice. The diversity strategy will include sites with the potential to support the recruitment of diverse and underrepresented populations.

4.2.3. Rationale for Comparator

The comparator arm for this study is placebo + enzalutamide. ARPI's such as enzalutamide are efficacious and established SOC in mCSPC based on the randomized Phase 3 trial, ARCHES, which evaluated enzalutamide + ADT vs placebo + ADT. The risk of radiographic progression or death was significantly reduced in the interventional arm versus placebo + ADT (HR=0.39, 95% CI 0.30–0.50; p<0.0001). Median rPFS was not reached in the enzalutamide arm compared versus 19.0 months (95% CI: 16.6, 22.2) in the placebo arm (Armstrong et al, 2019). OS data were not mature at the time of rPFS analysis; however, final prespecified OS analysis demonstrated a significant improvement in OS (HR=0.66, 95% CI 0.53-0.81; p<0.001) (Armstrong et al, 2022).

Additionally, enzalutamide was also tested in the Phase 3 study, ENZAMET which evaluated enzalutamide + ADT vs nonsteroidal antiandrogen therapy (bicalutamide, nilutamide, or flutamide) + ADT in participants with mCSPC. Primary endpoint of OS was met, demonstrating improvement in survival of enzalutamide + ADT compared to standard of care (HR=0.67; 95% CI 0.52-0.86) (Davis et al, 2019).

Given these data, enzalutamide is considered SOC and is widely approved in mCSPC. Accordingly, current guidelines recommend use of enzalutamide + ADT as an option for mCSPC, and therefore it is an appropriate active comparator for this study (Parker et al, 2020; Lowrance et al, 2023).

4.2.4. Choice of Contraception/Barrier Requirements

Mevrometostat has not yet been tested for teratogenicity/fetotoxicity based on available weight of evidence supporting a clear risk of embryo-fetal development toxicity based on the established role of EZH2 in development. The target EZH2 is abundantly expressed during embryonic development, and knockout of EZH2 causes embryonic lethality in mice.

In addition, an embryo-fetal toxicity study in mice (study 9785-TX-0009) showed that enzalutamide induced premature deliveries in dams and dose-dependent increases in the incidence of decreased anogenital distance and skeletal abnormalities, such as cleft palate associated with absent palatine bone. These effects are assumed to be related to the pharmacology of enzalutamide because they were previously reported in rats treated with bicalutamide (Iswaran et al, 1997) as well as mice and rabbits treated with chlormadinone acetate (Takano et al, 1966). Based on the embryo-fetal toxicity study and the known reproductive and developmental toxicity of other antiandrogens, it is assumed that enzalutamide may cause fetal harm and is thus contraindicated in pregnant women.

Based on information and findings for teratogenicity/fetotoxicity all participants receiving mevrometostat/enzalutamide who are, in the opinion of the investigator, sexually active with female partners of reproductive potential must agree to use highly effective contraception throughout the study and for up to 3 months after the last dose of medication (Appendix 4).

4.3. Justification of Dose

Based on the totality of data from Study 1001, including safety, efficacy, PK/PD, and E-R analyses, the recommended dose for MEVPRO-3 and the subsequent clinical development of mevrometostat in combination with enzalutamide was determined to be 875 mg BID with food.

Extensive dose exploration has been conducted for mevrometostat in combination with enzalutamide within a Phase 1 dose escalation (Part 2A) portion of Study 1001 in participants with CRPC.

Eight mevrometostat dose levels, administered on empty stomach, were evaluated in combination with the approved dose of enzalutamide 160 mg QD: 150 mg BID (n=4), 250 mg BID (n=3), 375 mg BID (n=3), 500 mg (n=14), 625 mg (n=3), 750 mg (n=4), 875 mg BID (n=6), 1250 mg BID (n=10). This combination of mevrometostat + enzalutamide was well tolerated across the evaluated dose range, with 1 DLT of Grade 3 weakness observed in a participant dosed at mevrometostat 1250 mg BID dose administered on an empty stomach.

There is an approximately 60% reduction in mevrometostat steady-state AUC_{tau} when given in combination with enzalutamide as compared to mevrometostat monotherapy due to the known strong CYP3A mediated induction effect of enzalutamide. No MTD has been

determined for either monotherapy or combination regimens. Based on the totality of the safety, anti-tumor activity, PK and PD data from study Part 2A dose escalation in combination with enzalutamide in participants with CRPC, mevrometostat 1250 mg BID administered on an empty stomach was selected as the recommended dose for expansion to further characterize the safety and efficacy of the combination in Part 2B of Study 1001.

Exploratory exposure-response analyses for key efficacy endpoints indicated that higher mevrometostat plasma exposures are associated with increased rPFS as well as increased probability of PSA response, decrease >50% from baseline (PSA50) response. In addition, as an EZH2 target engagement pharmacodynamic marker, intra-tumoral H3K27Me3 reduction was seen to be dose dependent within the range of 500 mg BID – 1250 mg BID in combination with enzalutamide, with 1250 mg BID on empty stomach providing maximum inhibition. In contrast, no E-R relationships have been identified for the safety endpoints of clinical interest, with the exception of any grade diarrhea.

In summary, current data from the Phase 1 Study 1001 indicates that plasma exposures associated with the 1250 mg BID dose administered on empty stomach represent an efficacious and well tolerated exposure for combination with enzalutamide in CRPC.

Preliminary safety data from mevrometostat administration with food indicated a trend toward lower incidence of diarrhea as compared to administration on empty stomach conditions. Therefore, an exposure-matched dose of mevrometostat under fed conditions that will provide equivalent plasma exposures as 1250 mg BID on empty stomach was evaluated. Based on available data, the 875 mg BID dose administered with food results in similar mevrometostat plasma exposures as that of 1250 mg on empty stomach. This supports mevrometostat 875 mg BID administered with food as the recommended dose for the further clinical development of mevrometostat in combination with enzalutamide.

4.4. End of Study Definition

The end of the study globally is defined as the date of the LPLV.

A participant is considered to have completed the study if they have completed all periods of the study, including LTFU, or until criteria for study discontinuation have been met.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes it will include collection of information that reflects the enrollment of a diverse participant population, including, where permitted under local regulations, age, and race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in this study only if all of the following criteria apply:

Age and Sex:

1. Male participants aged 18 years of age or older (or the minimum age of consent in accordance with local regulations) at screening.

Refer to Appendix 4 for reproductive criteria (Section 10.4.1).

Disease Characteristics:

2. Histologically or cytologically confirmed adenocarcinoma of the prostate without small cell features (neuroendocrine differentiation and other histologic components are permitted if adenocarcinoma is the primary histology). For participants without a prior histological diagnosis, a baseline de novo biopsy must be used to confirm the diagnosis.

3. Metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesion(s) on CT or MRI scan (for soft tissue/visceral disease).

    a. Measurable soft tissue/visceral disease (per RECIST v1.1) is required if there is not an evaluable bone lesion (per PCWG3 criteria).

    b. For participants with measurable soft tissue disease only, regional lymph node disease (eg, below aortic bifurcation) alone does not qualify the participant for the study.

    c. PET and SPECT are not evaluable imaging modalities for this study.

    d. A bone scan showing intense symmetric activity in the bones (referred to as a superscan) is not considered evaluable.

4. Resolution of acute effects of any prior therapy to either baseline severity or CTCAE Grade ≤1 (except for AEs which do not constitute a safety risk in the investigator's judgement).

Allowed Prior Treatments:

5. Participants cannot have received any cytotoxic chemotherapy, ARPIs (eg, enzalutamide, apalutamide, abiraterone acetate, or darolutamide), any other systemic anticancer therapies for mCSPC, with the following exceptions:

    a. ADT (chemical or surgical) must be started prior to randomization and must continue throughout the study. Prior therapy with up to 3 months of ADT (with or without antiandrogens) is allowed with no radiographic evidence of disease progression or rising PSA levels indicative of disease progression prior to Day 1.

b. Treatment with estrogens, cyproterone acetate or first-generation antiandrogens is allowed until randomization, but must be discontinued prior to randomization.

c. Participants may have received 1 course of palliative radiation or surgery for symptomatic control secondary to prostate cancer, which should be completed at least 2 weeks prior to randomization.

Note: Radical prostatectomy or definitive radiotherapy (including concurrent radiotherapy) to the primary prostate tumor for mCSPC with curative intent is not permitted.

Other Inclusion criteria:

6. Participants must have ECOG PS 0 or 1 (Appendix 11).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Any medical or psychiatric condition including any active suicidal ideation in the past year or suicidal behavior in the past 5 years or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

    a. HIV/HBV/HCV testing is not required unless mandated by local health authorities.

    b. Participants with known HIV or AIDS-related illness, or active hepatitis B or C are excluded.

    Active HBV is defined as any of the following:

    - HBsAg reactive or detectable [qualitative] HBV DNA

    Note: Participants who are HBsAg(-), HBcAb(+) are eligible and should be monitored/treated as per local standard of care.

    Active HCV is defined as:

    - Detectable [qualitative] HCV RNA

    c. Participants with a known history of chronic liver diseases including alcoholic liver disease, primary biliary cirrhosis, primary sclerosing cholangitis autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, or other chronic liver disease are excluded.

d. Participants with a known history of active inflammatory gastrointestinal disease, chronic diarrhea, or previous gastric resection or lap-band surgery are excluded.

2. Clinically significant cardiovascular disease, defined as:

   a. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Class III or IV), cerebrovascular accident, or symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease, congenital long QT syndrome, Torsade de Pointes, clinically important arrhythmias, left anterior hemiblock (bifascicular block), ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, or other clinically significant cardiovascular disease as assessed by the investigator. If a participant has a cardiac rhythm device/pacemaker placed and QTcF >470 ms, the participant may be considered eligible. QTcF >480 ms on screening ECG.

3. CNS pathology/neurological findings:

   a. Known or suspected brain metastasis or active leptomeningeal disease.

   b. Symptomatic or impending spinal cord compression or cauda equina syndrome.

   c. Participants with epidural disease, canal disease and prior cord involvement are NOT excluded if those areas have been treated, are stable and not neurologically impaired.

   d. Clinically significant history of seizure or any condition that may predispose to seizure (eg, prior cortical stroke, significant brain trauma). Also history of unexplained loss of consciousness or transient ischemic attack within 12 months of randomization.

4. Any history of myelodysplastic syndrome, acute myeloid leukemia, or any other prior malignancy except for any of the following:

   a. Carcinoma in situ or nonmelanoma skin cancer.

   b. Any prior malignancies ≥3 years before randomization with no subsequent evidence of recurrence or progression regardless of the stage.

   c. Stage 0 or Stage 1 cancer <3 years before randomization that has a remote probability of recurrence or progression in the opinion of the investigator.

5. In the opinion of the investigator, any clinically significant gastrointestinal disorder affecting absorption.

Prior/Concomitant Therapy:

6. Current use of any prohibited concomitant medication(s) or unwillingness or inability to use a required concomitant medication(s). Refer to Section 6.9.

    a. Current use or anticipated need for drugs that are known strong CYP3A4/5 inhibitors and inducers (with the exception of enzalutamide as part of this study) outlined in Section 6.9.1 and Section 6.9.2, including their administration within 10 days or 5 half-lives, whichever is longer prior to randomization.

    b. Current use of prednisone >10 mg/day (or equivalents) is prohibited within 28 days prior to randomization.

    c. Current use of 5-alpha reductase inhibitors is prohibited within 28 days prior to randomization.

7. Prior treatment with:

    a. ADT in the adjuvant/neoadjuvant setting, where the completion of ADT was <12 months prior to randomization and the total duration of ADT was >36 months.

    b. ARPI's such as abiraterone, apalutamide, darolutamide, enzalutamide or other investigational ARPI's.

    c. Cytochrome P17 enzyme inhibitors such as oral ketoconazole as anticancer treatments for prostate cancer.

    d. Chemotherapy including docetaxel or immunotherapy for prostate cancer.

    e. Radiopharmaceuticals (ie, 177Lu-PSMA-617, radium-223)

    f. CDK4/6 inhibitors

    g. Any other anticancer treatment for metastatic prostate cancer, excluding palliative radiotherapy/surgery and ADT as discussed above.

Prior/Concurrent Clinical Study Experience:

8. Previous administration of an investigational product (drug or vaccine) which does not meet exclusion criterion 7 within 30 days or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Participation in studies of other investigational products (drug or vaccine) at any time during participation in this study.

Diagnostic Assessments:

9. Inadequate renal function defined by an eGFR <45 mL/min/1.73 m^2. Based upon participant age at screening, eGFR is calculated using the recommended formulas in Appendix 7 Section 10.7.1 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events. For eligibility assessment based upon estimated renal function, the higher of the screening and baseline eGFR values may be used.

10. Hepatic dysfunction defined as having any 1 of the following, which may be confirmed by a single repeat test, if necessary:

    a. Total bilirubin ≥1.5 x ULN (≥3 x ULN for participants with documented Gilbert's syndrome, direct bilirubin >ULN is exclusionary)

    b. AST >2.5 x ULN

    c. ALT >2.5 x ULN

11. Hematologic abnormalities defined as having any 1 of the following, which may be confirmed by a single repeat test, if necessary:

    a. ANC <1500/mm^3

    b. Platelets <100,000/mm^3, independent of transfusion within 14 days of randomization

    c. Hemoglobin <9 g/dL, independent of transfusion within 14 days of randomization

Other Exclusion Criteria:

12. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

13. Inability to swallow oral medications.

14. Major surgery (as defined by investigator) from which the participant has not fully recovered at least 28 days prior to randomization.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or qualified designee will confirm with the participant that they and their partner(s) are using an appropriate method of contraception from the permitted list of contraception methods (see Appendix 4 Section 10.4.2) and will confirm that the participant

has been instructed in its consistent and correct use. The investigator will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in the SoA, the investigator will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their partner's risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the partner.

If the participant is capable of ejaculating, instruct the participant to use a condom to avoid partner/fetal exposure and instruct the participant not to donate sperm for 3 months after last dose of study intervention. For these participants the investigator is to confirm correct contraception use or note changes in contraception use in the participant's medical record.

5.3.2. Photosensitivity

Participants will be advised to report any reaction to sun exposed skin. If a photosensitivity reaction occurs in a participant, special precautions should then be taken to limit any potential photo irritation effect, by minimizing the participants' exposure to light including sunlight, and exposure to high intensity UVB light sources such as tanning beds, tanning booths and sun lamps. Furthermore, for photosensitive participants, these individuals should be encouraged to apply sunscreen/sunblock daily and to wear clothing that covers areas of exposed skin when outdoors during daylight hours.

5.3.3. Meals and Dietary Restrictions

Participants must be instructed to take mevrometostat/placebo with food. Participants should be instructed to take their medication at approximately the same time each day (approximately every 12 hours) and to not take more than the prescribed dose at any time.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAEs.

5.4.1. Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only once. Rescreened participants will be screen failure under the original SSID and then will be entered as a new participant and receive a new SSID. When rescreening, if

earlier assessments are within 28 days of rescreening, the assessments will not need to be repeated.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified IMPs and NIMPs/AXMPs, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1. Study Intervention(s) Administered

Study Intervention(s)			
Intervention Name	Mevrometostat	Placebo for Mevrometostat	Enzalutamide
Type	Drug	Drug	Drug
Use	Experimental	Placebo	Background treatment
IMP or NIMP/AxMP	IMP	IMP	IMP
Dose Formulation	Tablet	Tablet	Capsule/tablet[a]
Unit Dose Strength(s)	125 mg, 250 mg	Placebo for mevrometostat 125 mg, 250 mg	40 mg[a]
Dosage Level(s)	875 mg BID Refer to Section 6.6.1	0 mg BID	160 mg QD
Route of Administration	Oral	Oral	Oral
Sourcing	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Study intervention will be provided in blinded bottles. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in blinded bottles. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in open-label packaging. Each package will be labeled as required per country requirement.[a]
SRSD	IB	N/A	IB
Current/Former Name(s) or Alias(es)	PF-06821497	N/A	XTANDI®

a. Local variations may apply, please see the IP manual for more information.

Study Arm(s)		
Arm Title	Arm A	Arm B
Arm Description	Mevrometostat dosed 875 mg BID + enzalutamide 160 mg QD. Treatment will be administered until confirmed disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, or study termination.	Placebo BID + enzalutamide 160 mg QD. Treatment will be administered until confirmed disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, or study termination.

Participants who are not orchiectomized will also continue to receive a GnRH (gonadotropin releasing hormone) agonist or antagonist on study.

6.1.1. Administration

Administration of study interventions will be performed at the site by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

6.1.1.1. Mevrometostat/Placebo

Mevrometostat/placebo will be self-administered by mouth outside the clinic, except on days of site visits; participants will withhold their dose until after assessments are complete per SoA. On these days, study medications should be taken in the clinic under the supervision of the study site personnel.

Mevrometostat/placebo will be provided in bottles containing 125 mg or 250 mg tablets appropriate to the dose level the participant will receive. The participant will be dispensed a sufficient quantity of bottles/tablets (28 days up to C14D1 and then 56 days starting at C14D1 whenever possible) of continuous dosing, plus additional tablets to cover potential delays in visiting the site. Site personnel must ensure that participants clearly understand the directions in the dosing diary. Mevrometostat/placebo will be dispensed at the beginning of each treatment visit (or as otherwise indicated). Study participants should be instructed to keep their medication in the bottles provided and not transfer the tablets to any other container.

Mevrometostat/placebo will be administered with food orally BID on a continuous basis without adjustment for body size at every visit.

Participants must be instructed to take mevrometostat/placebo with food.

Participants will swallow the tablets whole and will not manipulate or chew the tablets prior to swallowing.

Participants are to be instructed to take their medication at approximately the same time each day (approximately every 12 hours) and to not take more than the prescribed dose at any time.

If a participant misses a morning or evening dose by more than 6 hours, they must be instructed not to “make it up” but to resume subsequent doses at the next scheduled dose as prescribed. In addition, if a participant vomits any time after taking a dose, they must be instructed not to “make it up” but to resume subsequent doses the next scheduled dose as prescribed.

If a participant inadvertently takes 1 extra dose during a day, the participant should not take the next dose of mevrometostat/placebo (Section 6.8).

6.1.1.2. Enzalutamide

Enzalutamide is provided as 40 mg soft gel capsules in bottles (local variations may apply, please see the IP manual for more information).

The study participant will be dispensed a sufficient quantity of product (28 days up to C14D1 and then 56 days starting at C14D1 whenever possible) for continuous dosing, plus additional capsules to cover potential delays in visiting the site (local variations may apply, please see the IP manual for more information). Site personnel must ensure that participants clearly understand the directions in the dosing diary. Enzalutamide will be dispensed at the beginning of each treatment visit (or as otherwise indicated). Study participants should be instructed to keep their medication in the packaging provided and not transfer the capsules to any other container (local variations may apply, please see the IP manual for more information).

Enzalutamide will be administered orally with or without food, and without adjustment for body size. Enzalutamide can be given QD at the same time as mevrometostat/placebo.

Enzalutamide will be administered QD on a continuous basis. Participants will swallow the capsules whole and will not manipulate or chew the capsules prior to swallowing (local variations may apply, please see the IP manual for more information).

Participants should be instructed to take their medication at approximately the same time each day and to not take more than the prescribed dose at any time.

If a participant misses a day of treatment, they must be instructed not to “make it up” but to resume subsequent doses the next day as prescribed.

If a participant vomits any time after taking a dose, they must be instructed not to “make it up” but to resume subsequent doses the next day as prescribed.

If a participant inadvertently takes 1 extra dose during a day, the participant should not take the next dose of enzalutamide.

6.2. Preparation, Handling, Storage and Accountability

1. The investigator or qualified designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage

locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution, (where applicable) or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. **Returned study intervention must not be re-dispensed to the participants.**

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IPM.

6.2.1. Preparation and Dispensing

See the IPM, local prescribing information, or equivalent for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.2.1.1. Mevrometostat/Placebo and Enzalutamide

A qualified staff member will dispense the mevrometostat/placebo and enzalutamide product (local variations may apply, please see the IP manual for more information) using unique container numbers assigned via an IRT system according to the SoA. The participant/caregiver should be instructed to maintain the product according to the instructions provided in the participant dosing card throughout the course of dosing. Participants are to keep the investigational product away from children, and return the investigational product to the site at the next study visit. Women who are or may become pregnant should not handle damaged or opened enzalutamide capsules without protection, eg, gloves.

6.3. Assignment to Study Intervention

An IRT will allocate participants to treatment group(s). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned treatment group. The site personnel will be provided with DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide confirmation report(s), which may contain the participant number, randomization number, and/or DU/container number(s) assigned. The confirmation report(s) must be stored in the site's files. Randomization will be stratified by:

- Disease volume (low vs high). High volume of disease is defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis
- De novo vs relapsed disease

Study intervention will be dispensed at the study visits summarized in the SoA.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.4. Blinding

This is a double-blind study. Participants will receive mevrometostat or matching placebo in a blinded fashion, as indicated in Section 6.1. Participants, investigators and site staff, and sponsor staff will be aware that participants in both study arms are receiving enzalutamide. Enzalutamide will be provided in an open-label manner to participants in each treatment arm.

6.4.1. Blinding of Participants

Participants and their caregivers will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to the participant's assigned study intervention.

6.4.3. Blinding of the Sponsor

Sponsor staff will be blinded to participant's assigned study intervention, except for sponsor staff involved in the assignment or distribution of study intervention.

A third-party vendor not directly involved with the conduct of this study will prepare aggregate safety data and documentation containing unblinded data while the study is ongoing to support interactions with the E-DMC (see Section 10.1.5.1).

After the PCD (Section 3), the sponsor will be unblinded to the initial treatment assignments to conduct the analysis for the PCD-CSR (refer to Section 9). If the need arises for early modeling-based PK and exposure-response analyses (before database lock and release of the randomization codes for the study), an early PK/PD unblinding plan will be developed. PK/PD analyst(s) and supporting colleagues who are not associated with the study will conduct the analysis to avoid unblinding of the study team. Further details will be outlined in the data blinding plan.

6.4.4. Sensitive Clinical Data

Sensitive clinical data are data collected in this study that have the potential to unblind a participant's treatment assignment. Access to sensitive clinical data will be restricted to authorized individuals until the study has been unblinded. The following data variables are considered sensitive clinical data: PK data (if the need arises for early modeling-based PK and exposure-response analyses before database lock and release of the randomization codes for the study) (Section 6.4.3 and Section 8.5).

6.4.5. Breaking the Blind

The method for breaking the blind will be using the IRT system. In case of an emergency, the investigator has the sole responsibility for determining if unblinding a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.5. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning,

counting returned tablets/capsules, etc during the site visits and documented in the source documents and patient diaries. Deviation(s) from the prescribed dosage regimen should be recorded on the CRF.

A record of the number of mevrometostat/placebo tablets and enzalutamide product dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded on the CRF.

6.6. Dose Modification

6.6.1. Mevrometostat/Placebo Dose Modifications

Every effort should be made to administer investigational product on the planned dose and schedule.

Participants who require a treatment interruption >4 weeks should discontinue the study drug thought to be responsible for the treatment interruption unless agreed with the investigator and sponsor medical monitor.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed and the relatedness to the offending agent. Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in 1 of 3 ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: dosing administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

If mevrometostat/placebo is dose reduced, dose-modified, or discontinued, enzalutamide dose can remain at the same dose provided the investigator has determined that the cause of the AE is due to mevrometostat/placebo only.

Table 2. Mevrometostat/Placebo Dose Modification Levels for Adverse Reactions

Dose Level	Dose	Administration of Dose
Starting Dose	875 mg	Three 250 mg tablets and one 125 mg tablet BID
First Dose Reduction	750 mg	Three 250 mg tablets BID
Second Dose Reduction	625 mg	Two 250 mg tablets and one 125 mg tablet BID

6.6.2. Enzalutamide Dose Modifications

Dose modifications and reductions are to occur per the local prescribing information and institutional practice. Toxicities will be managed as defined in the local prescribing information or manufacturer's prescribing information and institutional practice.

Dose modification of enzalutamide could have an impact on mevrometostat plasma exposure therefore, the mevrometostat/placebo dose will need to be modified as described below.

If enzalutamide dose is held or dose-modified for a short time period (less than or equal to 1 week), the mevrometostat/placebo dose can remain at the same dose provided the investigator has determined that the cause of the AE is due to enzalutamide only. If enzalutamide is held for more than 1 week, then mevrometostat/placebo should be dose reduced to the next lower dose level, based on the current mevrometostat/placebo dosage (and would remain reduced).

If enzalutamide is permanently discontinued, mevrometostat/placebo administration will also be discontinued.

6.6.3. Modifications Due to Abnormal Liver Tests

Both mevrometostat/placebo and enzalutamide are to be withheld if liver enzymes abnormalities are reported as per guidance in Table 3. Participants who develop abnormal liver tests (AST, ALT, total bilirubin), abnormal INR values, or signs or symptoms consistent with hepatitis during study intervention may meet the criteria for temporarily withholding or permanently discontinuing (Section 7.1.2) study intervention. Participants who have abnormal liver tests or meet the criteria for permanent discontinuation or temporary withholding of study intervention will be followed according to the recommendations in this section and Table 7. All cases meeting the criteria for an AE or SAE should be reported as per the criteria and timeframe detailed in Appendix 3. Potential Hy's law cases (refer to Appendix 6) or related cases resulting in permanent study intervention discontinuation are to be reported as SAEs.

If liver test abnormalities meet the criteria of potential cases of DILI (Appendix 6) all study interventions must be held. When study intervention is temporarily withheld or permanently discontinued due to a potential drug-induced liver injury, a period of close observation is to commence until the liver test abnormalities return to baseline or normal values. The evaluations listed in Table 7 should be performed.

Rechallenge with enzalutamide may only be considered according to local label.

6.6.4. Dose Reductions for Mevrometostat/Placebo

Following dosing interruption due to toxicity, the mevrometostat/placebo dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1 or 2 treatment-related toxicity. However, investigators should always manage their participants according to their medical judgment based on the particular clinical circumstances.

Dose reduction of mevrometostat by 1 and, if needed, 2 dose levels (see Table 2) will be allowed depending on the type and severity of toxicity encountered. Participants requiring more than 2 dose reductions will be discontinued from the treatment and entered into the Follow-Up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the participant's source notes and CRF.

Once a dose has been reduced for a given participant, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intraparticipant dose re-escalation is not allowed.

In some cases, participants experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

Recommended dose modifications for mevrometostat/placebo are described in Table 3. Recommended prophylaxis and treatment for dysgeusia are described in Table 4.

Table 3. Dose Modifications for Mevrometostat/Placebo-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Serum bilirubin[a]	Continue at the same dose level	Continue at the same dose level	When serum bilirubin >3x ULN: • Hold administration until recovery to Grade ≤1 (total serum bilirubin ≤1.5x ULN) or baseline and reduce by 1 dose level (only 1 dose reduction is allowed). • If toxicity reoccurs despite dose reduction, permanently discontinue treatment.	Discontinue treatment
Grade ≥3 AST or ALT levels	N/A	N/A	• Hold mevrometostat / placebo until recovery to baseline or normal levels and dose reduce by 1 level. • If toxicity recurs despite dose reduction, permanently discontinue.	Discontinue treatment

Table 3. Dose Modifications for Mevrometostat/Placebo-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
			• Rechallenge may be considered if an alternative cause for the abnormal liver tests is discovered and the laboratory abnormalities resolve to normal or baseline values. • Rechallenge is not permitted if these abnormalities are accompanied with signs or symptoms consistent with drug-induced liver toxicity or meet permanent discontinuation criteria. • Mevrometostat / placebo must be permanently discontinued if any elevation persists for more than 7 days. Guidelines for follow-up for possible DILI and for resuming after the liver test abnormalities resolve to baseline grade are provided in Section 10.6 and Section 6.6.3. The criteria for permanent discontinuation are provided in Section 7.1	
Nonhematologic toxicity considered related to mevrometostat / placebo, except abnormal liver tests and diarrhea	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is Grade ≤1 (Grade ≤2 if not considered a safety risk for the participant), then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.	Permanent discontinuation of for treatment-related Grade 4 adverse events of any duration. (Exclusion included discontinuation for emesis, and clinically insignificant laboratory abnormalities that resolve within two days on optimum treatment, additional exclusions will require agreement between the investigator and sponsor).

Table 3. Dose Modifications for Mevrometostat/Placebo-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level or reduce level by 1 dose level. If Grade ≥3 toxicity recurs after the dose reduction, hold mevrometostat/placebo and implement supportive care per local guidelines. Monitor weekly until toxicity Grade ≤2, then resume at a further reduced dose. If Grade ≥3 toxicity persists for >4 weeks without recovery to Grade ≤2 despite supportive care measures, discontinue mevrometostat/placebo and refer to a hematologist for evaluation.	Same as Grade 3
Lymphocyte counts decreased	Continue at the same dose level.	Continue at the same dose level[b]	Withhold dose until toxicity is Grade ≤2 or has returned to baseline within 2 weeks. Resume treatment at the same dose level or 1 dose level lower. Consider obtaining a CD4 count. If CD4 <200/µL, consider prophylaxis for PJP.	Same as Grade 3
Diarrhea	Start loperamide (up to 16 mg daily) at first sign of loose stool. Participant to be instructed to notify investigator.	Hold mevrometostat/placebo dosing until it resolves to Grade 1. After resolution to Grade 1, restart at same dose level. If	Hold mevrometostat/placebo dosing until it resolved to Grade 1, followed by 1 dose level reduction. Consider IV fluids, electrolyte replacement, and hospitalization for signs of dehydration.	Permanently discontinue mevrometostat/placebo.

Table 3. Dose Modifications for Mevrometostat/Placebo-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
		Grade 2 recurs, upon resolution to Grade 1, restart 1 dose level lower.		

a. If concurrent elevation of AST or ALT ≥3x ULN and total bilirubin ≥2x ULN occurs, refer to the DILI section (Section 10.6) for management.
b. For Grade 3 lymphocyte counts (<500/µL), consider obtaining CD4 counts.
Re-treatment following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met. If these conditions are met within 4 weeks of treatment interruption, study intervention may be resumed.
ANC ≥1,000/mm3
platelet count ≥50,000/mm3
Grade ≥3 nonhematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator's discretion, Grade ≤2 if not considered a safety risk for the participant)

Table 4. Dysgeusia Management and Dose Modification Guidance

Initial Management or Low-Grade Symptoms	Follow-up or Higher-Grade Symptoms
For prophylaxis and treatment, consider recommending that participants: • Take mevrometostat/placebo with abundant water • Minimize the time the tablets stay in contact with the mouth mucosa • Rinse their mouth with water after dosing	For Grade 2 dysgeusia, consider dose interruption and dose reduction by 1 level if associated with other symptoms such as decreased appetite or weight loss until dysgeusia returns back to baseline and nutritional consult if dysgeusia is associated with weight loss and decreased appetite.

6.6.5. Dosing Interruptions

With respect to study intervention, participants experiencing AEs should have their treatment interrupted as described in mevrometostat/placebo dose modification Table 2. Refer to enzalutamide prescribing information for dose interruption of enzalutamide.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in the Dose Delays (Section 6.6.6).

Doses may be held up to 4 weeks until toxicity resolution.

If the AE that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Table 2 or as applicable, unless expressly agreed otherwise following discussion between the investigator and the sponsor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >4 weeks, treatment resumption will be decided in consultation with the sponsor.

Specific guidance for dose modifications in mevrometostat/placebo are available in Section 6.6.1. Specific guidance for dose modifications in enzalutamide are available in Section 6.6.2.

6.6.6. Dose Delays

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

Refer to the Dose Reductions (Section 6.6.4) for AEs requiring dose reduction at the time of treatment resumption.

If participants require discontinuation of study intervention for more than 4 weeks at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the sponsor.

If a treatment interruption continues beyond Day 28 of the current cycle for mevrometostat/placebo + enzalutamide or enzalutamide alone, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

6.7. Continued Access to Study Intervention After the End of the Study

For participants who continue to derive clinical benefit from treatment (as judged by the PI and discussed with the sponsor) at the time the end of study has been reached, and they have no other treatment options outside a clinical study, they may be provided continued access to mevrometostat. In this case, the participant will be followed as per the site's standard of care and safety follow-up will be assessed and reported as described in Section 8.4.

6.8. Treatment of Overdose

For this study, any dose of mevrometostat/placebo or enzalutamide greater than the prescribed dose of study intervention (ie, extra pill[s] or extra full dose) will be considered an overdose.

There is no specific treatment for an overdose of mevrometostat/placebo. Local prescribing information should be consulted in the setting of an overdose of enzalutamide.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

3. Document the quantity of the excess dose as well as the duration of the overdose on the CRF.

4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis (mevrometostat/placebo) within 2 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the study medical monitor as needed based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

Ongoing androgen-deprivation therapy with a GnRH agonist or antagonist or bilateral orchiectomy must be initiated prior to randomization, but no earlier than 3 months prior to randomization, and must continue throughout the study (refer to Inclusion Criteria 5a, Section 5.1).

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician with the exception of concomitant treatment listed in Inclusion and Exclusion Criteria, Section 5.1 and Section 5.2.

All concomitant treatments, including authorized/approved COVID-19 vaccines, blood products, as well as nondrug interventions received by participants from screening until the end of treatment visit will be recorded on the CRF.

Background Treatment

For participants receiving LHRH agonists, treatment with first-generation antiandrogen is recommended but should be discontinued prior to study treatment.

The concurrent treatment with ADT will be provided by the local institution/pharmacy and the dose and schedule of administration will be consistent with the local prescribing information and guidelines.

Concurrent ADT (chemical or surgical) must be documented in the source data and recorded in the CRF.

For the purposes of this protocol, study intervention refers to those summarized in Section 6.1.

6.9.1. Prohibited During the Study

No additional anti-tumor treatment will be permitted while participants are receiving study intervention, including any hormonal therapy (eg, bicalutamide, nilutamide, flutamide, estrogens, 5-alpha reductase inhibitors), cancer-related surgery, or concurrent radiotherapy

(excluding palliative radiotherapy). Additionally, treatment for prostate cancer outlined in the exclusion criteria are prohibited during study (refer to Section 5.2 Prior/Concomitant Therapy).

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from sponsor to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Prohibited Medication Due to Potential DDI with Enzalutamide

- Strong CYP2C8 inhibitors: Use of strong CYP2C8 inhibitors should be avoided. If participants must be co-administered a strong CYP2C8 inhibitor, reduce the enzalutamide dose to 80 mg once daily. If coadministration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

- Certain CYP3A4, CYP2C9, or CYP2C19 substrates with narrow therapeutic index: Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. The coadministration of enzalutamide decreases the concentrations of certain CYP3A4, CYP2C9, or CYP2C19 substrates, which may reduce the efficacy of these substrates. Avoid the coadministration of enzalutamide with certain CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (eg, phenytoin, warfarin) or CYP2C19 (eg, S-mephenytoin) substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate. If the coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites. If coadministration with warfarin cannot be avoided, conduct additional INR monitoring.

- Direct oral anticoagulants: Rivaroxaban and apixaban (both are direct oral anticoagulants and are substrates of CYP3A4 and P-gp) should be avoided as enzalutamide might result in reduced plasma exposure which may lead to loss of efficacy or bleeding complications. Switch to warfarin and apply additional monitoring as stated above. Dabigatran and edoxaban (direct oral anticoagulants that are substrates for P-gp but not for CYP3A4) should be used with caution given the mild clinical effect of enzalutamide on P-gp inhibition; additional monitoring should be conducted as warranted.

Prohibited Medication Due to Potential DDI with Mevrometostat

- Strong CYP3A4/5 inhibitors: Since the inhibition of CYP3A4/5 isoenzymes may increase mevrometostat plasma exposure leading to potential increases in toxicities, the use of known strong inhibitors is not permitted within 10 days or 5 half-lives of the CYP3A4/5 inhibitors, whichever is longer, prior to the first dose of investigational product and should be avoided during study conduct. Strong CYP3A4/5 inhibitors may include grapefruit juice or grapefruit/grapefruit related citrus fruits (eg, Seville oranges, pomelos), ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan.

- Strong CYP3A4/5 inducers: Since the induction of CYP3A4/5 isoenzymes may decrease mevrometostat exposure leading to potential decrease in efficacy, the use strong CYP3A4/5 inducers are not permitted within [10 days or 5 half-lives of CYP3A4/5 inducers, whichever is longer] prior to the first dose of investigational product, with the exception of enzalutamide as part of this study. Strong CYP3A4/5 inducers may include phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, and St. John's Wort.

6.9.2. Permitted with Caution During the Study

- Moderate CYP3A4/5 inhibitors and/or inducers: It is preferred that moderate CYP3A4/5 inhibitors and/or inducers be replaced prior to the first dose of study intervention and during study conduct. Moderate CYP3A4/5 inhibitors may include erythromycin, ciprofloxacin, verapamil, diltiazem, atazanavir, fluconazole, darunavir, delavirdine, amprenavir, fosamprenavir, aprepitant, imatinib, tofisopam, and cimetidine. Moderate CYP3A4/5 inducers may include bosentan, efavirenz, etravirine, modafinil, and nafcillin. If the replacement is not possible, then caution should be exercised with coadministration of mevrometostat with moderate CYP3A4/5 inhibitors and/or inducers.

- Concomitant use of mevrometostat and a substrate of the MATE-1, OATP1B1, OATP1B3, or OCT1 transporter may increase the exposure of the substrate. Therefore, caution is warranted for coadministration of mevrometostat with MATE-1, OATP1B1, OATP1B3, OCT1 substrates. The current list of substrates can be found on the FDA website (FDA).

- Granulocyte-colony stimulating factors (Section 6.9.5)

- Primary prophylaxis of diarrhea, nausea, and vomiting (Section 6.9.6)

- Herbal medicine: Use of herbal medicine is not recommended or should be used with caution.

6.9.3. Permitted During the Study

- Palliative radiotherapy for symptomatic treatment of bone metastases present at baseline or to control symptoms related to the primary prostate tumor such as lower urinary tract symptoms, hematuria and pain.
    - The investigator must clearly indicate that the need for radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of mevrometostat with radiotherapy, mevrometostat/placebo treatment should be interrupted during palliative radiotherapy, stopping 5 days before and resuming treatment after recovery to baseline; or a shorter interruption period may be considered for participants after discussion with the Pfizer Medical Monitor designee.
- Treatment with bisphosphonates or denosumab during the study is permitted.
- Authorized or approved vaccines may be provided to participants, including COVID-19 vaccine, per local/institutional guidelines or regulations.

6.9.4. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current ASCO guidelines.

Treatment with 4 gm or less of acetaminophen/paracetamol (eg, no more than 1 gm per single dose) is permitted. However, in the case of increased liver function tests, bilirubin, or alkaline phosphatase, discontinuation of acetaminophen/paracetamol use is recommended.

6.9.5. Hematopoietic Growth Factors

Primary use of colony stimulating factors is not permitted, but they may be used to treat treatment-emergent neutropenia as indicated by the current ASCO guidelines (Smith et al, 2015).

6.9.6. Antidiarrheal, Antiemetic Therapy

Antidiarrheal Therapy

Participants should receive appropriate supportive care measures as deemed necessary by the Investigator. For diarrhea cases of any grade, consider recommending increased oral intake of fluids and dietary modifications (eg, eliminating lactose, dietary supplements with high-osmolar). Rule out alternative etiologies for diarrhea early in the course of the event and in recurrent or severe cases. For diarrhea refractory to mevrometostat/placebo dose hold, consider performing a colonoscopy and investigations to rule out infectious causes.

See Table 3 for dose modifications for mevrometostat/placebo diarrhea treatment-related adverse events.

Antiemetic Therapy

Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Participants should be strongly encouraged to maintain liberal oral fluid intake. The choice of prophylactic drug as well as the duration of treatment is up to the investigator assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatment(s) section (Section 6.9.1).

6.9.7. Corticosteroids

Chronic systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purposes is not permitted. Physiologic replacement of corticosteroids is permissible (eg 1.5 mg of dexamethasone or equivalent daily [10 mg prednisone]). Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

6.9.8. Surgery

Caution is advised for any surgical procedures during the study. The appropriate interval of time between surgery and mevrometostat/placebo required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping mevrometostat/placebo is recommended at least 5 days prior to surgery. Postoperatively, the decision to reinitiate mevrometostat/placebo treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6.9.9. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with mevrometostat/placebo or enzalutamide; standard medical supportive care must be provided to manage the AEs. Refer to Table 2 for dose modifications.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention may include the following:

- BICR-determined radiographic progression;
    - Participants with confirmed disease progression assessed by BICR who are continuing to derive clinical benefit from the study intervention will be eligible to continue receiving study intervention, provided that the treating physician has determined that the benefit/risk for doing so is favorable. Participants with investigator-assessed disease progression, but without confirmed disease progression assessed by BICR, should continue with radiographic, PSA and serum testosterone assessments per protocol schedule. PSA increase or PSA

progression should not trigger discontinuation of study treatment unless radiological progression is assessed by BICR.

- Participants should meet the following criteria to continue study intervention despite progression of disease:
  - Absence of symptoms and signs indicating clinically significant progression of disease.
  - No decline in ECOG performance status
  - Absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression)
  - At the time of radiographic progression of disease, an ICD addendum will be reviewed and signed by the participant

- Unacceptable toxicity or AE leading to permanent discontinuation. If the unacceptable toxicity is attributed to mevrometostat/placebo, the investigator (may consult the sponsor's medical monitor to discuss) may continue treatment with enzalutamide (see Section 6.6.1).
- Global deterioration of health status requiring discontinuation;
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Physician decision
- Study terminated by sponsor;
- Death.

The investigator should discuss temporary or permanent discontinuation of study intervention with the study medical monitor in a timely manner.

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy, including survival at EOT, Safety Follow-Up, and LTFU visits. If clinically feasible, participants should not start subsequent anticancer therapy until BICR-documented progression (Section 8.2.2). See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention only or if the participant is also discontinuing from study procedures, further study follow-up, and/or collection of additional information (see Section 7.2.1 for further details).

When the participant permanently discontinues all study intervention, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations per the SoA will supersede those of the scheduled visit. The EOT visit should occur no more than 1 week after the discontinuation of all study intervention. All participants who permanently discontinue all study intervention will remain in the study, complete Safety Follow-Up, and subsequently commence LTFU, which may include imaging for participants who have not yet had confirmed radiographic progression. Crossover will not be allowed in the trial.

Safety Follow-Up:

At least 28 calendar days, and no more than 35 calendar days after last dose of study intervention or prior to initiation of any new anticancer therapy (whichever comes first), participants will return to undergo the assessments as reported in the SoA. Any SAEs occurring during this period must still be reported in Pfizer Safety irrespective of any intervening treatment. See Section 8.4.1 for details on AE/SAE reporting requirements.

Long-Term Follow-Up:

All participants in the LTFU period will be monitored and data will be collected every 8 weeks until Week 25 and then every 12 weeks from randomization until the participant dies, the participant withdraws consent for follow-up, or the study is terminated by the sponsor. Data collected during the LTFU period may include evaluation for symptomatic skeletal events and ePRO assessments. Participants that discontinue study treatment without BICR confirmed disease progression will continue to have tumor assessments, serum testosterone collections, and PSA collections until BICR confirmation of disease progression. The LTFU period will conclude at the time of the final OS analysis.

Participants will allow the sponsor continued access to medical records so that information related to participant's health condition, including disease status and survival, may be obtained per local regulations.

Survival Follow-Up:

During the Survival Follow-Up period (SoA), post-treatment survival status will be collected throughout LTFU. Participants will be contacted (eg, telephone, email, site visits, family member contact) for survival status and collection of subsequent anticancer therapies (eg, start and stop dates, date of disease progression of the therapy), until death, withdrawal of consent, lost to follow-up, or end of study, whichever occurs first. On sponsor request, participants may be contacted for survival information, eg, prior to each protocol-specified interim and final analysis. As permitted by local law, study site personnel may use public

databases, perform an internet search, or review obituaries to determine date of death. Survival information should be recorded in the CRF.

7.1.1. Potential Cases of Acute Kidney Injury

The investigator should consult with the sponsor for any suspected cases of kidney injury.

In the event of new changes in kidney function (≥30% increase in serum creatinine from baseline or decrease ≥30% in eGFR), there should be further evaluation to rule out acute kidney injury. Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and herbal supplements), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals. If there is a reason to expect obstruction of the urinary tract as a cause of the changes in kidney function, evaluation for obstruction should be considered, and additional assessments such as renal ultrasound may also be obtained if appropriate. Other assessments that may be performed include: urine protein excretion UACr, UPCr, urine protein (spot or 24 hour), urine volume, and urine microscopic examination. A nephrology consult may be requested for further clarification. If decreased kidney function is suspected, participants should return to the clinic as soon as possible to confirm abnormal results and to conduct additional assessments if needed.

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of drug-induced kidney injury if no other reason for the kidney function abnormalities is identified.

7.1.2. Liver Injury

Study intervention should be permanently discontinued if any of the following criteria are met, and no alternative cause explains the laboratory abnormalities:

- Participants with AST/ALT and total bilirubin baseline values within the normal range who subsequently present with AST **OR** ALT values ≥3 × ULN **AND** a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available (Note: in the presence of elevated alkaline phosphatase associated with bone metastases, GGT should be tested, and the results should be within the reference range);

- For participants with baseline AST **OR** ALT **OR** total bilirubin values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

    - Preexisting values of total bilirubin above the normal range: total bilirubin level increased from baseline value by an amount of ≥1 × ULN **OR** if the value reaches ≥3 × ULN (whichever is smaller).

- Participants with AST/ALT >5 × ULN that persists for more than 7 days (AST/ALT >8 × ULN for participants with hepatic involvement).
    - Participants with AST/ALT >20 × ULN that persists for longer than 3 days.
    - Participants with total bilirubin >3 × ULN that persists for longer than 7 days (>5 × ULN for participants with Gilbert's disease).

Criteria for temporary withholding of study intervention in association with liver test abnormalities is outlined in Section 6.6.3. All cases meeting the criteria for an AE or SAE should be reported as per the criteria and timeframe detailed in Appendix 3. Potential Hy's law cases (refer to Appendix 6) or cases resulting in permanent study intervention discontinuation are to be reported as SAEs.

7.1.3. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

7.1.4. Rechallenge

Rechallenge with enzalutamide may only be considered according to prescribing information. The investigator and sponsor should discuss and agree with any decision to rechallenge any of the assigned study interventions. Rechallenge with mevrometostat/placebo following liver test abnormalities is not permitted if these abnormalities are accompanied with signs or symptoms consistent with drug-induced liver toxicity or meet permanent discontinuation criteria. Rechallenge with mevrometostat/placebo may be considered at the same dose or at 1 lower dose level once an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. Following rechallenge, participants should be closely monitored for signs and symptoms of hepatitis and/or abnormal liver test results.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study may include:

- Refused further follow-up
- Lost to follow-up
- Death

- Study terminated by sponsor

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent for collection of future information, no further evaluations will be performed and no additional data will be collected except for publicly available information (see Section 7.2.1 for further details). The sponsor may retain and continue to use any data collected before such withdrawal of consent in accordance with local law.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures, post-treatment study follow-up, contact with the participant or other individual such as a family member, and/or review of medical records and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and establish whether the participant wishes to continue, if eligible to do so;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

The investigator must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Scans (CT chest, CT or MRI of the abdomen and pelvis and whole body radionuclide bone scans) conducted within 42 days of Day 1; and laboratory tests (hematology/chemistry) obtained within 7 days of Day 1 as part of the participant's standard of care and obtained before signing of the ICD may be utilized for eligibility provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The Pfizer study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The planned total blood sampling volume for individual participants in this study is approximately 35 mL per study visit during the treatment period. The actual collection times of blood sampling may change if judged necessary by the sponsor. Additional blood samples may be taken for safety assessments as needed, provided the total volume taken during the study is not expected to exceed 550 mL during any period of 56 consecutive days.

8.1.1. Population Characteristics

8.1.1.1. Demographics

Demographic characteristics (eg, date of birth (age), sex, and race/ethnicity) should be entered in the CRF.

8.1.1.2. Medical History

Medical history findings (eg, previous diagnoses, disease, or surgeries) meeting all criteria listed below will be collected and recorded in the CRF:

- Not pertaining to the study indication
- Start before signing of the ICD. Detailed instructions on the differentiation between medical history and AEs can be found in Section 8.4.1.

History of prostate cancer will be collected separately from the general medical history. This includes, but is not limited to:

- Date of diagnosis
- Staging (performed at diagnosis)
- Gleason score prior to randomization
- Prostate cancer history
- Disease status at study entry
- Prior diagnosis and therapeutic procedures
- Prior prostate cancer treatments (any therapy that is ongoing should be reported as concomitant medication). Prior radiotherapy on primary tumor and/or metastatic sites will be reported, including the sites and date of completion of radiation.

Medical history and history of medication use will be collected at screening based on participant self-reporting via a detailed medical history interview. If the investigator deems that medical records are required to adequately assess the participant's eligibility, the site should pursue obtaining such records with written release by the participant in order to consider the participant for study entry.

8.1.1.3. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Assessments that may be performed during a telehealth visit are described below.

The following assessments are mandatory to be performed at a telehealth visit if they are required to be performed at the corresponding in-clinic visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact.
- Review and record any updates to concomitant medications since the last contact, including new concomitant medications or changes to ongoing concomitant medications.
- Review and record contraceptive method.

Participants must be reminded to promptly notify site staff about any change in their health status. Participants may request an unscheduled telehealth or in-person visit with site staff.

Any telehealth visit may be changed to an in-person visit based on participant preference or investigator discretion.

8.2. Efficacy Assessments

8.2.1. Assessment of Efficacy

Study assessments of efficacy are measures of prostate cancer status to evaluate the primary and secondary study endpoints. These assessments will include disease status, survival status, PSA, symptomatic skeletal events, pain scores, quality of life, and PFS2.

8.2.2. Assessment of Primary Efficacy Endpoint: rPFS

The primary efficacy endpoint is BICR assessed rPFS per RECIST v1.1 (soft tissue disease) and PCWG3 (bone disease) which will be assessed radiographically by blinded central radiology review(s) at the time points specified in the SoA by CT of chest and CT or MRI of abdomen and pelvis. Bone disease status will be assessed by whole body radionuclide bone scan (ie radionuclide [Tc-99m] bone scintigraphy).

PET and SPECT are not evaluable imaging modalities for this study. However, if a PSMA PET is conducted as SOC, this data should be entered on the CRF.

When medically acceptable, contrast enhanced CT scan is the preferred method for assessment of soft tissue disease and will be performed on the chest, abdomen, and pelvis. Participants who are intolerant to CT contrast agents should undergo CT scans without contrast enhancement of the chest and contrast enhanced MRI scans of the abdomen and pelvis for assessment of soft tissue disease. As a final alternative, CT scans without contrast enhancement of the chest, abdomen, and pelvis are also acceptable. Soft tissue response and progression will be evaluated per RECIST v1.1 (Eisenhauer et al, 2009). Whole body bone scans will be performed to assess the presence of bone disease. Bone disease is not to be assessed by CT or MRI; progression of bone disease will be evaluated per PCWG3 (Scher et al, 2016).

In order to ensure consistency in assessment of imaging throughout the study, the imaging modality(s) used for soft tissue assessment of a given lesion at screening should remain the

same throughout the study, unless doing so would compromise participant safety. The investigator is asked to inform the sponsor prior to a change in soft tissue imaging modality and the reason for doing so, prior to the radiographic assessment, whenever possible.

The scheduling of imaging assessments should be fixed according to the calendar, regardless of treatment schedule, treatment delays or interruptions. Imaging assessments are to be scheduled using the randomization dates as a reference date for all time points and are NOT to be scheduled based on the date of the previous imaging time point.

All images will be read by site staff at the study site and locally determined assessments will be entered in the appropriate CRF. Each study site should designate a radiologist or investigator to ensure that all images are read as specified by the protocol and to ensure consistency in the readings. All participants' files and radiologic images must be available for source verification and for potential peer review.

8.2.2.1. Blinded Independent Central Review of Tumor Assessments

A third-party core imaging laboratory will perform BICR of radiographic images for all participants to determine the protocol defined endpoint of radiographic disease progression.

It is important to the integrity of the study that the following materials are provided to BICR as each participant enrolls and progresses through the study: imaging studies for all participants; screening, Active Treatment Phase, Follow-Up images. Additionally, it is important to the integrity of the study that all imaging studies, clinical information (as applicable) are provided to BICR on an ongoing basis (as soon as they are available) until confirmation of objective disease progression by BICR as per RECIST v1.1 and/or PCWG3, regardless of the discontinuation study treatment.

8.2.2.2. Expedited Blinded Independent Central Review for Disease Progression

To mitigate the potential for bias in determining disease progression, expedited BICR will be performed for investigator-assessed disease progression. Upon investigator-assessed disease progression, the radiographic images as well as all other information reported as per Section 8.2.2.1 will be submitted to the BICR for expedited review. See the Study Imaging Manual for process details. If clinically feasible, participants must not start subsequent anticancer therapy until BICR-documented disease progression.

8.2.2.3. Imaging Tumor Response Assessments Management of Incidental Findings

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study but is unrelated to the purpose and beyond the aims of the study.

Tumor assessment images will be reviewed by a central review facility. The purpose of this review is to evaluate images for disease assessment. Central image review is not a complete medical review of the participant. If, during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study

sponsor for disclosure to the PI. All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-participant relationship. The PI will be responsible for reporting any AEs identified from incidental findings as described in the AE reporting section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

8.2.3. Assessment of Secondary Efficacy Endpoints

The study assessments of efficacy for the secondary endpoints will include standard radiographic and imaging methods to evaluate OS, ORR, DoR, PSA response ≥50%, time to PSA progression, time to initiation of antineoplastic therapy, time to first SSE, and time to CRPC at time points specified in the SoA.

Blood samples will be drawn for analysis of PSA levels to determine biochemical response and progression. PSA will be assessed throughout the study until radiographic progression according to the SoA. Investigators are strongly discouraged from discontinuing study interventions or initiating new systemic therapy due to a rising PSA, where study intervention administration should continue until study intervention discontinuation criteria (Section 7.1) are met.

Symptomatic skeletal event evaluation includes tumor-related symptomatic fractures, surgery, or radiotherapy to the bone and spinal cord compression. All fractures and spinal cord compression (including those that are asymptomatic or unrelated to prostate cancer) must be recorded in the CRF as an AE.

Time to first symptomatic skeletal event will be defined as the time from randomization to use of radiation therapy (external beam radiation therapy or radionuclides) or surgery to bone for prostate cancer, findings of clinically apparent pathologic bone fracture or of spinal cord compression.

Time to CRPC will be defined as the time from date of randomization to the date of first castration-resistant event (radiological progression, PSA progression or symptomatic skeletal events, whichever occurs first).

8.2.4. Patient-Reported Outcomes Assessments

PRO assessments will be collected by electronic device at timepoints specified in the SoA. Questionnaires should be completed alone before the first dose of study treatment on C1D1. At all subsequent visits, questionnaires should be completed alone in the same order and before any other study activities. Investigators are not required to review PRO data, and PRO data will not be utilized for the AE/SAE reporting procedures in Section 8.4.

BPI-SF

The BPI-SF pain questionnaire is a validated instrument that is a participant self-rating scale assessing level of pain, effect of the pain on activities of daily living and analgesic use

(Cleeland & Ryan, 1994). The BPI used in this study is the short form and contains 9 questions. BPI-SF pain items use a 0-10 NRS, and the symptom items have verbal anchors of 0= 'No Pain' and 10= 'Pain as bad as you can imagine'.

EORTC QLQ-PR25

The EORTC QLQ-PR25 is a validated 25-item module designed to assess QoL in participants with prostate cancer (van Andel et al, 2008). The extent of occurrence of 25 defined symptoms related to bowel, bladder and hormones as well as interest in and occurrence of sexual activity are rated by selecting 1 of 4 categories ranging from not at all to very much.

EQ-5D-5L

The EQ-5D-5L is a validated QoL instrument for self-reported assessment of 5 domains of health: mobility, selfcare, usual activities, pain/discomfort and anxiety/depression (Herdman et al, 2011). Each domain is rated by selecting 1 of 5 standardized categorizations (no problems, slight problems, moderate problems, severe problems, or extreme problems). The final question is a visual analogue scale to rank health status from best health imaginable to worst health imaginable.

FACT-P

The FACT-P questionnaire is a validated multi-dimensional, self-reported QoL instrument specifically designed for use with participants with prostate cancer (Esper et al, 1997). It consists of 27 core items that assess patient function in 4 domains: physical, social/family, emotional, and functional wellbeing, which is further supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale and then combined to produce subscale scores for each domain, as well as the FACT-P total score, with higher scores representing better health-related quality of life.

BFI

The BFI is a validated tool consisting of three questions assessing the severity of fatigue and six questions assessing the impact of fatigue on the patient's mood, social functioning and physical functioning (Mendoza et al, 1999). Each question is asked in relation to the last 24 hours and is scored on an 11-point numerical rating scale, with higher scores indicating greater fatigue and interference with functionality.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

Safety endpoints include adverse events (graded according to the NCI CTCAE, version 5.0), physical examination (including blood pressure and pulse), and laboratory tests (hematology and chemistry).

8.3.1. Physical Examination

Physical examinations will be conducted according to the SoA. At screening, this will constitute an assessment of systems (eg, general appearance, head, eyes, ears, nose, mouth, throat, skin, heart, lung, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal). During treatment, systems will be assessed per standard of care at the study site or as clinically indicated by symptoms.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

PEs may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

PE findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.4.1 to 8.4.3.

8.3.2. Vital Signs

Vital sign measurements (blood pressure, heart rate, and temperature [C]), height (cm), and weight (kg) will be assessed as shown in the SoA. Height is only required to be collected at screening.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2.1. Performance Status

The participant’s performance status will be assessed using the ECOG PS (Appendix 11).

8.3.3. Electrocardiograms

Standard 12-lead ECGs will be collected at times specified in the SoA of this protocol using an ECG system that automatically calculates the heart rate and measures PR interval, QT interval, QTcF, and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position. If scheduled at the same nominal time, ECGs should be collected before blood sampling.

The participant should undergo additional ECG monitoring if a) a post-dose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer. A cardiologist should be consulted if QTcF

values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8. Any clinically significant changes from the baseline ECG may potentially be AEs (see Appendix 8) and should be evaluated further, as clinically warranted.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory guidance (eg, manual) and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

Laboratory test results will be graded according to NCI CTCAE v5.0 as defined in Section 10.3.2.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

There is no need to repeat a clinical laboratory assessments on Cycle 1 Day 1 if the baseline assessment was performed within 7 days prior to that date.

8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Safety laboratory evaluations and ECGs are conducted at local laboratories which have been specified at the beginning of the study. In the event that a participant is not able to attend one of those local laboratories protocol-specified safety laboratory evaluations or ECGs may be conducted at a different local laboratory once it is approved by the investigator and the sponsor. The additional local laboratory may be a standalone institution or within a hospital.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

Only routine safety assessments will be performed by alternative facilities.

8.3.5. Symptomatic Skeletal Event Evaluation

Symptomatic skeletal event evaluation includes tumor-related symptomatic fractures, surgery, or radiotherapy to the bone and spinal cord compression. All fractures and spinal cord compression must also be recorded in the CRF as an AE. This assessment will occur throughout the treatment phase and in LTFU as per the SoA.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the applicable method as described in Appendix 3 Section 10.3.4.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of these data being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting.

8.4.1.2. Reporting Second Primary Malignancies

Any diagnoses of second primary malignancies (with the exception of nonmelanoma skin cancers) are to be reported to Pfizer Safety as an SAE regardless of the active collection period and irrespective of study intervention, investigator's opinion of causality or time of diagnosis. In addition, investigators should report any cases of MDS, T-LBL, and AML as they become aware of irrespective of causality attribution for up to 4 years after the initiation of mevrometostat treatment.

8.4.1.3. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist

in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposure to the study intervention under study is reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A participant who is receiving or has discontinued study intervention inseminates a partner.
- A nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
  - A family member or healthcare provider reports that they are pregnant after exposure to study intervention by ingestion.
  - A family member or healthcare provider who has been exposed to the study intervention by ingestion then inseminates their partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant's partner after the start of study intervention and until 3 months after the end of treatment, the investigator must report this information to Pfizer Safety, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 30 days after the last dose of mevrometostat.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to their partner. The investigator must document in the source documents

that the participant was given the Pregnant Partner Release of Information Form to provide to their partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a family member or healthcare provider who reports breastfeeding after having been exposed to study intervention by ingestion.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding individuals (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Cardiovascular AEs, if meeting the definition of seriousness (Appendix 3) will be reported according to the standard process for expedited reporting of SAEs. Death is considered an outcome and not an AE. AEs with a death outcome will be reported according to the standard process for expedited reporting of SAEs.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease", or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression that cannot be determined as exclusively due to progression of the underlying malignancy or do not fit the expected pattern of progression for the disease under study are to be reported to Safety and recorded in the CRF as AEs or SAEs. Complications from progression of the underlying

malignancy (including any hospitalization) should be recorded as AEs or SAEs in the CRF only.

8.4.8. Adverse Events of Special Interest

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported to Pfizer Safety.

8.4.9. Medical Device Deficiencies

Not Applicable

8.4.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the AE Page of the CRF	Reported to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;

- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours **only when associated with an SAE.**

8.5. Pharmacokinetics

8.5.1. Plasma for PK Analysis of Mevrometostat

Blood samples (2 mL) to provide approximately 1 mL plasma for PK analysis will be collected into appropriately labeled tubes containing EDTA (anticoagulant) as outlined in the SoA. For participants who receive mevrometostat and enzalutamide, PK samples will be analyzed for mevrometostat concentrations.

On days when participants have clinical visits where PK assessments are to be obtained, the morning dose of mevrometostat/placebo should be held (NOT taken) prior to the study visit. On those days, the mevrometostat/placebo morning dose should be taken after the study procedures required immediately prior to the mevrometostat/placebo morning dose have been performed.

In addition to samples collected at the scheduled times, an additional blood sample may be collected from participants experiencing unexpected and/or serious AEs and the date and time of blood sample collection and of last dosing prior to PK collection will be documented on the CRF. All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing as outlined in the SoA, and the exact time of the sample collection will be noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor.

PK samples will be assayed for mevrometostat using a validated analytical method in compliance with Pfizer/vendor SOPs. The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

As part of understanding the PK of the investigational product, samples may be used for the evaluation of the bioanalytical method, as well as for other internal exploratory purposes. If performed, data from these assessments will not be included in the CSR.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetics are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s) and cancer. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the SoA and central laboratory manual.

Retained Research Samples will not be collected from participants enrolled in China.

8.7. Biomarkers

Tumor tissues and/or blood samples will be used to evaluate biomarkers (genes and proteins) involved in the biology of the participant's disease, and mechanisms of sensitivity or resistance to mevrometostat in combination with enzalutamide, and to conduct genomic, and/or molecular profiling analyses. These biomarkers may include, but are not limited to those involved in AR and EZH2 regulation as well as prostate cancer biology, eg, AR, TP53, PTEN, RB1, DDR gene alterations. In addition, quantitative changes (on treatment from baseline) of ctDNA concentration in the participant's blood will be analyzed to estimate its potential as a molecular measure of treatment responses.

Unless prohibited by local regulations or ethics committee decision, biospecimens will be collected to analyze DNA, RNA, protein and/or metabolic biomarkers for achieving study objectives. Specific analyses may not be performed if emerging data indicate that they would no longer support study objectives. Details regarding the types of biospecimen and purposes of collection are listed below.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Tumor Biopsy for Biomarker Analysis (Section 8.7.1)
- Blood Samples for Circulating Cell Free Nucleic Acids Analyses (Section 8.7.2)

Optional samples for biomarker research that should be collected from participants in the study as appropriate are the following:

- Tumor tissue sample collection at the EOT visit.

Additional information on tissue collection procedures, sample preparations including processing, storage, and shipment to the sponsor designated laboratories for biomarkers analysis will be provided in the Laboratory Manual.

Note: For participants in China, sample collection and biomarker testing will not be performed until approval by HGRAC.

8.7.1. Tumor Tissue for Genetic/Biomarker Analysis

Tumor biospecimens from archival (if available) and/or de novo biopsies collected at baseline will be used to analyze candidate nucleic acid and protein biomarkers, or relevant signature of markers, for their ability to identify those participants who are most likely to benefit from treatment with the study drugs. Biomarkers may include, but are not limited to target expression, nucleic acid analyses, as well as cell types and constituents of the tumor microenvironment. RNA and/or DNA sequencing analysis, which may include targeted and/or whole exome sequencing and/or transcriptome and/or epigenetic analyses, may be performed to examine genomic landscape, correlations between gene mutation status or gene expression signatures and clinical outcome.

Archival (if available) or newly acquired pretreatment tumor tissue (preferably tumor block; if not, unstained slides are also acceptable) will be submitted for biomarker analysis (see SoA). The baseline tissue chosen should be the most recently collected specimen before the start of the study therapy.

An optional de novo tumor biopsy may be collected at the EOT visit only for participants who discontinue treatment due to disease progression and when, in the investigator's judgment, such biopsy is feasible and can be safely performed. The EOT tumor tissue will be used to determine possible mechanisms of resistance.

Information on tissue collection procedures can be found in the Laboratory Manual.

8.7.2. Blood Samples for Circulating Cell Free Nucleic Acids Analyses

Whole blood samples processed into plasma for cf nucleic acids analyses will be collected pre-dose at each time point as per the SoA. These samples may be used to: 1) evaluate correlations of baseline ctDNA burden and baseline vs on-treatment changes in ctDNA burden with assessments of treatment efficacy; 2) explore ctDNA gene alterations (eg, mutations, copy number variations) in association with treatment outcome and to understand potential mechanisms of resistance to study intervention(s); 3) explore ctRNA transcripts, including splice variant transcripts, for androgen receptor and/or other genes, including changes with treatment and potential associations with clinical outcome. Additional analyses may be warranted based on emerging data.

A targeted sequencing panel may be used for these analyses. Exploratory whole exome/genome sequencing and/or epigenetic analyses may be performed.

For participants in China, one 10 mL whole blood sample optimized for plasma ctDNA analysis will be collected pre-dose at each time point as per the SoA.

8.8. Immunogenicity

Immunogenicity testing is not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

The following statistical hypothesis will be tested to address the primary objective of rPFS:

H_{01}: $HR_{rPFS}=1$ vs. H_{11}: $HR_{rPFS}\neq 1$,

where HR_{rPFS} is the HR of rPFS for mevrometostat + enzalutamide vs. placebo + enzalutamide based on BICR assessment.

In addition, the following statistical hypothesis will be tested to address the key secondary objective of OS:

H_{02}: $HR_{OS}=1$ vs. H_{12}: $HR_{OS}\neq 1$

where HR_{OS} is the HR of OS for mevrometostat + enzalutamide vs. placebo + enzalutamide.

The study will be considered positive if the null hypotheses H_{01} is rejected and $HR_{rPFS} <1$. To preserve the overall study-wise type I error at 2-sided 0.05, a hierarchical gatekeeping testing procedure will be used to test OS. Specifically, H_{02} will be tested only if H_{01} is rejected.

9.1.1. Estimands

9.1.1.1. Primary Estimand

rPFS: treatment effect, estimated in the analysis population, of the experimental arm on PFS based on BICR per RECIST v1.1 (soft tissue disease) and PCWG3 (bone disease) compared with the control arm from randomization to PD or death due to any cause.

- Variable: rPFS is defined as the time from randomization until PD based on BICR assessment per RECIST v1.1 (soft tissue disease) and PCWG3 (bone disease), or death due to any cause, whichever occurs first.

- Censoring: rPFS data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD based on BICR assessment per RECIST v1.1 [soft tissue disease] and PCWG3 [bone disease] or death due to any cause), for participants who start a new anticancer therapy prior to an event, or for participants with an event after 2 or more missing tumor assessments. Participants who do not have an adequate baseline tumor assessment or who do not have an adequate postbaseline tumor assessment will be censored on the date of randomization.

- Analysis population: all randomized participants regardless of tolerability, duration of study intervention.

- Population-level summary measure: log-rank p-value, HR for rPFS and 95% CI for HR calculated based on Cox's proportional hazard model stratified by the randomization strata and including data from all randomized participants.

9.1.1.2. Secondary Estimand

OS: treatment effect, in the analysis population, of the experimental arm on OS compared with the control arm from randomization to the date of death due to any cause or the last known alive date.

- Variable: OS defined as the time from the date of randomization until the date of death due to any cause.

- Censoring: data for participants not known to have died are censored on the date of last known alive.

- Analysis population: all randomized participants. Survival status is expected to be collected irrespective of study treatment discontinuation or participant's request to discontinue study procedures. All participants who have not withdrawn consent for further participation in the study should be followed for survival until the end of the study.

- Population-level summary measure: log-rank p-value, HR for OS and 95% CI for HR calculated based on Cox's proportional hazard model stratified by the randomization strata and including data from all randomized participants.

9.1.2. Multiplicity Adjustment

Alpha protected efficacy analyses will include tests for the primary endpoint rPFS and key secondary endpoint OS. The study-wise type I error will be controlled by using a hierarchal testing approach. If the primary analysis of rPFS is successful, then OS will be tested using the full alpha of 0.05. If the primary analysis of rPFS is not successful, then formal testing of

OS will not be done. Two interim and one final analyses are planned for OS, the Lan-DeMets (O'Brien-Fleming) α-spending function will be used to control the alpha level for the multiple testing of OS.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined.

Participant Analysis Set	Description
Full Analysis Set	All randomized participants in the study. Participants will be analyzed according to the study intervention assigned at randomization.
Safety Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of any study intervention. Participants will be analyzed according to the study intervention assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period in which case participants will be analyzed according to the actual study intervention received.
PK Analysis Set	All participants who received at least 1 dose of mevrometostat and provided an evaluable PK sample.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

All efficacy analyses will be performed using the full analysis set and all safety analyses will be performed using the safety analysis set.

In general, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the SAP.

The rates of binary proportions for each treatment arm will be presented along with a 2-sided 95% CI. Time-to-event endpoints will be summarized using the Kaplan-Meier method and will include the median and 95% CIs based on the Brookmeyer-Crowley method.

- Statistical analyses will be performed using SAS® version 9.4 or higher.

9.3.2. Primary Endpoint/Estimand/Analysis

rPFS is defined as the time from the date of randomization to first objective evidence of radiographic progression as assessed in soft tissue per RECIST v1.1 or in bone per PCWG3 guidelines by BICR, or death, whichever occurs first, and will be summarized in months using the following calculation:

rPFS (months) = [date of first objective evidence of radiographic progression, death, or censoring – randomization date +1]/30.4375.

rPFS will be compared between mevrometostat + enzalutamide and placebo + enzalutamide using a 2-sided stratified log-rank test. The stratified analysis will be based on the stratification factors at randomization:

- Disease volume (low vs high). High volume of disease is defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis

- De novo vs relapsed mCSPC

The HR (experimental/control) and the associated 95% CI will be estimated using a Cox proportional hazards model stratified by the randomization stratification factors. A hazard ratio <1 indicates a prolonged time-to-event for participants randomized to the experimental arm compared with participants randomized to the control arm.

Kaplan-Meier curves will be used to estimate the time-to-event distributions. The 50^{th} percentile of Kaplan-Meier estimates will be used to estimate the median duration of each treatment arm. A 2-sided 95% CI based on the Brookmeyer-Crowley method will be provided for this estimate.

Median follow-up time will be estimated according to the Kaplan-Meier estimate of potential follow-up by the reverse Kaplan-Meier method.

A sensitivity analysis of rPFS counting all disease progressions and deaths as events, regardless of timing of the event or missing tumor assessments, that is, no censoring due to initiation of new anticancer therapy prior to the event or due to 2 or more missed tumor assessments, will be performed. Another sensitivity analysis to assess the effect of patient discontinuation for reasons other than toxicity or disease progression by BICR will also be performed. Additional sensitivity analyses, including rPFS by investigator, will be conducted for the primary endpoint to assess the robustness of the primary analysis. Details will be provided in the SAP.

As exploratory analyses, subgroup analyses may be conducted for primary and key secondary endpoint. Subgroup analyses may include an analysis of PFS and OS by disease volume (low vs. high) and disease status (de novo vs relapsed) at baseline.

Detailed methodology for all subgroups analyses will be provided in the SAP.

9.3.3. Secondary Endpoint(s)/Estimands Analysis

9.3.3.1. Key Secondary Endpoint

OS is the key secondary endpoint and is defined as the time from randomization to the date of death due to any cause. Participants last known to be alive will be censored at the date of last contact.

A 2-sided log-rank test stratified by randomization stratification factors will be performed on OS. The Cox proportional hazards model stratified by randomization stratification factors will be fitted to compute the HR and the corresponding 95% CIs.

OS associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically.

9.3.3.2. Other Secondary Efficacy Endpoints

BICR- and Investigator-assessed objective response in measurable soft tissue disease

The proportion of participants with measurable soft tissue disease at baseline who have a confirmed objective response of CR or PR per RECIST v1.1 will be summarized along with the 95% CI. Soft tissue responses must be confirmed by a follow-up radiographic assessment at least 4 weeks later with no evidence of confirmed bone disease progression on repeated bone scans at least 6 weeks apart per PCWG3 criteria. Participants without documented CR or PR will be considered non-responders. Comparison in ORR between treatment arms will be performed using a CMH test controlling for the stratification factors. The p-value from the stratified CMH test will be reported. In addition, a two-sided 95% exact confidence interval for each treatment arm will be reported using the Clopper-Pearson method.

BICR- and Investigator-assessed duration of response in measurable soft tissue disease

Duration of response is defined as the time from the first objective evidence of a CR or PR (per BICR) to the first objective evidence of disease progression (assessed in soft tissue per RECIST v1.1 or in bone upon subsequent confirmation per PCWG3 guidelines) or death, whichever occurs first, and will be analyzed in the subset of participants entering with measurable soft tissue disease. Kaplan-Meier methods will be used to graph the duration and calculate the median and its associated 95% CI for each treatment arm.

Proportion of participants with PSA response ≥50% (PSA Response)

The proportion of participants with a 50% decline from baseline in PSA that is confirmed by a second consecutive value at least 21 days later in participants with detectable PSA values at baseline will be calculated for each treatment arm. Comparison in PSA response between treatment arms will be performed using a CMH test controlling for the stratification factors. The p-value from the stratified CMH test will be reported. In addition, a two-sided 95% exact confidence interval for each treatment arm will be reported using the Clopper-Pearson method (Clopper & Pearson, 1934).

Time to PSA progression

Time to PSA progression is defined as the time from randomization to the date of the first PSA value demonstrating progression, while participants are on study intervention which is subsequently confirmed at least 3 weeks later. Time to PSA progression will be compared between treatment groups using a 2-sided log-rank test. The HR and 95% CI will be provided. The median time to event and 95% CI for the median will be provided for each treatment arm.

Time to initiation of new antineoplastic therapy

Time to first use of new antineoplastic therapy is defined as the time from randomization to first use of new antineoplastic therapy for prostate cancer. This will include medications used specifically for prostate cancer treatment including hormonal treatments, immunotherapy, chemotherapy, and investigative agents. Participants not starting treatment with a new antineoplastic therapy at the time of analysis will be censored at the date of last assessment before the analysis data cutoff date. It will be compared between treatment groups using a 2-sided stratified log-rank test. The HR and 95% CI will be provided. The median time to event and 95% CI for the median will be provided for each treatment arm.

Time to first symptomatic skeletal event

The time to first symptomatic skeletal event is defined as the time from randomization to the date of the first tumor-related symptomatic bone fracture, surgery or radiotherapy to the bone, and spinal cord compression as reported on the Symptomatic Skeletal Events CRF page, whichever occurs first. Because skeletal events are expected to occur after radiographic progression, the analysis of time to first symptomatic skeletal event will be performed with the final OS analysis. It will be compared between treatment groups using a 2-sided log-rank test. The HR and 95% CI will be provided. The median time to event and 95% CI for the median will be provided for each treatment arm.

Time from randomization to CRPC

The time from randomization to CRPC is defined as the time from randomization to the first date of CRPC event (radiological progression, PSA progression or symptomatic skeletal events, whichever occurs first). Participants not progressing into CRPC at the time of analysis will be censored at the date of last assessment before the analysis data cutoff date. It will be compared between treatment groups using a 2-sided log-rank test. The HR and 95% CI will be provided. The median time to event and 95% CI for the median will be provided for each treatment arm.

9.3.3.2.1. PRO Analyses

The BPI-SF, BFI, FACT-P, EORTC QLQ-PR25, and EQ-5D-5L will be analyzed for the FAS.

Descriptive summary statistics and longitudinal mixed effect-model analyses will be used to assess change from baseline in worst pain (Item #3), pain severity, interference in daily

activities from pain as per BPI-SF, fatigue severity and fatigue interference, as per BFI, health status as per EQ-5D-5L, HRQoL, functioning and symptoms as per FACT-P and functioning and symptoms as per the EORTC QLQ-PR25 between the two treatment groups. Any missing responses will be handled per the scoring manuals of each questionnaire administered. Compliance rates will be summarized by listing the numbers and proportions of participants who completed the PRO assessments at each timepoint by treatment arm.

Time to deterioration analyses will be conducted using a 2-sided stratified log-rank test. The stratified analysis will be based on the stratification factors used at randomization and summarized using the Kaplan-Meier method which will include the median and 95% CIs based on the Brookmeyer-Crowley method. In addition, stratified proportional hazard (Cox) regression model will be used to produce corresponding hazard ratio with 95% CI.

- Pain is measured using the BPI-SF Item #3. Confirmed deterioration in pain is defined as ≥2-point increase from the baseline pain score and confirmed at the next consecutive assessment ≥4 weeks apart or an initial deterioration followed by death before the next assessment (Dworkin et al, 2008).

- Definitive deterioration in participant-reported FACT-P scales is defined as ≥x-point decrease from baseline, and no subsequent observation with <x-point decrease from baseline. The value of x for each scale considered is given in Table 5 below.

- Definitive deterioration in patient-reported functioning is defined as ≥10 point decrease from baseline and no subsequent observations with a <10 point decrease from baseline EORTC QLQ-PR25.

- Definitive deterioration in patient-reported symptoms is defined as ≥10 point increase from baseline and no subsequent observations with a <10 point decrease from baseline EORTC QLQ-PR25.

- Time to confirmed deterioration in participant-reported fatigue will be measured using the BFI. Time to fatigue intensity progression is defined as the time interval from randomization to the first date a patient experience an increase by ≥2 points from baseline in the worst BFI intensity item (item 3) observed at 2 consecutive evaluations ≥4 weeks apart. Fatigue interference progression is defined as an increase of ≥1.25 points from baseline in the average BFI interference score observed at 2 consecutive evaluations ≥4 weeks apart.

Table 5. Clinically Meaningful Deterioration Cutoff Values

Subscale	Cutoff Value for Clinically Meaningful Deterioration
FACT-P Pain subscale	2
FACT-P subscales (except pain), FAPSI-8	3
FACT-G Total Score	7
FACT-P Trial Outcome Index	9
FACT-P Total Score	10

9.3.4. Exploratory Endpoint(s) Analysis

The details of exploratory endpoint analyses will be described in the SAP or in a separate exploratory analysis plan.

PFS on next line therapy (PFS2)

PFS2 is defined as the time from the date of randomization to the first occurrence of investigator-determined disease progression (PSA progression, progression on imaging, or clinical progression) or death due to any cause, whichever occurs first, while the participant was receiving first subsequent therapy for prostate cancer. PFS2 will be compared between treatment groups using a 2-sided log-rank test. The HR and 95% CI will be provided. The median PFS2 and 95% CI for the median will be provided for each treatment arm.

Time to initiation of opioids

Time to first use of opioids is defined as the time from randomization to first use of new opioids for prostate cancer. Participants not starting a new opioid at the time of analysis will be censored at the date of last assessment before the analysis data cutoff date. It will be compared between treatment groups using a 2-sided stratified log-rank test. The HR and 95% CI will be provided. The median time to event and 95% CI for the median will be provided for each treatment arm.

Results of exploratory endpoint analyses will be described in the CSR to the extent possible. Due to the exploratory nature of the endpoints, the associated data analyses may not be completed at the time of the CSR preparation. If results of exploratory endpoint analyses cannot be included in the CSR, they will be disseminated to the scientific community to the extent possible through presentation at scientific meetings and/or publication in peer-reviewed scientific journals.

9.3.5. Safety Analyses

Safety will be evaluated for the safety population using AE, laboratory, and vital signs data. Treatment-emergent safety data will be defined as events from the first dose of study intervention through approximately 28 days after the last dose, or upon initiation of a new antineoplastic therapy, whichever occurs first.

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, PR, cardiac monitoring results, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet

the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.5.1. Adverse Events

All analyses will be based on treatment-emergent events unless otherwise specified; events not considered treatment-emergent will be flagged in data listings.

All AEs will be coded to PT and SOC using current MedDRA. AEs will be presented with and without regard to causality based on the investigator's judgment and by frequency of overall toxicity categorized by NCI CTCAE (version 5.0) grades. Summary tables will include system organ class and/or preferred term; these will be described in the full SAP.

In case a participant has events with missing and non-missing toxicity grades, the maximum of the non-missing grade will be displayed. Missing grade will only be displayed in the event that only one event has been reported for a participant and the grade is missing

9.3.5.2. Laboratory Test Abnormalities

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

9.3.6. PK Analyses

PK analyses will be performed using the PK analysis set.

PK data analyses will include descriptive summary statistics of the pre-dose and post-dose plasma concentrations of mevrometostat by study visit.

In addition, the PK data from this study may be used alone or combined with PK data from other studies, to develop a population PK model. The relationships between mevrometostat exposure in combination with enzalutamide and biomarker, efficacy and safety endpoints will be explored if data allows. If performed, the results of these modeling analyses will be reported separately from the CSR.

9.4. Interim Analyses

There will be no interim analysis for the primary endpoint rPFS. There will be two interim analyses and a final analysis of OS.

The first interim efficacy analysis for OS will be performed at the time of the final analysis of rPFS. It is anticipated that approximately 129 deaths (51% of the information fraction) will have occurred at that time. The efficacy boundary will be determined using a prespecified Lan-DeMets α-spending function. With 129 events, the efficacy boundary will

be p-value ≤0.003. The efficacy boundary will be adjusted according to the actual number of observed events at the time of the analysis.

There will be a second interim OS analysis when approximately 189 OS events (75% of the information fraction) were observed. The efficacy boundary will be determined using the prespecified Lan-DeMets α-spending function. With 189 events, the efficacy boundary will be p-value ≤0.018. The efficacy boundary will be adjusted according to the actual number of observed events at the time of the analysis.

9.5. Sample Size Determination

Approximately 1000 participants will be enrolled into the study and randomized with 1:1 ratio to the 2 treatments arms (ie, 500 participants per arm).

A total of 227 rPFS events will provide approximately 90% power to detect a target HR of 0.65 using a 2-sided log-rank test with a 5% level of significance.

For OS, a total of 252 events will provide approximately 80% power to detect a target HR of 0.70 using a 2-sided log-rank test with a 5% level of significance and a 3-look group sequential-design with a Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries.

To control the overall Type I error rate for the study, a hierarchical testing approach will be used, whereby rPFS will be tested first at 5% level. If it is significant, then OS will be tested at a 2-sided 5% level of significance.

The median rPFS in the control arm is assumed to be 48 months based on the ARCHES trial results (Armstrong et al, 2022). The median OS in the control arm, which may not be reached at the final analysis, is assumed to be 99 months based on a 78% survival rate at 36 months observed from ARCHES trial and an exponential distribution assumption.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European MDR 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or qualified designee will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The investigator may not delegate obtaining consent to a local healthcare professional.

The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant’s personal data.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct their personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current IRB/EC version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an E-DMC. The E-DMC is independent of the Pfizer study team and includes only external members. The E-DMC charter describes the role of the E-DMC in more detail.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC will be forwarded

to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities and investigators, as appropriate.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements following the end of the study globally.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available

18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the Data Management Plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The

investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source record) that supports the information entered on the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be reidentified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), and participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;

- Inadequate recruitment of participants by the investigator;

- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

If the sponsor decides to terminate the study for a reason unrelated to the safety of mevrometostat, participants may continue to receive study intervention(s) per the investigator's judgment and protocol-specified safety assessments will continue to be performed for these participants until the end of the study as defined in Section 4.4. The following non-safety-related study procedures and assessments may be stopped upon written notification from the sponsor. The procedures may also be stopped when the required number of OS events has occurred per Section 9.4.

- Radiographic imaging and PSA assessment will no longer be required after sponsor communication once the PCD has been achieved (Section 9.4)
- LTFU will no longer be required after sponsor confirms that the desired number of OS events for the OS analysis has been achieved (Section 9.4)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.11. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation

and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. When applicable, editorial or technical support provided by a third party and paid for by Pfizer, or provided by a Pfizer employee, may be a reportable transfer of value under the Sunshine Act for US licensed physicians or other healthcare professionals. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.12. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

All clinical lab tests will be performed at local laboratories.

Table 6. Core Lab Tests

Hematology	Chemistry	Additional
Hemoglobin	ALT	PSA
Platelets	AST	sT
WBC with differential	Alkaline phosphatase	Consider obtaining a CD4 count (unscheduled - if the lymphocyte count <500/µL)
ANC	Sodium	
Lymphocytes[c,d]	Potassium	
Monocytes[c,d]	Calcium	
Eosinophils[c,d]	Total bilirubin[a]	
Basophils[c,d]	BUN or urea	
RBC	Creatinine[b]	
Hematocrit	Scys[c]	
Neutrophils[c,d]	eGFR[b,e]	
	Albumin	
	Total protein	
	Magnesium	
	Glucose	
	Direct bilirubin	

a. For Hy's law potential cases, in addition to repeating AST, ALT, total bilirubin and alkaline phosphate, laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, and eosinophils (%)
b. For suspected acute kidney injury or creatinine increased, laboratory tests should include Screat, Scys (if available and feasible at laboratory performing safety assessment), and UPCr OR UACr.
c. If available and feasible at laboratory performing safety assessments.
d. Absolute values are to be entered in the eCRF. If only percentages are provided by the local laboratory, percentages can be entered. If %neutrophils are not provided, but % segmented neutrophils and % neutrophil bands are provided, these should be entered in the eCRF. In the event that % segmented neutrophils and % bands are provided OR only % neutrophils are provided without ANC, the site must manually calculate ANC by using the formula at https://www.mdcalc.com/absolute-neutrophil-count-anc
e. Screening (eGFR creatinine and/or cystatin [if applicable])

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic.

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that reporting SAE information to Pfizer safety is not the same as recording on the AE page of the CRF. When the same data are collected, these 2 reporting methods must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the reporting method used for reporting of SAE information to Pfizer Safety.

Safety Event	Recorded on the CRF	Reported to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured on the CRF, unless the study is managed via SAE+	All instances of EDP are reported (whether or not there is an associated SAE) All instances of EDB are reported (whether or not there is an associated SAE)
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information on the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety when the reporting method is paper (eg, in lieu of completion of the CT SAE Report Form/AE or SAE CRF page).
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 Use of Medical Records for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the categories listed below (as defined by the NCI CTCAE system).

If required on the AE page of the CRF, the investigator will use the following definitions of severity in accordance with the current CTCAE version to describe the maximum intensity of the AE:

GRADE	Clinical Description of Intensity
1	MILD AE
2	MODERATE AE
3	SEVERE AE
4	LIFE-THREATENING; urgent intervention indicated
5	DEATH RELATED TO AE

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Once the causality assessment is determined, the investigator must document it in the CRF and, for safety reporting purposes, document the relatedness as "Yes" (for related) or "No" (for unrelated).

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the selected reporting method and in accordance with the SAE reporting requirements.

Outcome Assessment

Record the appropriate outcome of the event in relation to the participant's status:

- Fatal: The termination of life as a result of an AE.
- Not Recovered/Not Resolved: One of the possible results of an AE outcome that indicates that the event has not improved or recuperated.
- Recovered/Resolved: One of the possible results of an AE outcome that indicates that the event has improved or recuperated.
- Recovered/Resolved with Sequelae: One of the possible results of an AE outcome where the participant recuperated but retained pathological conditions resulting from the prior disease or injury.
- Recovering/Resolving: One of the possible results of an AE outcome that indicates that the event is improving.
- Unknown: Not known, not observed, not recorded, or refused.

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Capture
• The primary mechanism for reporting an SAE to Pfizer Safety will be the EDC (eg, eSAE or SAE+) or PSSA. • For studies managed via SAE+, information pertaining to EDP or EDB is collected in the EDC and sent to Pfizer via PDF file. • If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours. • The site will enter the SAE data into the EDC or PSSA or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the EDC will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the backup method to transmit this information to Pfizer Safety in case the EDC or PSSA is unavailable for more than 24 hours. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the study intervention period and for at least 3 months after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) *plus* an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either:

- Be persistently abstinent from heterosexual intercourse and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- The participant should be advised of the benefit for an IOCBP partner using a highly effective method of contraception with a failure rate of <1% per year, as described in Section 10.4.2.

10.4.2. Contraception Methods

Contraceptive use by participants should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation
2. Intrauterine device (Copper IUD)
3. Intrauterine hormone-releasing system (Hormonal IUS/IUD)
4. Bilateral tubal occlusion (eg, bilateral tubal ligation)
5. Vasectomized participant

   - Vasectomized participant is a highly effective contraceptive method provided that the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Sexual Abstinence

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Further details of sample purpose(s) are given in Section 8.6. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- Retained Research Samples will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

Further details of sample purpose are given in Section 8.6.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI after excluding other causes of liver injury. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are “adaptors” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede total bilirubin elevations (>2 × ULN) by several days or weeks. The increase in total bilirubin typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and total bilirubin values will be elevated within the same laboratory sample). In rare instances, by the time total bilirubin elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to total bilirubin that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and total bilirubin baseline values within (or below) the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** total bilirubin values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

    - Preexisting values of total bilirubin above the normal range: total bilirubin level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

When study intervention is temporarily withheld or permanently discontinued due to a potential DILI, a period of close observation is to commence until the liver test abnormalities return to baseline or normal values. The evaluations listed in the table below should be performed.

Table 7. Monitoring of Liver Tests for Potential DILI

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]) and INR Tests
After the initial liver test abnormality	Within 48 hours
If AST or ALT ≥3 x ULN and total bilirubin ≥2 x ULN or INR > 1.5 x ULN	Every 24 hours until laboratory abnormalities improve
If AST or ALT ≥3 x ULN and total bilirubin or INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the participant is asymptomatic	Frequency may decrease

As DILI is a diagnosis of exclusion, it is important to initiate investigation of alternative causes for abnormal liver tests, which may include consultation with a hepatologist. Contact the sponsor with questions regarding sufficient follow-up tests.

Rises in AST/ALT and total bilirubin separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and total bilirubin for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. . Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and total bilirubin elevation defined above should be considered potential DILI (Hy's law) cases

if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Age-Specific Kidney Function Calculations

10.7.1.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

eGFR (mL/min/1.73 m²)

2021 CKD-EPI Screat only	Screat *(mg/dL)*	Scys *(mg/L)*	Recommended eGFR Equation[a]
Male	if ≤ 0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$

a. Adapted from (Inker et al, 2021)

10.7.2. Kidney Function Calculations

The sponsor recommends the following online calculators to calculate age- and sex-specific kidney function.

The United States National Kidney Foundation online calculators:

- Adults (18 years and above) - 2021 CKD-EPI creatinine online calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected if local laboratories are used and that they provide the units used for assessments. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer study team and medical monitor, if needed.

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl or creatinine) will be according to CTCAE criteria for adult participants.

CTCAE Term (2017)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
AKI	NA	NA	Hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
AKI: A disorder that is characterized by acute loss of kidney function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidneys), renal (kidney damage), or post-renal causes (ureteral or bladder outflow obstruction).					

CTCAE Term (2017)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine increased	>ULN to 1.5 × ULN	>1.5 to 3.0 × baseline OR >1.5 to 3.0 × ULN	>3.0 to 6.0 × baseline OR >3.0 to 6.0 × ULN	>6.0 × ULN	NA
CKD	eGFR ≥60 to 89 mL/min/1.73 m²	eGFR 30 to 59 mL/min/1.73 m²	eGFR 15 to 29 mL/min/1.73 m²	eGFR <15 mL/min/1.73 m² OR Dialysis indicated	Death
Proteinuria	Proteinuria 1+ OR Proteinuria >0.5 to <1.0 g/24 h	Proteinuria 2+ or 3+ OR Proteinuria 1.0 to <3.5 g/24 h	Proteinuria 4+ OR Proteinuria ≥3.5 g/24 h	NA	NA
CKD: A disorder characterized by gradual and usually permanent loss of kidney function resulting in kidney failure.					

KDIGO Albuminuria (A) Criteria	**A1**	**A2**	**A3**
UACr	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by ≥60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation to >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex >120 ms).
• New-onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) (“sustained” = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30-second duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 second duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The major events of potential clinical concern listed above are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what is to be reported as AEs/SAEs.

10.9. Appendix 9: Country-Specific Requirements

10.9.1. European Union

This study will be conducted in compliance with Regulation (EU) No 536/2014. The recruitment plans for each EU Member State concerned are included in the respective Recruitment and Informed Consent Procedure documents.

The sponsor will notify EU Member States concerned of the following:

- Annual safety reports via submission to CTIS
- Any SUSAR via reporting to the EudraVigilance database no later than 7 days or 15 days for a fatal or life-threatening SUSAR or non-fatal or non-life-threatening SUSAR, respectively, after becoming aware of that event. A SUSAR is defined as a serious adverse reaction, the nature, severity, or outcome of which is not consistent with the reference safety information.
- Any unexpected event that affects the benefit risk-profile of the study, but are not SUSARs, no later than 15 days of becoming aware of that event
- Any serious breach, as described in Section 10.1.1.1, no later than 7 days of becoming aware of that breach
- Any urgent safety measure, as described in Section 10.1.1.1, no later than 7 days of the measure being taken
- Any inspection report of a third-country authority concerning the study

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 25 years or longer if required by other European Union law.

10.9.2. France

Contrat Unique

1. GCP Training

   Before enrolling any participants, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice training course (“Pfizer GCP Training”) or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

   No participants or third-party payers will be charged for study intervention.

3. Urgent Safety Measures

   In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

4. Termination Rights

   Pfizer retains the right to discontinue development of mevrometostat at any time.

10.9.3. China

In compliance with HGRAC regulations, below is the list of analysis samples, vendors in China that will conduct testing and analysis of human genetic resource samples, and disposal of remaining samples:

Testing Name	Testing and Analysis Unit	Destruction Unit
ctDNA analyses	Shanghai Jince Clinical Laboratories Co., Ltd.	Shanghai Solid Waste Disposal Co., Ltd.

Note: For participants in China, sample collection and biomarker testing will not be performed until approval by HGRAC.

10.9.4. Japan

Implantable progestogen only-hormone contraception associated with inhibition of ovulation (Section 10.4.2) is not approved in Japan and therefore cannot be used in Japan.

10.9.5. Switzerland

For advanced therapy medicinal products (ATMPs) including oncological ATMPs investigated in a clinical trial, all cases of death that occur during the clinical trial in Switzerland must be reported to Swissmedic.

In order to comply with this requirement, all deaths (including fatal disease progression) for all ATMPs in this study that occur during the active reporting period must be reported to Pfizer Safety within 24 hours.

10.10. Appendix 10: RECIST v1.1 and PCWG3 Criteria

10.10.1. Assessment of Soft Tissue Disease

Modification of RECIST 1.1 (Eisenhauer et al, 2009) is a requirement for progression by imaging (omitting progression by digital photography or physical examination for superficial lesions), as described in Section 8.2.2. CT, MRI, X-ray, and nuclear medicine whole body bone scans (ie, radionuclide [Tc-99m] bone scintigraphy) will be reviewed at the investigational site by site staff trained for this trial and may be requested by the sponsor for peer review.

10.10.1.1. Image Included in the Assessment

- CT is the preferred method of assessment. IV contrast is required, unless the participant has an allergy to contrast that cannot be controlled with pre-medications. Anatomy scanned should include the chest (starting above the lung apices), abdomen, and pelvis (coverage to include the symphysis pubis). Slice thickness should be no greater than 5 mm, with no gaps. Details of the imaging protocols will be provided to sites in an imaging manual.

- If participants are unable to receive iodinated CT contrast, the preferred imaging is non-contrast CT of the chest, and MRI of the abdomen and pelvis with contrast.

- For non-infiltrative and distinct skin nodules, CT or MRI remains the preferred method of assessment. Digital photography will not be acceptable as a method of radiographic assessment of skin lesions. Discrete skin nodules that are not visible using CT or MRI should be considered non-measurable, nontarget lesions.

- The CT portion of a PET/CT can be considered acceptable for lesion measurement only in case it is documented that the CT performed as part of the PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

- Chest X-ray is permitted by the RECIST v.1.1 guidelines to assess lung lesions, but CT of the chest is strongly preferred.

- The same method of assessment, the same technique and, whenever possible, the same reviewer should be used to characterize each identified and reported lesion at baseline and during the study.

- For the purpose of this study, bone metastatic lesions, with the exception of lytic or mixed lytic-blastic bone lesions with soft tissue components seen on CT or MRI (see Section 10.10.1.3), should not be recorded as target or nontarget lesions according to RECIST 1.1 criteria, but they will be recorded at baseline and followed during treatment using PCWG3 criteria (see Section 10.10.2).

10.10.1.2. Overview of Assessment Process

The tumor burden will be documented at baseline. First, a reviewer will determine which lesions are appropriate for repeated quantitative assessment (measurable lesions). From the measurable lesions, the reviewer will choose a set of lesions to be followed quantitatively throughout the trial (target lesions). Target lesions will be selected based on size reproducibility of measurement, and whether the group of lesions represents the disease distribution. A value for the target tumor burden (sum of diameters) will be calculated. All tumor lesions that are not chosen for quantitative assessment will be documented and followed qualitatively as nontarget lesions.

At each follow-up visit, the reviewer will assess the target lesions by making measurements that correspond to measurements made at baseline. The Reviewer will verify the calculated sum of diameters, and the comparison of that sum to the baseline value (for determining partial response) and to the nadir, the smallest value seen until that point (to look for progression). The Reviewer will assess the nontarget lesions qualitatively and will search for new lesions. Information about target, nontarget, and new lesions will be combined to produce an overall visit response for the participant. After all visit assessments are completed, the reviewer will verify each visit response, and the visit responses will be used to derive information relevant to the endpoints (such as the date of progression and the best overall response).

10.10.1.3. Measurable and Non-Measurable Disease

Eligibility of lesions for quantitative assessment will be determined at baseline, with target lesions selected from the measurable lesions identified. After baseline, target lesions will always be assessed quantitatively, and nontarget lesions will be assessed qualitatively, with no further evaluation of measurability according to these definitions.

10.10.1.3.1. Measurable Disease

- A lesion is considered measurable if it has a diameter of ≥10 mm in the axial plane on CT or MRI, assuming that the slice thickness is 5 mm or less. If the slice thickness is greater than 5 mm, the minimum size increases to two times the slice thickness (slice thickness is the total distance between the tops of two adjacent slices, including any gap).

- Record changes in liver, lung, adrenal, and CNS separately.

- Malignant lymph nodes are considered measurable if the short axis (greatest dimension perpendicular to the longest diameter) is ≥15 mm at baseline.

- Record changes in pelvic (regional) lymph nodes vs extrapelvic (distant/metastatic) nodes separately.

If chest X-ray is used, a lesion is considered measurable if it is completely surrounded by aerated lung with clear boundaries, and has a diameter of 20 mm. In the unlikely event that a non-spiral CT scanner is used, the minimum size for measurability is 20 mm.

10.10.1.3.2. Non-Measurable Disease

- A lesion is considered evaluable, but not measurable, if it does not meet the measurability criteria described above, but which is a manifestation of malignancy that can be followed qualitatively as an indicator of disease progression or treatment response.
    - By RECIST v.1.1 definitions, a lymph node that has a short axis diameter of 10-14.9 mm is considered evaluable, but not measurable. Nodes with a short axis diameter of <10 mm are considered normal.
    - Palpable skin nodules that are not discernible using CT or MRI are considered evaluable but not measurable for this study.
- Non-measurable lesions are those the reviewer strongly believes to be malignant, but which do not meet the definitions above.
    - Bone lesions that are lytic or mixed lytic-blastic with soft tissue components seen on CT or MRI, and which meet size criteria above, may be measurable (Note: for the purpose of this study, bone lesions with no soft tissue components are excluded from the assessment by RECIST 1.1 and must be assessed with PCWG3 criteria, see Section 10.10.2).
    - Simple cysts are considered benign by default. Cystic metastases may be considered measurable, but solid lesions are preferred for selection as target.
    - Malignant ascites or pleural/pericardial effusions, lymphangitic infiltration of skin or lung, leptomeningeal disease, inflammatory breast disease, and infiltrative disease without clear borders are all examples of disease considered intrinsically non-measurable.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of previous treatment.

10.10.1.4. Baseline Lesion Selection and Documentation

- Target lesions will be chosen from among the measurable lesions. The lesions chosen should be the largest, most reproducible, and most representative of the overall disease distribution.
- All measurable lesions up to a maximum of 5 lesions total, and 2 lesions per organ, should be selected as target lesions (Note: any remaining measurable lesions will be evaluated as nontarget lesions, see below). Paired organs (lungs, kidneys, adrenals, ovaries) are considered one organ. The lymph nodes collectively are considered one organ.

- Non-nodal target lesions are measured (on CT or MRI) in the longest diameter in the axial plane and in the short axis diameter (greatest dimension perpendicular to the longest diameter). Malignant lymph nodes are always measured in the short axis diameter. The appropriate measurements for all target lesions chosen at baseline will be added to produce the sum of diameters.

- The sum of the diameters (long axes of all non-nodal target lesions with the short axes of all target lymph nodes lesions) for all target lesions will be reported as the baseline sum of the diameters. The baseline sum of the diameters will be used as reference by which to characterize the objective tumor response.

- Other disease present at baseline (including remaining measurable lesions not selected as target lesions) should be recorded as 'Nontarget lesions.' Multiple nontarget lesions in a single organ can be recorded as one entry during assessment, as nontarget lesions are assessed as a whole during follow-up.

10.10.1.5. Assessment of Response for Soft Tissue Disease

The overall response for each visit is a combination of target lesion response, nontarget lesion response, and the presence or absence of new lesions.

- Target lesions measurements should be performed in the same manner as at baseline. The sum of diameters of all target lesions must be calculated and compared to the baseline value and to the nadir value (the smallest value previously seen during the trial, which may be the same as baseline). The following special rules apply to lesion measurements:

  - If two target lesions coalesce the longest diameter measurement of the coalesced mass is used. If a large target lesion splits, the longest diameter of each fragment is measured, and the sum is used.

  - Measurements for target lesions that become small should continue to be recorded, as long as the Reviewer is confident in the accuracy. If a target lesion is considered to have completely disappeared, 0 mm should be recorded. If a lesion is determined to be present but too small to measure, the lesion status will indicate "too small to measure and judged to be less than 10 mm" and a default value of 5 mm will be used in the calculation of the sum of the diameters.

  - When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

- Target lesion response categories are defined as follows:

  - **CR**: Disappearance of all non-nodal target lesions. Target lymph nodes must reduce to <10 mm in short axis.

- **PR**: At least a 30% decrease in the sum of diameters of target lesions, compared to the sum at baseline.

- **PD**: At least a 20% increase in the sum of target lesion measurements, compared to the smallest sum on study (including baseline). Also, the absolute increase in the sum has to be at least 5 mm.

- **SD**: Neither PR nor PD criteria are met.

  - SD can follow PR only in rare cases, when the sum increases by less than 20% from the nadir, but enough that a previously seen 30% decrease from baseline no longer holds.

- **NE**: One or more target lesions cannot be assessed because assessment methods are not comparable to baseline (eg, change of modality), lesion visibility is poor due to image quality or lesion features (except where the lesion is too small to measure), or one or more lesions that were excised or locally irradiated have not reappeared or increased; and the other lesions do not show sufficient growth to qualify for PD on their own.

- **Nontarget lesion response** assessment is qualitative. Categories are defined as follows:

  - **CR**: Disappearance of all non-nodal non-target lesions. Nontarget lymph nodes must reduce to <10 mm in short axis.

  - **PD**: Unequivocal progression of nontarget lesions, evaluated as a whole, such that it is clear that treatment has failed and disease is progressing, regardless of the status of the target lesions.

  - **Non-CR/Non-PD**: Neither CR nor PD criteria are met.

  - **NE**: One or more nontarget lesions cannot be assessed because assessment methods are not comparable to baseline (eg, change of modality), lesion visibility is poor due to image quality or lesion features (except where the lesion is too small to measure), or one or more lesions that were excised or locally irradiated have not reappeared or increased; and the other lesions do not show sufficient growth to qualify for PD on their own.

- **New lesion response** is classified as present or not ("Yes" or "No"). The response is "Yes" if there is at least one lesion that the reviewer considers unequivocal new tumor.

  - Lesions that are equivocal (for example, due to small size) should not be considered new until they are confirmed by later scanning. Once confirmed, they can be retrospectively called new lesions at the time they were first seen.

- A lesion identified in an area not previously scanned is considered a new lesion.

- Overall visit response is determined by combining the target, nontarget, and new lesion responses using Table 10.

If an initial CR or PR is noted, confirmatory scans must be performed at least 4 weeks later.

10.10.1.6. Supplemental Investigations

If CR determination depends solely on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

10.10.1.7. Determination of Best Overall Response According to RECIST 1.1

The best overall response is the best response recorded from randomization until disease progression (taking as reference for progressive disease the smallest sum on study). For CR and PR, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow-up measurements must have met the SD criteria at least once after randomization at a minimum interval of 6 weeks.

10.10.2. Assessment of Bone Disease

10.10.2.1. Response Description of the PCWG Process for Assessment of Bone Lesions

The rules for evaluation of response and progression based on bone lesions were created by the PCWG and published as part of both PCWG2 and PCWG3 (Scher et al, 2016). However, for the purpose of the study, all bone lesions (with the exceptions of bone lesions with soft tissue components evaluated according to RECIST 1.1, see Section 10.10.1.5) are evaluated according to only the PCWG3 rules, including assessment at screening/baseline and evaluation of response.

10.10.2.2. Imaging Methods

The PCWG rules were designed based on the radionuclide (Tc-99m) bone scintigraphy. Other modalities, including FDG-PET, sodium fluoride PET, bone MRI, etc. may have individual advantages, but the PCWG rules were not created with the performance characteristics of these methods in mind and should not be used instead of radionuclide bone scan (ie radionuclide [^{99m}Tc] bone scintigraphy).

Only bone lesions seen by bone scan may be followed for assessment of bone tumor treatment response. Bone disease seen by CT only (not visible on bone scan) is presumed not to represent active disease and should not be documented as a bone lesion (sclerotic lesions seen on CT may represent healed disease or non- malignant confounders such as bone infarcts or other benign findings).

10.10.2.3. Documentation of Bone Lesions at Baseline

For this study, bone metastatic lesions - with the exception of lytic bone lesions or mixed lytic-blastic bone lesions with identifiable soft tissue components seen on CT or MRI – will be assessed by bone scan (ie, bone scintigraphy), and followed using the PCWG3 criteria, and not RECIST 1.1.

At baseline, bone lesions seen on bone scan with no soft tissue involvement should not be documented as nontarget lesions but reported via the PCWG3 CRF.

10.10.2.4. Assessment of Bone Response at Subsequent Imaging Time Points

At all follow-up timepoints, bone disease will be classified as PD, PDu, Non-PD, NED, or NE. The definitions are summarized in the following table and described in more detail below.

Table 8. Bone Disease Response Definitions

Bone Response	Definition
PD	Within the Flare window (<12 weeks): 2+2 Rule: at least 2 new lesions compared to baseline attributed to metastatic prostate cancer present at Week 9, followed by an additional 2 new lesions at Week 17 scan. OR Outside the Flare Window (>12 weeks): Two new lesions attributed to metastatic prostate cancer relative to the week 9 scan confirmed on a subsequent scan at least 6 weeks later.
PDu	Temporary marker of possible PD, to be updated to PD or non-PD once a subsequent scan is available. If this is the final visit, the visit response will remain PDu
Non-PD	There are <2 new bone lesions since baseline.
NE	The response cannot be evaluated (mixed response eg, some existing lesions disappear while new lesions appear, or a change in scan method since baseline , etc)
NED	No lesion attributed to metastatic prostate cancer seen on bone scan.

10.10.2.5. Descriptions of Bone Response Categories

NED: No lesions attributed to metastatic prostate cancer seen on bone scan at this visit. Either none were seen at baseline or all completely resolved on subsequent imaging.

Non-PD: At least one bone lesion attributed to metastatic prostate cancer is present on the scan at this visit but the conditions for progression have not been met because there are not at least two new lesions present since baseline.

PDu: At least two new lesions are present, but an additional scan is required for confirmation. This response category is meant as a placeholder that reflects temporary uncertainty and is updated to PD or non-PD once a subsequent bone scan is available.

PD: Within the Flare window (<12 weeks): 2+2 Rule: at least 2 new lesions attributed to metastatic prostate cancer present at Week 9, followed by an additional 2 new lesions at Week 17 scan.

OR

Outside the Flare Window (> 12 weeks): Two new lesions attributed to metastatic prostate cancer relative to the week 9 scan confirmed on a subsequent scan at least 6 weeks later.

Confirmation of Progression: Radiographic progression of bone lesions attributed to metastatic prostate cancer is defined as the appearance of ≥2 new bone lesions on radionuclide bone scan. When ≥2 new bone lesions are first observed, this is classified as PDu, which marks the possibility of progression that will be resolved by the next scan.

For New Lesions Within the Flare Window (<12 Weeks): After a scan classified as PDu within the first 12 weeks of treatment, if the next bone scan outside the flare window shows at least 2 additional new bone lesions attributed to metastatic prostate cancer (in addition to the new lesions seen on the prior scan), the initial progression is considered confirmed and the bone scan response updated to PD. Because this required at least 2 new lesions, followed by another 2 new lesions, this is known as the '2+2' rule.

If the next bone scan outside the flare window does not show at least two additional new bone lesions attributed to metastatic prostate cancer, the lesions seen on the prior scan within the flare window are considered to be preexisting lesions that became more visible because of the tumor flare phenomenon.

The Bone Response at the Prior Visit is Updated to Non-PD: The bone lesions seen within the flare window are ignored for the purposes of counting new lesions at later timepoints since they were not new. This may be referred to as re-baselining.

For New Lesions Outside the Flare Window (>12 Weeks): After a scan classified as PDu after the first 12 weeks of treatment, if at least 2 of the new lesions attributed to metastatic prostate cancer seen on that scan persist on the next bone scan performed at least 6 weeks later, this confirms the initial progression (Note: the new bone lesions do not all have to appear at the same time). The prior response is then updated to PD. If the new lesions have disappeared on this later scan, the prior response is updated to non-PD because these lesions are presumed to be non-malignant in nature. No re-baselining of lesions will occur in this scenario.

Superscan: The 'superscan' is a distinct imaging pattern of radioisotope uptake potentially mimicking a normal bone scan. It is characterized by diffuse, intense, and relatively symmetrical osseous radiotracer uptake, often with faint or absent tracer uptake in the urinary system and soft tissues. Additionally, renal radiotracer uptake in a 'superscan' is lower than that in the adjacent ribs, and bone metastases may not appear as distinct foci of metabolically active lesions (Manohar et al, 2017; Askari et al, 2024).

If there is a true superscan at screening/baseline, identifying new bone lesions and determining progression based on bone lesions may be impossible: a participant with a finding of superscan at screening/baseline will be considered not eligible for the study.

If a superscan occurs after baseline, the participant's bone response will be recorded as PD. No subsequent imaging will be required for confirmation, because a superscan is extremely unlikely to be caused by benign conditions or tumor flare.

Management Following Confirmed PD:

If repeat imaging does confirm PD, participants will be discontinued from study intervention, unless still deriving clinical benefit from study intervention, provided that the treating physician has determined that the benefit/risk for doing so is favorable. Please refer to Section 7.1 "Discontinuation of Study Intervention" for details.

Of particular note is the use of the 2+2 rule to distinguish flare from true progression.

10.10.2.6. Criteria for Evidence of Bone Progression

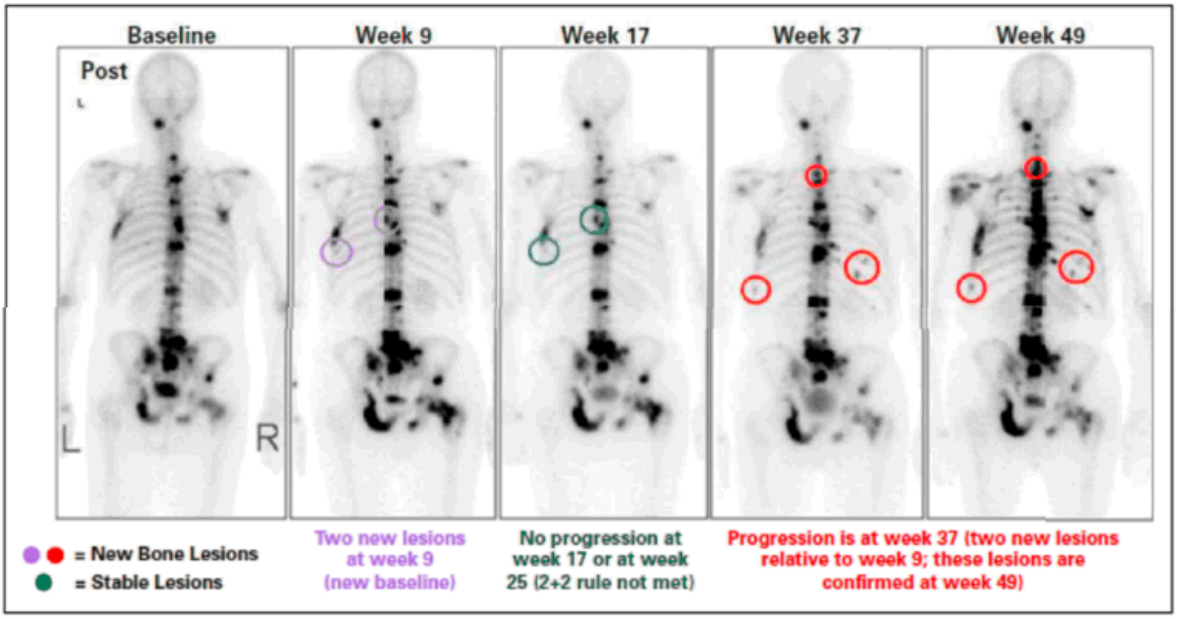
The table and figure below provide examples for the determination of bone progression.

Table 9. Criteria for Evidence of Bone Progression

Date Progression Detected (Visit)[a]	Criteria for Progression	Criteria to Confirm Progression	Criteria to Document Disease Progression
Week 9	2 or more new lesions compared to baseline bone scan	At least 6 weeks after progression identified or at Week 17 visit[b]	Persistence of at least 2 lesions seen at Week 9 AND 2 or more new bone lesions on bone scan compared to Week 9 scan
Week 17 or later	2 or more new lesions on bone scan compared to **Week 9** bone scan	At least 6 weeks after progression identified or at next imaging timepoint[b]	Persistence of at least 2 of the lesions identified as new compared to Week 9

a. Progression detected by bone scan at an unscheduled visit during the flare window should follow the confirmation criteria outlined for Week 9. Progression detected by bone scan at an unscheduled visit after the flare window should follow the confirmation criteria specified for Week 17 or later.
b. Confirmation must occur at the next available scan. When 3 or more successive unconfirmed PD events exist that are less than 6 weeks apart, but the 1st and 3rd unconfirmed PD events are ≥6 weeks apart, the 1st unconfirmed PD becomes the confirmed date of bone progression. Confirmation of PD must also occur at the next available scan after the flare window in case there is a single new bone lesion appearing at each of two subsequent scans (1+1).

Figure 1. Controlling for Flare by Applying the 2 + 2 Rule Using the First Post-Treatment Scan as Baseline



Adapted from (Scher et al, 2016)

In summary, PCWG3 criteria for bone disease consider the following:

- Tumor flare may occur within the first 12 weeks on treatment
- This implies that the bone scan obtained at Week 9 may present a number of bone lesions apparently new that were likely already present at baseline but not detected
- In this case, the Week 9 bone scan will be considered a new baseline for comparison of the subsequent scans
- Confirmed progression is determined by the presence of at least 2 new bone lesions (which may each occur at different timepoints) in subsequent scans as compared to baseline scan (if there was no flare). During the flare timeframe (<12 weeks) progression can only be confirmed by presence of 2 additional new lesions on the very next scan (Week 17).

10.10.3. Additional Notes

10.10.3.1. Radiographic Progression and Continued Clinical Benefit From Study Intervention

If a participant has confirmed radiographic progression according to RECIST 1.1 and/or according to PCWG3 criteria as defined above but is deriving a clinically meaningful benefit from the study intervention as assessed by investigator, the participant will be eligible to

continue receiving study intervention, provided that the treating physician has determined that the benefit/risk for doing so is favorable. In this case, if study intervention is continued, tumor imaging should continue as per local clinical practice. To ensure that participants are not exposed to unreasonable risks by continued use of the investigational agent despite progression of disease, ensure the following:

- There is an absence of symptoms and signs indicating clinically significant progression of disease,
- No decline in ECOG performance status, and
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression).

10.10.3.2. Clinical Progression

Participants requiring discontinuation of treatment due to global deterioration of their clinical status with no objective evidence of disease progression according to RECIST 1.1 nor according to PCWG3 criteria should not be reported as PD on tumor assessment CRFs. This should be indicated on the End of Treatment CRF as the "off treatment" reason due to global deterioration of clinical status. In this case, every effort should be made to document objective progression according to RECIST 1.1 and/or according to PCWG3 criteria even after discontinuation of treatment.

Adapted from (Eisenhauer et al, 2009).

Table 10. Objective Response Status at Each Evaluation

Target Lesions	Nontarget Disease	New Lesions	Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The following table will be used for participants with nontarget disease when PCWG3 evaluable bone disease is also present:

Table 11. Objective Response Status at Each Evaluation for Participants with Nontarget Disease Only

Nontarget Disease	New Lesions	Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

10.11. Appendix 11: ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair (Oken et al, 1982).

Table 12. ECOG Performance Status Categories

Status	Definition
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, eg, light housework 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

10.12. Appendix 12: Abbreviations

The following may be used in the protocol.

Abbreviation	Definition
^{99m}Tc	technetium-99m
ADT	androgen-deprivation therapy
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
AKI	acute kidney injury
ALT	alanine transaminase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AR	androgen receptor
ARPI	androgen receptor pathway inhibitor
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATMP	advanced therapeutic medicinal product
AUC_{tau}	area under plasma concentration-time curve over dosing interval
AV	atrioventricular
AxMP	auxiliary medicinal products
BFI	Brief Fatigue Inventory
BICR	blinded independent central review
BID	twice daily
BOR	best overall response
BP	blood pressure
BPI-SF	Brief Pain Inventory – Short Form
BUN	blood urea nitrogen
C	cycle
CBC	complete blood cell count
CD4	cluster of differentiation 4
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization

Abbreviation	Definition
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
CSR	clinical study report
CT	computed tomography, clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTIS	Clinical Trials Information System
ctRNA	circulating tumor RNA
CYP	cytochrome P450
D	day
DCT	data collection tool
DDI	drug-drug interaction
DDR	DNA damage response
DICI	drug-induced creatinine increase
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
DU	distribution unit
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDC	electronic data capture
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	ethylenediaminetetraacetic acid
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
eICD	electronic informed consent document
EORTC QLQ-PR25	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer 25
EOT	end-of-treatment
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality of Life 5-dimensions 5-level
E-R	exposure-response
eSAE	electronic SAE
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EZH2	enhancer of zeste homolog-2
EZH2i	enhancer of zeste homolog-2 inhibitor

Abbreviation	Definition
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FAPSI-8	FACT Advanced Prostate Cancer Index - 8
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FIH	first-in-human
FOXA1	forkhead box A1
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GnRH	gonadotropin releasing hormone
H3K27Me3	tri-methylated lysine 27 on histone 3
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HGRAC	Human Genome Resource Administration of China
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HSPC	hormone-sensitive prostate cancer
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IHD	ischemic heart disease
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IOCBP	individual of childbearing potential
IP	investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine system
IV	intravenously
KDIGO	Kidney Disease: Improving Global Outcomes
LBBB	left bundle branch block
LD	longest diameter

Abbreviation	Definition
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LPLV	last participant last visit
LTFU	long-term follow-up
MATE	multidrug and toxin extrusion protein
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MDR	medical device regulation
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MQI	medically qualified individual
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
NCI	National Cancer Institute
NE	non-evaluable
NED	no evidence of disease
NEPC	neuroendocrine prostate cancer
NIMP	non-investigational medicinal product
NR	not reached
NRS	numeric rating scale
OATP	organic anion transporting peptide
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
PCD	primary completion date
PCWG	Prostate Cancer Working Group
PD	pharmacodynamic(s); progressive disease
PDu	progressive disease (unconfirmed)
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PFS2	PFS on next line therapy
P-gp	P-glycoprotein
PI	principal investigator
PJP	pneumocystis jirovecii pneumonia
PK	pharmacokinetic(s)
PPD	personal protected data
PR	partial response; pulse rate
PRC	polycolmb repressor complex
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PS	performance status

Abbreviation	Definition
PSA	prostate-specific antigen
PSA50	decrease >50% from baseline in PSA
PSMA	prostate-specific membrane antigen
PSSA	Pfizer's SAE Submission Assistant
PT	prothrombin time
PTEN	phosphatase and tensin homolog
PVC	premature ventricular contraction
QD	daily
QoL	quality of life
QTcF	QTc (Fridericia method)
QTL	quality tolerance limit
RB	retinoblastoma
RBC	red blood cell
RCT	randomized clinical trials
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis set
Screat	serum creatinine
Scys	serum cystatin C
SD	stable disease
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SPECT	single-photon emission computed tomography
SRSD	single reference safety document
SSE	symptomatic skeletal event
SSID	single subject identifier
SUSAR	suspected unexpected serious adverse reaction
sT	serum testosterone
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
T-LBL	T-cell lymphoblastic lymphoma
TP53	tumor protein 53
UACr	urine albumin/creatinine ratio
ULN	upper limit of normal
UPCr	urine protein/creatinine ratio
US	United States
UVB	ultraviolet B
WBC	white blood cell
WT	wild type

11. REFERENCES

American Cancer Society. Key Statistics for Prostate Cancer. Available from: https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html. Accessed: 9 Oct 2024.

Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2019;37(32):2974-86.

Armstrong AJ, Azad AA, Iguchi T, et al. Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2022;40(15):1616-22.

Askari E, Shakeri S, Roustaei H, et al. Superscan Pattern on Bone Scintigraphy: A Comprehensive Review. Diagnostics (Basel). 2024;14(19).

Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019;381(1):13-24.

Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. J Clin Oncol. 2021;39(20):2294-303.

Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap. 1994;23(2):129-38.

Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika. 1934;26(4):404-13.

Dardenne E, Beltran H, Benelli M, et al. N-Myc Induces an EZH2-Mediated Transcriptional Program Driving Neuroendocrine Prostate Cancer. Cancer Cell. 2016;30(4):563-77.

Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019;381(2):121-31.

Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9(2):105-21.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Esper P, Mo F, Chodak G, et al. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology. 1997;50(6):920-8.

FDA. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers Available from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed: 22 Oct 2024.

Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. Lancet. 2022;399(10336):1695-707.

Fong KW, Zhao JC, Kim J, et al. Polycomb-Mediated Disruption of an Androgen Receptor Feedback Loop Drives Castration-Resistant Prostate Cancer. Cancer Res. 2017;77(2):412-22.

Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA. 2005;294(4):433-9.

Freedland SJ, Sandin R, Sah J, et al. Treatment patterns and survival in metastatic castration-sensitive prostate cancer in the US Veterans Health Administration. Cancer Med. 2021;10(23):8570-80.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

Inker LA, Eneanya ND, Coresh J, et al. New equations to estimate GFR without race. Suppl Appendix; Table S10. N Engl J Med. 2021:1-87.

Iswaran TJ, Imai M, Betton GR, et al. An overview of animal toxicology studies with bicalutamide (ICI 176,334). J Toxicol Sci. 1997;22(2):75-88.

James ND, Spears MR, Sydes MR. Abiraterone in Metastatic Prostate Cancer. N Engl J Med. 2017;377(17):1696-7.

Kim J, Lee Y, Lu X, et al. Polycomb- and Methylation-Independent Roles of EZH2 as a Transcription Activator. Cell Rep. 2018;25(10):2808-20 e4.

Ku SY, Rosario S, Wang Y, et al. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. Science. 2017;355(6320):78-83.

Kupelian PA, Buchsbaum JC, Elshaikh M, et al. Factors affecting recurrence rates after prostatectomy or radiotherapy in localized prostate carcinoma patients with biopsy Gleason score 8 or above. Cancer. 2002;95(11):2302-7.

Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol. 2018;36(11):1080-87.

Lowrance W, Dreicer R, Jarrard DF, et al. Updates to Advanced Prostate Cancer: AUA/SUO Guideline (2023). J Urol. 2023;209(6):1082-90.

Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2019 with focus on breast cancer. Ann Oncol. 2019;30(5):781-87.

Manohar PR, Rather TA, Khan SH, et al. Skeletal Metastases Presenting as Superscan on Technetium 99m Methylene Diphosphonate Whole Body Bone Scintigraphy in Different Type of Cancers: A 5-Year Retro-prospective Study. World J Nucl Med. 2017;16(1):39-44.

Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer. 1999;85(5):1186-96.

National Cancer Institute Surveillance E, and End Results Program. Cancer Stat Facts: Prostate Cancer. Available from: https://seer.cancer.gov/statfacts/html/prost.html. Accessed: 9 Oct 2024.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

Park SH, Fong KW, Kim J, et al. Posttranslational regulation of FOXA1 by Polycomb and BUB3/USP7 deubiquitin complex in prostate cancer. Sci Adv. 2021;7(15).

Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(9):1119-34.

Saad F, Vjaters E, Shore N, et al. Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial. J Clin Oncol. 2024;10.1200/JCO-24-01798:JCO2401798.

Sayegh N, Swami U, Agarwal N. Recent Advances in the Management of Metastatic Prostate Cancer. JCO Oncol Pract. 2022;18(1):45-55.

Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18.

Schweizer MT, Penkov K, Choudhury AD, et al. Phase 1 trial of mevrometostat (PF-06821497), a potent and selective inhibitor of enhancer of zeste homolog 2 (EZH2), in castration-resistant prostate cancer (CRPC) [abstract]. Journal of Clinical Oncology. 2024;42:5061.

Schweizer MT, Calvo M, Moreno V, et al. Mevrometostat (PF-06821497), an enhancer of zeste homolog 2 (EZH2) inhibitor, in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC): A randomized dose-expansion study [abstract]. Journal of Clinical Oncology. 2025;43:LBA138.

Shankar E, Franco D, Iqbal O, et al. Dual targeting of EZH2 and androgen receptor as a novel therapy for castration-resistant prostate cancer. Toxicol Appl Pharmacol. 2020;404:115200.

Shore ND, Moul JW, Pienta KJ, et al. Biochemical recurrence in patients with prostate cancer after primary definitive therapy: treatment based on risk stratification. Prostate Cancer Prostatic Dis. 2024;27(2):192-201.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.

Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33.

Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022;386(12):1132-42.

Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33(28):3199-212.

Takano K, Yamamura H, Suzuki M, et al. Teratogenic effect of chlormadinone acetate in mice and rabbits. Proc Soc Exp Biol Med. 1966;121(2):455-7.

van Andel G, Bottomley A, Fossa SD, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer. 2008;44(16):2418-24.

van Leenders GJ, Dukers D, Hessels D, et al. Polycomb-group oncogenes EZH2, BMI1, and RING1 are overexpressed in prostate cancer with adverse pathologic and clinical features. Eur Urol. 2007;52(2):455-63.

Varambally S, Dhanasekaran SM, Zhou M, et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. Nature. 2002;419(6907):624-9.

Xu K, Wu ZJ, Groner AC, et al. EZH2 oncogenic activity in castration-resistant prostate cancer cells is Polycomb-independent. Science. 2012;338(6113):1465-9.

Yang YA, Yu J. EZH2, an epigenetic driver of prostate cancer. Protein Cell. 2013;4(5):331-41.

Zhao JC, Yu J, Runkle C, et al. Cooperation between Polycomb and androgen receptor during oncogenic transformation. Genome Res. 2012;22(2):322-31.