Medivation, Inc.

Study Title:	A Phase 3, Randomized, Efficacy and Safety Study of Enzalutamide Plus Leuprolide, Enzalutamide Monotherapy, and Placebo Plus Leuprolide in Men With High-Risk Nonmetastatic Prostate Cancer Progressing After Definitive Therapy
Protocol Identifier:	MDV3100-13 (C3431004)
Phase:	3
Investigational Product:	Enzalutamide (formerly MDV3100)
Indication:	Prostate Cancer
Sponsor:	Medivation, Inc., a wholly owned subsidiary of Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001 Telephone: +1 (212) 573-2323 Medivation and Astellas Pharma Global Development, Inc. are in a partnership to codevelop enzalutamide for the treatment of cancer
Reference Numbers:	United States IND CCI EudraCT 2014-001634-28
Original Protocol:	v1.0 – 03 Sep 2014
Amendment 1:	v2.0 – 09 Mar 2017
Amendment 2:	v3.0 – 20 Aug 2018
Amendment 3:	v4.0 – 31 Mar 2020
Amendment 4:	v5.0 – 29 Oct 2021
Amendment 5:	v6.0 – 18 May 2023
This study will be conducted according to the principles of Good Clinical Practice as described in International Council for Harmonisation guidelines, including the archiving of essential documents.	

Confidentiality Statement
The information contained in this document and all information provided to you related to enzalutamide are the confidential and proprietary information of Medivation, Inc. ("Medivation") and except as may be required by federal, state, or local laws or regulations, may not be disclosed to others without prior written permission of Medivation. However, the investigator may disclose such information to supervised individuals working on enzalutamide, provided such individuals agree to be bound to maintain the confidentiality of such information.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 5 (18 May 2023)

Overall Rationale for the Amendment: Primary endpoint analyses demonstrated that the primary efficacy endpoint of metastasis free survival (MFS) was established and the safety profile of enzalutamide was confirmed, therefore, the treatment codes for all patients will be unblinded and an open-label treatment period is being implemented. The final analysis of the key secondary endpoint overall survival (OS) will be performed as planned. Patients will continue to receive their originally assigned study treatment in this open-label study period. Patients assigned to the placebo plus leuprolide arm will no longer take the placebo capsules. No crossover treatment will be implemented.

For patients whose cancer has not progressed radiographically, locally (change was effective as of 31 March 2023) performed scans (CT/MRI and bone scan) will be conducted until the patient's cancer progresses radiographically. Scans read centrally by blinded independent central reviewer (BICR) ceased as of 31 March 2023. Prostate-specific antigen (PSA) levels will also be done at a local lab and monitored by the investigator per standard of care (SOC). Additionally, patients who are in treatment suspension (due to prior undetectable PSA at study Week 36) will have their PSA values done at the local lab and will be evaluated by the investigator every 3 months for possible treatment reinitiation per protocol criteria.

Patients who do not participate in the open-label treatment period (eg, patients who decide to discontinue treatment, withdraw consent from treatment, or patients who the investigator does not believe are continuing to benefit from study drugs) will continue long-term follow-up assessments per protocol. Long-term follow-up data including survival status, new antineoplastic therapies for prostate cancer, skeletal-related events, and progression on first subsequent therapy (PFS2) will be collected every 12 weeks until the final OS analysis. The associated endpoints will be summarized descriptively at the time of the final OS analysis.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Updates regarding the open-label and double-blind periods were added.	The double-blind period has concluded and the open-label period is ongoing. The complete details for the conduct of the open-label period are provided in Supplement 1: Open-Label Study Period. The completed double-blind protocol has not changed.	Synopsis
New section was added for description of activities during open-label period.	Complete details for the conduct of the open-label period are provided	Section 18. Supplement 1: Open-Label Study Period
Non-substantial Modification(s)		
Abbreviations section was moved to Appendix 7 and new abbreviations were added.	Protocol template structure updated	Appendix 7

Description of Change	Brief Rationale	Section # and Name
Updates regarding the double-blind and open-label periods were added.	Clarification regarding treatment periods.	Section 5.2
Regulatory and Ethical Considerations section was updated.	To comply with current regulations.	Section 13.1
Case Report Forms section was updated.	A clarification was added regarding deletion of participant data.	Section 13.2.2
Retention of Records section was updated.	To comply with current regulations.	Section 13.5
Dissemination of Clinical Study Data information was moved from Section 14 to Section 13.7 and updated.	To comply with current regulations.	Sections 13.7 and 14
Publication Policy information was moved from Section 14 to Section 13.8 and updated.	To comply with current regulations.	Sections 13.8 and 14
Investigator Signature page was removed from Protocol and provided separately.	To comply with current regulations.	Section 16
Minor administrative, editorial, typographical, or formatting changes	Updated for grammatical correctness, consistency, and/or clarity as applicable, including update to Protocol Table of Contents	Global

SYNOPSIS

Title of Study: A Phase 3, Randomized, Efficacy and Safety Study of Enzalutamide Plus Leuprolide, Enzalutamide Monotherapy, and Placebo Plus Leuprolide in Men With High-Risk Nonmetastatic Prostate Cancer Progressing After Definitive Therapy

Protocol Identifier: MDV3100-13 (C3431004)

Phase of Development: 3

Number of Patients: Approximately 1050 (350 per group)

Study Centers: Approximately 200 (international)

Study Objectives:
All efficacy and safety objectives will compare enzalutamide plus leuprolide and enzalutamide monotherapy versus placebo plus leuprolide.

Primary Endpoint: Metastasis-free survival (MFS) between enzalutamide plus leuprolide and placebo plus leuprolide.

Key Secondary Endpoints:
To evaluate efficacy, as measured by the following:

- MFS between enzalutamide monotherapy versus placebo plus leuprolide;
- Time to prostate-specific antigen (PSA) progression;
- Time to first use of new antineoplastic therapy;
- Overall survival.

Other Secondary Endpoints:

- Time to distant metastasis;
- Proportion of patients per group who remain treatment-free 2 years after suspension of study drug treatment at week 37 due to undetectable PSA;
- Proportion of patients per group with undetectable PSA 2 years after suspension of study drug treatment at week 37 due to undetectable PSA;
- Proportion of patients per group with undetectable PSA at 36 weeks on study drug;
- Time to resumption of any hormonal therapy following suspension at week 37 due to undetectable PSA;
- Time to castration resistance;
- Time to symptomatic progression;
- Time to first symptomatic skeletal event;
- Time to clinically relevant pain;
- Quality of life;
- Safety.

Exploratory Endpoint :

- Progression-free survival on first subsequent therapy (PFS2).

OPEN-LABEL PERIOD	As the study met the primary efficacy endpoint of MFS and the established safety profile of enzalutamide was confirmed, the treatment codes for all patients will be unblinded. Patients remaining on study treatment will continue to receive their originally assigned study treatment in an open-label study treatment period. Patients assigned to the placebo plus leuprolide arm will no longer take the placebo capsules. No crossover treatment will be implemented. For patients whose cancer has not progressed radiographically, locally performed scans (computed tomography [CT]/magnetic resonance imaging [MRI] and bone scan) will be performed per each institution's standard of care until the patient's cancer progresses radiographically. PSA levels will be done at a local lab and

	monitored by the investigator per standard of care. Patients who are in treatment suspension will have their assigned treatment reinitiated if subsequent local laboratory PSA values increase to ≥2.0 ng/mL for patients with prior prostatectomy or ≥5.0 ng/mL for patients who had prior radiation therapy. Patients will not continue in the open-label period if they have had radiographic cancer progression. Patients who do not participate in the open-label period or withdraw consent for further treatment will continue safety follow-up (within approximately 30 days after last dose) and long-term follow-up assessments per protocol. Long-term follow-up data (including survival status, new antineoplastic therapies for prostate cancer, skeletal-related events, and PFS2) will be collected every 12 weeks. Day 1 of the open-label period will occur after consent is signed and eligibility is verified. No crossover treatment will be implemented. Sites must have all open-label Day 1 visits completed within 16 weeks after Institutional Review Board (IRB)/Ethics Committee (EC) approval of this protocol amendment. Patients who will receive any other treatment for prostate cancer after unblinding will not be eligible for the open-label enzalutamide period (these patients will remain in the study, complete safety follow-up, and subsequently commence long-term follow-up). The complete details for the conduct of the open-label period are provided in Supplement 1: Open-Label Study Period.
DOUBLE-BLIND PERIOD	The double-blind period has concluded and the open-label period is ongoing. The completed double-blind protocol has not changed.

Methods: This is an international, phase 3, randomized study of enzalutamide plus leuprolide, enzalutamide monotherapy, and placebo plus leuprolide in approximately 1050 men with high-risk nonmetastatic prostate cancer progressing after radical prostatectomy or radiotherapy or both. No prior cytotoxic chemotherapy or androgen deprivation therapy (with exceptions) is allowed. The primary efficacy endpoint is MFS.

Central randomization (1:1:1) will be used to assign patients to one of the following study drug treatments:

- Enzalutamide plus leuprolide;
- Enzalutamide monotherapy;
- Placebo plus leuprolide.

Randomization will be stratified by screening PSA ≤10 ng/mL versus >10 ng/mL, PSA doubling time ≤3 months versus >3 to ≤9 months, and prior hormonal therapy versus no prior hormonal therapy. Treatment with enzalutamide monotherapy will be open label. Treatment with enzalutamide and placebo will be double-blinded in combination with open-label leuprolide.

Study drug treatments will be administered as follows, depending on treatment assignment:

- Enzalutamide will be administered as four 40 mg soft gelatin capsules by mouth once daily (160 mg/day) with or without food.
- Placebo capsules, identical in appearance to enzalutamide capsules, will be administered in the same manner as enzalutamide.
- Leuprolide acetate (leuprorelin acetate), 22.5 mg will be given as a single intramuscular or subcutaneous injection once every 12 weeks (for a minimum of 3 doses, providing 36 weeks of treatment).

PSA will be monitored throughout the study, and at week 37, study drug treatment will be suspended for patients whose PSA values are undetectable (<0.2 ng/mL) at week 36 as determined by the central laboratory; PSA and testosterone will be measured every 3 months thereafter by the central laboratory. As the PSA values will not be provided to study sites or patients, study sites will be notified whether a patient's PSA value meets the specified threshold to determine whether or not to continue or suspend study drug treatment at week 37. Study drug treatment may be suspended only once (at week 37) due to undetectable PSA and will be reinitiated if subsequent central laboratory PSA values increase to ≥2.0 ng/mL for patients with prior prostatectomy or ≥5.0 ng/mL for patients without prostatectomy. Study sites will be notified if the PSA value meets the threshold specified for reinitiation of study drug treatment. Patients with detectable PSA values at week 36 will continue treatment without suspension until permanent treatment discontinuation criteria are met.
All patients will have safety follow-up- after permanent discontinuation of randomized study drug treatment. Safety follow-up should occur approximately 30 days after the last dose of randomized study drug. Long-term follow-up will occur after safety follow-up (every 12 weeks based on the 12-week visit schedule determined at randomization).

Throughout the study, investigators are encouraged not to obtain PSA assessments at their local laboratory. Beginning 22 Feb 2019, investigators started to be notified when any of their patients develop protocol defined PSA progression with a PSA doubling time (PSADT) ≤10 months while on study treatment based on central laboratory assessments. Randomized study drug treatment must be permanently discontinued upon initiation of cytotoxic chemotherapy or antiandrogen therapy (eg, bicalutamide, nilutamide, or flutamide). All patients who permanently discontinue study drug treatment will remain in the study, complete safety follow-up, and subsequently commence long-term follow-up, which may include imaging for patients who have not yet had confirmed radiographic progression.

Patients are strongly encouraged to obtain an adequate intake of dietary calcium (at least 1000 mg per day, including supplements if necessary) and vitamin D (at least 800-1000 international units per day for adults 50 years of age and older) and to engage in regular exercise to maintain muscle strength and bone density.

Study Assessments:
The following assessments of prostate cancer status will be made during the course of the study: soft tissue disease on computed tomography (CT) scan or on magnetic resonance imaging (MRI), bone disease on whole-body radionuclide bone scans, survival status, PSA values, testosterone, resumption of any hormonal therapy, new antineoplastic therapy and surgery/interventions for prostate cancer, symptomatic skeletal events, pain using the Brief Pain Inventory (Short Form), and quality of life using the Functional Assessment of Cancer Therapy Prostate (FACT-P) questionnaire, European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L), and the Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) module.

Imaging with CT or MRI for soft tissue disease and whole-body radionuclide bone scans for bone disease will be conducted every 6 months to assess for radiographic progression. A bone scan will assess 5 regions of the skeleton including skull, thorax, spine, pelvis, and extremities. Radiographic progression for bone disease is defined as the appearance of 1 or more metastatic lesion on bone scan. Confirmation with a second imaging modality (plain film, CT, or MRI) will be required when bone lesions are found in a single region on the bone scan. Appearance of metastatic lesions in 2 or more of the 5 regions on a bone scan will not require confirmation with a second imaging modality. Assessment of soft tissue disease will be by CT or MRI. Radiographic progression for soft tissue disease is defined by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).

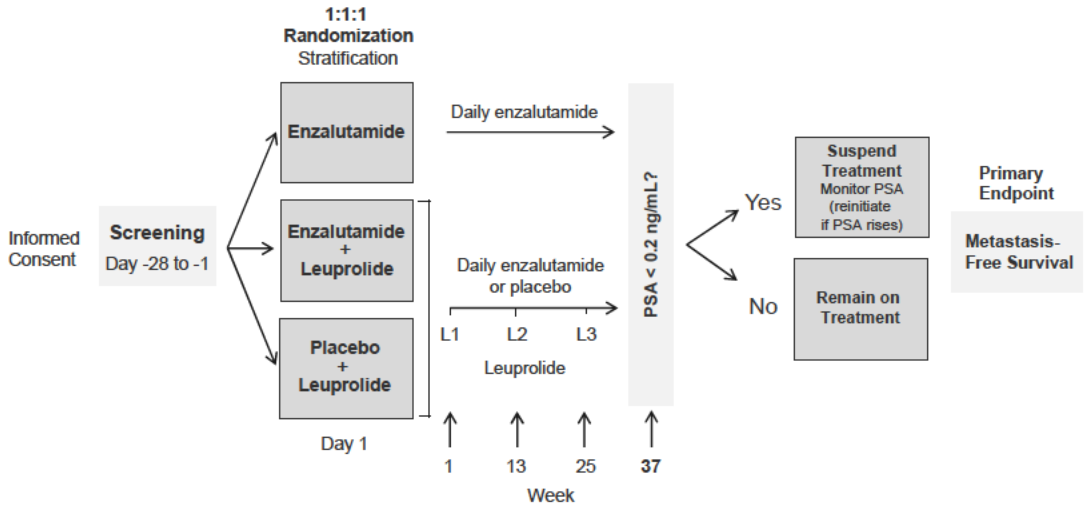
Determination of radiographic progression: Radiographic assessments will be obtained approximately every 6 months from the date of randomization until radiographic progression. Scans may be obtained sooner if disease progression is clinically suspected. The study films (CT/MRI and bone scan) will be read at the local study site and submitted to central imaging for independent, blinded radiology review. 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.

Patients should remain on study treatment until radiographic progression is confirmed by central imaging. Permanent treatment discontinuation due to radiographic progression will be based solely on blinded central reader assessment.

Assessments of safety will include adverse events, clinical laboratory tests, physical examinations, and vital signs. An independent data monitoring committee will periodically monitor safety data.

Long-term follow-up assessments will include monitoring survival status, subsequent therapies for prostate cancer, and symptomatic skeletal events.

Study Schematic:



Primary Assessment: Radiographic imaging approximately every 6 months

Key Eligibility Criteria:

The patients to be included in this study will have prostate cancer initially treated with curative intent by radical prostatectomy or radiotherapy or both, followed by disease recurrence as manifested by rising PSA. The prognostic factors to select men at high risk for morbidity and mortality from prostate cancer include PSA doubling time (≤9 months) as calculated by the sponsor and screening PSA. The screening PSA by the central laboratory must be ≥1 ng/mL for patients who had prior radical prostatectomy (with or without radiotherapy) and at least 2 ng/mL above the nadir for patients who had prior primary radiotherapy only. All patients must have serum testosterone values ≥150 ng/dL. Patients will have no prior or present evidence of distant metastatic disease; no prior hormonal therapy unless given as neoadjuvant/adjuvant therapy to treat prostate cancer ≤36 months in duration and ≥9 months before randomization, or as a single dose or a short course (≤6 months) of hormonal therapy given for rising PSA ≥9 months before randomization; and no prior cytotoxic chemotherapy or systemic biologic therapy, including immunotherapy, for prostate cancer.

Test Product, Dose, and Mode of Administration:

Enzalutamide; chemical name 4-{3-[4-cyano-3-(trifluoromethyl) phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide. Enzalutamide 160 mg/day will be administered as four 40-mg soft gelatin capsules by mouth once daily with or without food. Leuprolide acetate (leuprorelin acetate), 22.5 mg for 3-month administration, given as a single intramuscular or subcutaneous injection once every 12 weeks. If leuprolide acetate, 22.5 mg for 3-month administration is not available, a suitable substitute may be allowed upon approval by the medical monitor.

The sponsor will provide enzalutamide capsules for unblinded and blinded treatment groups and leuprolide for the blinded treatment group.

Reference Therapy, Dose, and Mode of Administration:
Placebo capsules, identical in appearance to enzalutamide capsules, administered in the same manner as enzalutamide. The sponsor will provide blinded placebo capsules for the blinded treatment group. Leuprolide injections will not be blinded with a placebo injection.

Duration of Treatment:
Study drug treatment will continue uninterrupted in the absence of disease progression until the central laboratory PSA evaluation at week 36. Based on PSA values at week 36, study drug treatment will either continue or be suspended at week 37. Following week 37, PSA and testosterone will be measured every 3 months by the central laboratory. Study drug treatment will be reinitiated if subsequent central laboratory PSA values increase to ≥2.0 ng/mL for patients with prior prostatectomy or ≥5.0 ng/mL for patients without prostatectomy. Study drug treatment may be suspended only once during this study (at week 37) due to undetectable PSA. Patients with detectable PSA values at week 36 will continue treatment without suspension until permanent treatment discontinuation criteria are met.

Statistical Methods:

The primary efficacy analysis of MFS will be conducted using the intent to treat (ITT) population, defined as all patients randomly assigned to study treatment. Central randomization will be used, and treatment allocation will be 1:1:1. Randomization will be stratified as described in the Methods section. All efficacy analyses will incorporate the stratification factors used at randomization unless otherwise noted. The analytical approach will be described in detail in the statistical analysis plan. Treatment group comparisons will be between the combination arm of enzalutamide plus leuprolide versus placebo plus leuprolide and between enzalutamide monotherapy therapy versus placebo plus leuprolide.

Primary Efficacy Endpoint:
For the primary endpoint, MFS, the stratified log-rank test will be used to compare enzalutamide plus leuprolide versus placebo plus leuprolide. The primary efficacy endpoint is MFS using independent, blinded central radiology reviewer assessment of radiographic progression. MFS is defined as the duration of time in months between randomization and the earliest objective evidence of radiographic progression by central imaging or death.

The primary endpoint analysis will be performed when at least 197 MFS events occur in the 3 treatment groups combined, at which time approximately 142 MFS events are expected to occur in the 2 blinded treatment groups combined for the primary hypothesis.

Secondary Efficacy Endpoints:
A hierarchical approach will be utilized to preserve the family wise type I error rate. The family-wise type I error adjustment for key secondary endpoint analyses will be described in detail in the statistical analysis plan. Kaplan–Meier methods will be used to describe the distributions of all time-to-event endpoints with inferential testing conducted using the stratified log-rank test. If the combination demonstrates statistical significance compared to placebo plus leuprolide for MFS, alpha will be split to allow for the testing of key secondary endpoints between these arms and key secondary endpoints between enzalutamide monotherapy versus the placebo plus leuprolide. All secondary endpoints will be reported at the time of the primary MFS analysis except for symptomatic skeletal related events, which will be reported at the time of the final overall survival analysis.

Key Secondary Endpoints
Metastasis-free survival between enzalutamide monotherapy versus placebo plus leuprolide will be defined as above for the combination comparison.

Time to PSA progression is defined as the time from randomization to the date of the first PSA value demonstrating progression, while patients are on study treatment, which is subsequently confirmed at least 3 weeks later.

In patients who DO NOT have treatment suspended due to undetectable PSA at week 36: Those with PSA decline at week 25, the PSA progression date is defined as the date that a ≥25% increase and an absolute increase of ≥2 µg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline by week 25).

For patients who have treatment suspended due to undetectable PSA at week 36: Following treatment suspension and reinitiation of study drug, the PSA progression date is defined as the date that a ≥25% increase and an absolute increase of ≥2 µg/L (2 ng/mL) above the nadir at week 36 is documented, which is confirmed by a second consecutive value obtained at a subsequent study visit.

Time to first use of new antineoplastic therapy is defined as the time from randomization to first use of new antineoplastic for prostate cancer. Patients 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. This will include medications used specifically for prostate cancer treatment including hormonal treatments, immunotherapy, chemotherapy and investigative agents.

Overall survival is defined as the time between randomization and death of any cause. Overall survival will be compared between treatment groups using a 2-sided stratified log-rank test. Long-term follow-up data (survival status and skeletal related events and new prostate cancer therapies) will be collected every 12 weeks up until the final analysis of OS.

Other Secondary Endpoints
The time to distant metastasis is defined as the time in months from randomization to the earliest objective evidence of distant soft tissue metastases or metastatic bone disease by central imaging. Soft tissue disease including lymph nodes above the aortic bifurcation and outside the pelvis and any bone metastases will be counted as distant metastases.

The proportion of patients who remain treatment-free 2 years after suspension of study drug treatment at week 37 due to undetectable PSA will be compared between treatment groups using the stratified Cochran-Mantel-Haenszel test.

The proportion of patients per group with undetectable PSA at 36 weeks will be compared between treatment groups using the stratified Cochran-Mantel-Haenszel test.

The time to resumption of any hormonal therapy is defined as the time between the date of treatment suspension at week 37 due to undetectable PSA and the date that hormonal therapy is restarted.

The time to first symptomatic skeletal event is 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, or new use of opiate and/or systemic antineoplastic therapy due to bone pain, 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 overall survival analysis.

Time to castration resistance applies only to patients receiving leuprolide treatment and is defined as the first occurrence of radiographic disease progression, PSA progression (as defined above) or symptomatic skeletal event with castrate levels of testosterone (<50 ng/dL).

Time to symptomatic progression is defined as the time from randomization to development of a skeletal-related event, worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy, or development of adverse events and clinically significant signs and/or symptoms due to loco-regional tumor progression requiring opiate use, surgical intervention or radiation therapy, whichever occurs first.

Time to clinically relevant pain (defined as a 2-point increase from baseline on the Brief Pain Inventory [Short Form] question 3) and quality of life (measured by the time to a 10-point decline in global FACT-P quality of life score) will be compared between treatment groups using a 2-sided log-rank test. FACT-P, EQ-5D-5L, and QLQ-PR25 data will be summarized descriptively by study visit.

Exploratory Endpoints

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 occurred first, while the patient 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.

Safety will be evaluated by the incidence of serious adverse events, incidence and severity of adverse events, incidence of permanent treatment discontinuation due to adverse events, and incidence of new clinically significant changes in clinical laboratory values and vital signs. Safety data will be collected from the first dose of any randomized study drug treatment through 30 days after the last dose (ie, permanent discontinuation) of randomized study drug treatment, and includes the period following potential protocol-specified suspension and potential resumption of study drug treatment through subsequent permanent treatment discontinuation. All safety analyses will be performed using the safety population, defined as all patients who receive any amount of study drug. Adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and severity. Descriptive statistics will be used.

Laboratory values will be classified for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4. Laboratory shift tables of baseline results to each subsequent visit will be produced as appropriate.

Sample Size Considerations:
The following assumptions are used in determining the sample size for this study:

- Overall type I error rate: 0.05;
- Patient accrual rate: An adaptive enrollment rate has been modified into two arms to fit into EAST v6.4 software from Cytel;
- Randomization: 1:1:1;
- Median MFS for the control group: 55 months.

An observed 142 MFS events in the 2 blinded treatment groups will provide approximately 90% power to detect a target hazard ratio of 0.58 using a 2-sided log-rank test with a 0.05 level of significance. This target hazard ratio corresponds to a difference of approximately 40 months in median MFS assuming an exponential distribution in the duration of MFS and a constant hazard rate for each group. For the key secondary hypothesis of MFS for the monotherapy arm, the target effect size, and expected number of MFS events will be the same as the primary hypothesis in the combination arm. As a 2-sided alpha of 0.03 will be utilized for the monotherapy comparison, the power for this analysis will be 86% with 142 MFS events observed. At the time of the final analysis, at least 197 MFS events total are required for the 3 treatment groups. An enrollment of approximately 1050 patients (350 in each group) is required to achieve the targeted total of 197 MFS events allowing for a 5% loss to follow-up as outlined in the Statistical Analysis Plan.

The actual enrollment of 1068 patients will also allow for an assessment for the key secondary endpoint of OS, assuming a 5-year OS rate of 80% for the control arm and hazard ratio of 0.67.

The significance level associated with the test of OS, in blinded treatment arm and monotherapy arm comparisons, will depend on the outcome of the key secondary endpoints. If the key secondary endpoints of time to PSA progression and time to first use of antineoplastic therapy, for the blinded treatment arms, are statistically significant then an alpha of 0.02 will be contributed to the comparison of OS according to the gatekeeping procedure. Similarly, if the key secondary endpoints of MFS, time to PSA progression, and time to first use of antineoplastic therapy, for the monotherapy treatment arm, are statistically significant then an alpha of 0.03 will be contributed to the comparison of OS. With 191 deaths the power to detect a hazard ratio of 0.67 is 79.0% (if all key secondary endpoints are significant for both the blinded arm and monotherapy arm comparisons), 72.3% (if the key secondary endpoints are significant for the monotherapy arm only) or 67.0% (if the key secondary endpoints are significant for the blinded arms only) using a 2-sided log-rank test at a significance level of 0.05, 0.03 or 0.02, respectively, and a 2-look group sequential design with a Haybittle-Peto efficacy boundary.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

CCI

1. INTRODUCTION

1.1. Background

Prostate cancer progresses through a series of characteristic clinical states that reflect both the natural history of the disease and response to treatment.[1] Following the initial evaluation and diagnosis of prostate cancer, approximately 90% of men in the United States undergo primary localized treatment with curative intent.[2] Of those, approximately one-third experience rising prostate-specific antigen (PSA) or biochemical recurrence after primary therapy.[3] This rise in PSA uniformly represents recurrence of prostate cancer, the likely presence of micrometastatic disease, and an increased risk of morbidity and mortality from prostate cancer.[4],[5]

Despite the recurrence of prostate cancer, most men with biochemical recurrence after primary therapy do not develop metastases or die from prostate cancer.[5],[6],[7] However, a subset of men with rising PSA following primary therapy will develop clinically apparent metastases and will die as a result of the disease.[6],[8] Despite available prognostic factors, no therapies are approved for hormone-sensitive high-risk nonmetastatic prostate cancer with evidence of disease recurrence by PSA but without overt metastases.

To benefit men with early-stage disease and features indicating a high risk of morbidity and mortality from prostate cancer progression, a desirable therapy must demonstrate a favorable safety profile and good efficacy in terms of delaying metastasis and death from prostate cancer, that is, in prolonging metastasis-free survival (MFS). Ideally, short-term treatment with such a therapy may eradicate or suppress the disease manifestations for a prolonged period, thereby decreasing the need for exposure to the harmful effects of Long-term surgical or medical castration.

This phase 3 randomized study is designed to address this unmet medical need in a defined patient population of men with hormone-sensitive high-risk nonmetastatic prostate cancer progressing after definitive therapy, and will determine whether enzalutamide plus leuprolide or enzalutamide monotherapy is more effective than placebo plus leuprolide. High-risk prostate cancer is defined in this study as biochemical recurrence with a PSA doubling time ≤9 months and screening PSA by the central laboratory of ≥1 ng/mL for patients who had prior radical prostatectomy (with or without radiotherapy) and at least 2 ng/mL above the nadir for patients who had prior primary radiotherapy only.

The rationale for repowering the study's primary endpoint and reassessing relevant secondary endpoints is based on recent clinical trial results of enzalutamide and other androgen targeting agents in similar comparator populations wherefrom it became apparent that the original statistical analysis plan for EMBARK was too conservative with a target hazard ratio of 0.75 for MFS. The PROSPER[9] (hazard ratio = 0.29; refer to Section 1.2) and SPARTAN[10] (hazard ratio = 0.28) studies demonstrated statistically significant and clinically meaningful improvement in MFS in patients with nonmetastatic castration-resistant prostate cancer. Additionally, data from a subpopulation of STAMPEDE showed[11] robust clinical and radiological activity in patients similar to EMBARK with nonmetastatic hormone-sensitive prostate cancer. The nonmetastatic population from STAMPEDE

represents the best analog for clinical data in this setting. While not identical, the primary endpoint of MFS (hazard ratio = 0.21) (which includes PSA, clinical and radiographic progression) had a hazard ratio of 0.21, suggesting a robust effect of abiraterone in the nonmetastatic-hormone-sensitive setting. Historically, treatment with enzalutamide has shown robust activity in relevant endpoints in all prostate cancer studies thus far ranging from earlier nonmetastatic castration-resistant prostate cancer (CRPC) stage to metastatic CRPC post-multiple lines of chemo as in the PREVAIL and AFFIRM studies (refer to Section 1.2) thus further supporting the expectation of a significant treatment effect.

1.2. Summary of Relevant Clinical Experience with Enzalutamide

The US Food and Drug Administration (FDA) first approved Xtandi (enzalutamide) capsules in August 2012 based on a benefit in overall survival for men with metastatic CRPC who previously received docetaxel therapy.[12] Xtandi was later approved in Canada, the European Union, and other countries for use in this patient population. Xtandi has subsequently been approved in multiple countries for the treatment of all patients with metastatic or nonmetastatic castration-resistant prostate cancer and metastatic castration-sensitive cancer (in the US).[13],[14]

Medivation, a wholly owned subsidiary of Pfizer, and Astellas Pharma Global Development, Inc. are in a partnership to codevelop enzalutamide for the treatment of cancer.

The key clinical studies evaluating enzalutamide in men with CRPC are described briefly as follows:

CRPC2 (AFFIRM): A phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide (160 mg daily) in patients with progressive CRPC previously treated with docetaxel-based chemotherapy was conducted in 1199 men, 800 of whom received treatment with enzalutamide.[12] The primary endpoint was overall survival. The prespecified interim analysis at the time of 520 events demonstrated a statistically significant improvement in overall survival in patients treated with enzalutamide versus placebo (hazard ratio 0.63 [95% confidence interval (CI): 0.53, 0.75]; p <0.0001). Current marketing application approvals are based on the results of this pivotal study.

MDV3100-03 (PREVAIL): A phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide (160 mg daily) in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy was conducted in 1717 men, 871 of whom received treatment with enzalutamide. The coprimary endpoints were overall survival and radiographic progression-free survival. The prespecified interim analysis at the time of 540 death events demonstrated statistically significant improvements in overall survival and radiographic progression-free survival in patients treated with enzalutamide versus placebo. Enzalutamide treatment resulted in prolongation of overall survival (hazard ratio 0.71 [95% CI: 0.60, 0.84]; p <0.0001) and radiographic progression-free survival (hazard ratio 0.19 [95% CI: 0.15, 0.23]; p <0.0001).

MDV3100-14 (PROSPER): A phase 3, randomized (2:1), double-blind, placebo-controlled efficacy and safety study of enzalutamide (160 mg daily) was conducted in 1401 men with nonmetastatic, castration-resistant prostate cancer and a PSA doubling time of 10 months or less, continuing on androgen-deprivation therapy received enzalutamide or placebo once daily. The primary end point was MFS. The median MFS was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (hazard ratio for metastasis or death, 0.29; 95% confidence interval, 0.24 to 0.35; P<0.001). The time to the first use of a subsequent antineoplastic therapy was longer with enzalutamide treatment than with placebo (39.6 vs. 17.7 months; hazard ratio, 0.21; P<0.001; such therapy was used in 15% vs. 48% of patients) as was the time to PSA progression (37.2 vs. 3.9 months; hazard ratio, 0.07; P<0.001; progression occurred in 22% vs. 69% of patients). At the third interim and final analysis of OS, conducted when 466 deaths were observed, a statistically significant improvement in overall survival was demonstrated in patients randomized to receive enzalutamide compared with patients randomized to receive placebo with a 26.6% reduction in risk of death (hazard ratio = 0.734; 95% CI: 0.608, 0.885; p = 0.0011).

In addition to the clinical studies in men with metastatic CRPC, a key clinical study evaluated enzalutamide monotherapy in men with hormone-sensitive prostate cancer as follows:

9785-CL-0321: A phase 2, open-label, single-arm, multicenter, efficacy and safety study of enzalutamide monotherapy (160 mg daily) was conducted in 67 patients with hormone-naïve prostate cancer for whom androgen deprivation therapy was indicated. The primary objective was to determine the incidence of patients with a ≥80% PSA response at week 25. Secondary objectives included evaluation of safety and tolerability; exploratory objectives included evaluation of lipids, body mass, bone density, markers of bone turnover, and quality of life. At week 25, the PSA response was 93% (62 of 67 patients; 95% CI, 86%-99%) and the median PSA decrease was 99.6%.

Including these studies, approximately 8000 subjects and patients have been enrolled worldwide in completed and ongoing clinical trials evaluating enzalutamide, including more than 7000 men with prostate cancer.

In the phase 3 study CRPC2 (AFFIRM; N = 1199), the most common adverse drug reactions (≥5%) in patients treated with enzalutamide (N = 800) were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Discontinuations due to adverse events were reported for 16% of enzalutamide-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the enzalutamide-treated patients and none (0%) of the placebo-treated patients.

In the phase 3 study MDV3100-03 (PREVAIL; N = 1717 enrolled), enzalutamide was generally well tolerated with an overall safety profile consistent with that observed in study CRPC2, with a lower seizure rate observed in study MDV3100-03 (1 patient [0.1%] each in the enzalutamide and placebo treatment groups). The new adverse drug reactions observed in study MDV3100-03, gynecomastia and restless legs syndrome, were uniformly nonserious events occurring at low frequency (3.3% and 2.1%, respectively, in enzalutamide-treated patients vs 1.3% and 0.4%, respectively, in placebo-treated patients).

In the phase 2 study 9785-CL-0321, enzalutamide monotherapy was well tolerated. Most common treatment-emergent adverse events were grade 1, and included gynecomastia (36%), fatigue (34%), nipple pain (19%), and hot flush (18%). Five patients had serious adverse events; none of the events were assessed as related to enzalutamide treatment. Mean changes from baseline for fasting metabolic variables were +5.0% total cholesterol, +8.9% triglycerides, -3.5% hemoglobin A1C, and +19.7% insulin resistance (homeostasis model assessment-estimated insulin resistance). Total body bone mineral density was maintained (-0.3% from baseline). Quality of life scores at 1 year demonstrated maintenance of global health status, and decreased sexual activity and sexual functioning.

Additional information on the clinical experience with enzalutamide is provided in the Enzalutamide Investigator Brochure.

1.2.1. Pharmacokinetics and Drug Metabolism

In pharmacokinetics (PK) investigations in men with CRPC, enzalutamide was absorbed rapidly after oral administration, with the time to maximum plasma concentration (T_{max}) after a single dose typically occurring at 1 hour postdose. At steady state, enzalutamide showed approximately dose proportional PK over the daily dose range of 30 to 360 mg. Due to the long terminal half-life (approximately 5.8 days), it took approximately 1 month to reach steady state. With daily oral administration, enzalutamide accumulation was observed at steady state with an 8.3-fold higher exposure (steady-state area under the curve, AUC) relative to a single dose. Based on the mean peak-to-trough ratio, the average difference between the peak (maximum plasma concentration, C_{max}) and trough (predose plasma concentration, C_{trough}) concentrations was ≤25%. As a result of the low daily fluctuations, plasma profiles at steady state resembled a constant infusion. The C_{trough} values in individual patients remained constant beyond day 28 of chronic therapy, suggesting time-linear PK once steady state was achieved. At steady state, plasma concentrations of enzalutamide and the active metabolite, N-desmethyl enzalutamide, were approximately the same.

In a drug-drug interaction study in male patients with CRPC (9785-CL-0007), a single oral dose of a substrate for cytochrome P450 (CYP) 2C8, CYP2C9, CYP2C19, or CYP3A4 was administered before and concomitantly with enzalutamide (after at least 55 days of dosing at 160 mg daily). Enzalutamide at steady state reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) administered orally by 86%, 56%, and 70%, respectively. Based on the magnitude of the decreases in exposure, enzalutamide is considered a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19 (Section 7.3.2). Orally administered substrates of CYP3A4, CYP2C9, and CYP2C19 with a narrow therapeutic index should be

avoided if possible, as enzalutamide may decrease plasma exposure of these drugs. If enzalutamide is coadministered with warfarin (CYP2C9 substrate), additional international normalized ratio (INR) monitoring should be conducted. Enzalutamide did not cause clinically meaningful changes in exposure to pioglitazone (CYP2C8 substrate).

In a drug-drug interaction study in healthy male volunteers (9785-CL-0006), a single 160-mg oral dose of enzalutamide was administered alone or after multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor). Gemfibrozil increased the composite area under the curve from time zero to infinity ($AUC_{0-\infty}$) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C_{max}; therefore, strong CYP2C8 inhibitors should be avoided if possible as they can increase plasma exposure to enzalutamide plus N-desmethyl enzalutamide. If coadministration with a strong CYP2C8 inhibitor is necessary, the dose of enzalutamide should be reduced to 80 mg once daily. If coadministration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used before initiation of the strong CYP2C8 inhibitor. The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated in vivo (Section 7.3.2.1.1).

In the drug-drug interaction study in healthy male volunteers (9785-CL-0006), a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of itraconazole (strong CYP3A4 inhibitor). Itraconazole increased the composite $AUC_{0-\infty}$ of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on C_{max}. As this small change is not clinically meaningful, no starting dose adjustment is needed when coadministering enzalutamide with CYP3A4 inhibitors. The effects of CYP3A4 inducers on the PK of enzalutamide have not been evaluated in vivo (Section 7.3.2.1.2).

Additional information on the PK and drug metabolism of enzalutamide is provided in the Enzalutamide Investigator Brochure.

1.3. Summary of Relevant Nonclinical Experience With Enzalutamide

A complete assessment of toxicity has been conducted with enzalutamide, including evaluation of impurities. The toxicity program was designed to support treatment of men with CRPC and included acute (single-dose) and repeat-dose (up to 26 weeks duration in rats, 13 and 49 weeks in dogs) oral toxicity studies, genotoxicity studies, safety pharmacology studies, specific assessment of the effects on and recovery of the male reproductive system in dogs, and studies to determine the phototoxicity potential. The species included in the toxicity program were mice, rats, dogs, and cynomolgus monkeys. Toxicokinetic evaluations demonstrated that all of these species produce the 2 major human metabolites of enzalutamide, N-desmethyl enzalutamide and an inactive carboxylic acid derivative. The toxicologic profile of N-desmethyl enzalutamide appears to be very similar to enzalutamide.

The toxicity studies tested enzalutamide formulated in Labrasol, the same excipient used in clinical studies and in the commercial product marketed for CRPC.

Based on nonclinical findings in repeat-dose toxicity studies, which were consistent with the pharmacologic activity of enzalutamide, male fertility may be impaired by treatment with enzalutamide. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥30 mg/kg/day (equal to the human exposure based on AUC). In 4-week and 13-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥4 mg/kg/day (0.3-times the human exposure based on AUC).

Long term carcinogenicity studies for enzalutamide include a completed 26-week study in Tg.rasH2 mice and a 2-year study in Wistar Han rats. There were no enzalutamide-related neoplastic findings in Tg.rasH2 mice. In the 2-year rat study, there were increased incidences of secondary urothelial carcinomas and tumors in hormone sensitive organs that included Leydig cell tumors, benign thymomas, pituitary gland adenomas and fibroadenomas of the mammary gland. The tumors in the hormone sensitive organs are considered related to the primary pharmacology of enzalutamide and the Leydig cell tumors are not considered relevant to humans. The human relevance of thymoma, pituitary adenoma and fibroadenoma of the mammary gland in rats is not well known but the potential cannot be ruled out.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the in vitro cytogenetic assay with mouse lymphoma thymidine kinase gene mutation or the in vivo mouse micronucleus assay.

Additional information on the nonclinical experience with enzalutamide is provided in the Enzalutamide Investigator Brochure (IB), which is the single reference safety document (SRSD) for this study

1.4. Enzalutamide Benefits and Risks Assessment

Approximately 8000 subjects and patients have been enrolled worldwide in completed and ongoing clinical trials evaluating enzalutamide, including more than 7000 men with prostate cancer. Available data for enzalutamide in men with metastatic prostate cancer that has progressed despite therapy with a luteinizing hormone-releasing hormone (LHRH) analogue or bilateral orchiectomy support a positive benefit-risk profile for the use of enzalutamide as an investigational agent for treatment in earlier-stage prostate cancer, including patients with high-risk nonmetastatic prostate cancer progressing after definitive therapy. The clinical experience with enzalutamide is discussed briefly in Section 1.2.

2. STUDY OBJECTIVES

All efficacy and safety objectives will compare enzalutamide plus leuprolide and enzalutamide monotherapy versus placebo plus leuprolide.

2.1. Primary Objective

To evaluate efficacy as measured by the following:

2.1.1. Primary Endpoint

To evaluate efficacy of the combination of enzalutamide plus leuprolide versus placebo plus leuprolide, as measured by MFS.

2.2. Secondary Objectives

To evaluate efficacy as measured by the following:

2.3. Key Secondary Endpoints

- To evaluate efficacy, as measured by MFS between enzalutamide monotherapy versus placebo plus leuprolide.
- Time to PSA progression:

Time to first use of new antineoplastic therapy;

Overall survival.

2.4. Other Secondary Endpoints

- Time to distant metastasis;
- Proportion of patients per group who remain treatment-free 2 years after suspension of study drug treatment at week 37 due to undetectable PSA;
- Proportion of patients per group with undetectable PSA 2 years after suspension of study drug treatment at week 37 due to undetectable PSA;
- Proportion of patients per group with undetectable PSA at 36 weeks on study drug;
- Time to resumption of any hormonal therapy following suspension at week 37 due to undetectable PSA;
- Time to first symptomatic skeletal event;
- Time to castration resistance;
- Time to symptomatic progression;
- Time to clinically relevant pain;
- Quality of life;
- Safety.

2.5. Exploratory Endpoint

- Progression-free survival on first subsequent therapy (PFS2).

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan: Description

This is an international, phase 3, randomized study of enzalutamide plus leuprolide, enzalutamide monotherapy, and placebo plus leuprolide in approximately 1050 men with high-risk nonmetastatic prostate cancer progressing after radical prostatectomy or radiotherapy or both. No prior cytotoxic chemotherapy or androgen deprivation therapy

(with exceptions) is allowed. The primary efficacy endpoint is MFS in the combination arm of enzalutamide plus leuprolide versus placebo plus leuprolide.

Central randomization (1:1:1) will be used to assign patients to one of the following study drug treatments:

- Enzalutamide plus leuprolide;
- Enzalutamide monotherapy;
- Placebo plus leuprolide.

Randomization will be stratified by screening PSA ≤10 ng/mL versus >10 ng/mL, PSA doubling time ≤3 months versus >3 to ≤9 months, and prior hormonal therapy versus no prior hormonal therapy.

Treatment with enzalutamide monotherapy will be open label. Treatment with enzalutamide and placebo will be double-blind in combination with open-label leuprolide.

Study drug treatments will be administered as follows, depending on treatment assignment:

- Enzalutamide will be administered as four 40 mg soft gelatin capsules by mouth once daily (160 mg/day) with or without food.
- Placebo capsules, identical in appearance to enzalutamide capsules, will be administered in the same manner as enzalutamide.
- Leuprolide acetate (leuprorelin acetate), 22.5 mg will be given as a single intramuscular or subcutaneous injection once every 12 weeks (for a minimum of 3 doses, providing 36 weeks of treatment).

PSA will be monitored throughout the study, and at week 37, study drug treatment will be suspended for patients whose PSA values are undetectable (<0.2 ng/mL) at week 36 as determined by the central laboratory; PSA and testosterone will be measured every 3 months thereafter by the central laboratory. As the PSA values will not be provided to study sites or patients, study sites will be notified whether a patient's PSA value meets the specified threshold to determine whether or not to continue or suspend study drug treatment at week 37. Study drug treatment may be suspended only once (at week 37) due to undetectable PSA and will be reinitiated if subsequent central laboratory PSA values increase to ≥2.0 ng/mL for patients with prior prostatectomy or ≥5.0 ng/mL for patients without prostatectomy. Study sites will be notified if the PSA value meets the threshold specified for reinitiation of study drug treatment. Patients with detectable PSA values at week 36 will continue treatment without suspension until permanent treatment discontinuation criteria are met.

All patients will have safety follow-up after permanent discontinuation of randomized study drug treatment. Safety follow-up should occur approximately 30 days after the last dose of

randomized study drug. Long-term follow - up will occur after safety follow-up (every 12 weeks based on the 12-week visit schedule determined at randomization).

Throughout the study, investigators are encouraged not to obtain PSA assessments at their local laboratory. Beginning 22 Feb 2019, investigators started to be notified when any of their patients develop protocol defined PSA progression with a PSADT ≤10 months while on study treatment based on central laboratory assessments. Randomized study drug treatment must be permanently discontinued upon initiation of cytotoxic chemotherapy or antiandrogen therapy (eg, bicalutamide, nilutamide, or flutamide). All patients who permanently discontinue study drug treatment will remain in the study, complete safety follow-up, and subsequently commence long-term follow-up, which may include imaging for patients who have not yet had confirmed radiographic progression.

Pain will be assessed using the Brief Pain Inventory (Short Form). Quality of life will be evaluated using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, the European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L), and the Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) module. Patients who are illiterate, blind, or dyslexic; have motor deficit of their hands or difficulty working with electronic devices; or are otherwise unable to independently complete the questionnaires are not required to complete the electronic questionnaires.

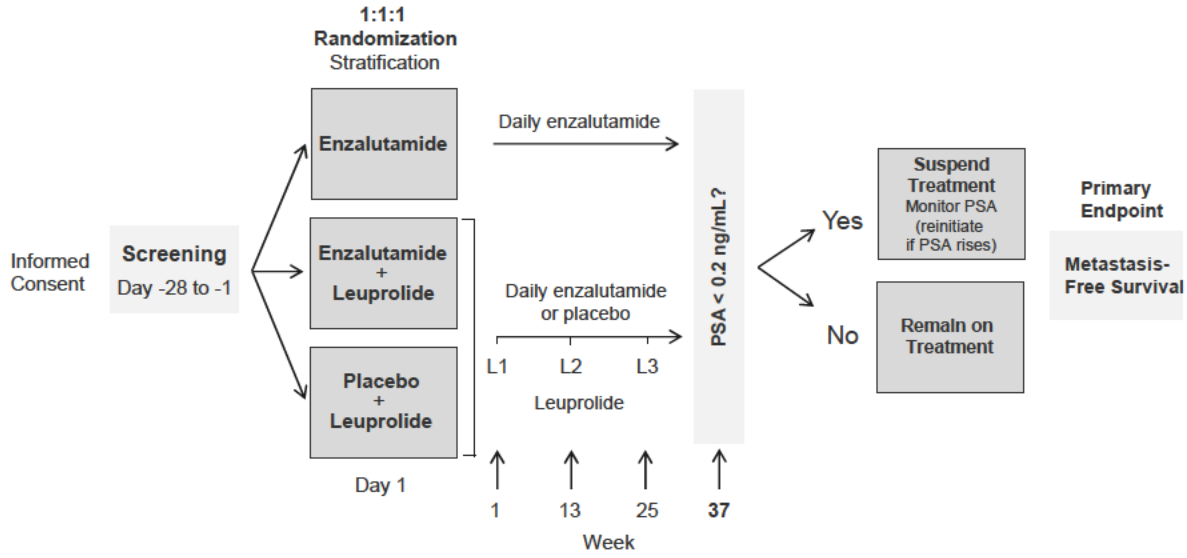
Patients are strongly encouraged to obtain an adequate intake of dietary calcium (at least 1000 mg per day, including supplements if necessary) and vitamin D (at least 800-1000 international units per day for adults 50 years of age and older) and to engage in regular exercise to maintain muscle strength and bone density.

Primary efficacy endpoint analyses have been completed and the safety profile is consistent with the product prescribing information. The open-label period of the study has been established and the study has been unblinded for all study patients. The final analysis of the key secondary endpoint OS will be performed as planned.

3.2. Study Schematic

The study schematic is provided in Figure 1.

Figure 1. Study Schematic



Primary Assessment: Radiographic imaging approximately every 6 months

3.3. Blinding

Treatment with enzalutamide monotherapy will be open label.

Treatment with enzalutamide and placebo will be double-blind in combination with open-label leuprolide.

All patients, study site personnel (including investigators), and sponsor staff and its representatives will be blinded to enzalutamide or placebo treatment assignment when administered in combination with leuprolide. The blinded control for enzalutamide will be placebo capsules identical in appearance to the enzalutamide capsules.

The procedure for breaking the blind in an emergency is provided in Section 8.2.2.

3.4. Duration of Study

The duration of this study until the final analysis will be approximately 90 months (time of first randomization until a total of at least 197 MFS events are observed in all 3 arms). One interim analysis and a final analysis of overall survival will be performed. The interim analysis for OS will be performed at the time of the final analysis of the MFS primary endpoint. Long-term follow-up data (survival status, skeletal-related events and new prostate cancer therapies) will be collected every 12 weeks until the final analysis of OS.

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 overall survival analysis.

3.5. Discussion of Study Design, Including Choice of Control Group

This study is designed to test whether enzalutamide plus leuprolide treatment or enzalutamide monotherapy can prolong MFS compared with placebo plus leuprolide treatment in men with biochemical recurrence of prostate cancer after primary therapy who are at high risk of morbidity and mortality. Prolongation of MFS is likely to delay or prevent prostate cancer symptoms and delay the need for subsequent therapies to treat prostate cancer (including cytotoxic chemotherapy).

The study population will be a subset of men with rising PSA following primary therapy that is at high risk for developing metastases, castration-resistant disease, and who will ultimately die as result of prostate cancer. High-risk prostate cancer is defined in this study as biochemical recurrence with a PSA doubling time ≤9 months and screening PSA by the central laboratory of ≥1 ng/mL for patients who had prior radical prostatectomy (with or without radiotherapy) and at least 2 ng/mL above the nadir for patients who had prior primary radiotherapy only. In theory, men who have rising PSA following definitive therapy have either occult metastatic disease or local progression, and it is likely that the great majority of these men have occult metastatic disease.[4],[15] Enzalutamide is hypothesized to be effective in this setting of minimal tumor burden and disease that is not yet castration resistant based on an understanding of the mechanism of action of enzalutamide and data obtained in patients with hormone-naïve prostate cancer treated with enzalutamide monotherapy.[16]

A key feature of the study design is to treat patients for a prespecified interval (36 weeks) and then to suspend treatment based on response as indicated by undetectable PSA (<0.2 ng/mL), thus potentially averting the adverse effects associated with long-term continuous androgen deprivation therapy. Study drug treatment may be reinitiated if PSA rises to ≥2.0 ng/mL for patients who had prior radical prostatectomy or ≥5.0 ng/mL for patients who had prior radiation therapy. For patients whose PSA values are detectable at 36 weeks, assigned study drug treatment will continue. Only 1 such study drug treatment suspension is permitted during this study.

The control group is placebo with androgen deprivation therapy using leuprolide. Androgen deprivation therapy is appropriate in this disease setting as it is commonly used when a decision is made to treat patients with high-risk nonmetastatic disease with biochemical recurrence following definitive therapy.

4. SELECTION OF STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all of the following criteria:

1. Age 18 years or older and willing and able to provide informed consent.

2. Histologically or cytologically confirmed adenocarcinoma of the prostate at initial biopsy, without neuroendocrine differentiation, signet cell, or small cell features.

3. Prostate cancer initially treated by radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent. Prostate cryoablation is not considered definitive therapy for this study, but its prior use is not exclusionary.

4. PSA doubling time ≤9 months as calculated by the sponsor.[17]

5. Screening PSA by the central laboratory ≥1 ng/mL for patients who had radical prostatectomy (with or without radiotherapy) as primary treatment for prostate cancer and at least 2 ng/mL above the nadir for patients who had radiotherapy only as primary treatment for prostate cancer.

6. Serum testosterone ≥150 ng/dL (5.2 nmol/L) at screening.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.

8. Estimated life expectancy of ≥12 months.

9. Able to swallow the study drug and comply with study requirements.

10. Throughout the study, the patient and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) from screening through 3 months after the last dose of study drug or per local guidelines where these require additional description of contraceptive methods. Two acceptable methods of birth control thus include the following:

    Condom (barrier method is required);

    - AND

    One of the following is required:

    - Established and ongoing use of oral, injected, or implanted hormonal method of contraception by the female partner;

    - Placement of an intrauterine device or intrauterine system by the female partner;

    - Additional barrier method including contraceptive sponge and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner;

- Tubal ligation in the female partner performed at least 6 months before screening;

- Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy), performed at least 6 months before screening.

11. Throughout the study, the patient must use a condom if having sex with a pregnant woman.

12. Must agree not to donate sperm from first dose of study drug through 3 months after the last dose of study drug.

4.2. Exclusion Criteria

Each patient eligible to participate in this study must NOT meet any of the following exclusion criteria:

1. Prior or present evidence of distant metastatic disease as assessed by computed tomography (CT) or magnetic resonance imaging (MRI) or chest x-ray for soft tissue disease and whole-body radionuclide bone scan for bone disease. Patients with soft tissue pelvic disease may be eligible if the short axis of the largest lymph node is < 20 mm for lymph nodes below aortic bifurcation. If the screening bone scan shows a lesion suggestive of metastatic disease, the patient will be eligible only if a second imaging modality (plain film, CT, or MRI) does not show bone metastasis. If the imaging results are equivocal or consistent with metastasis by central radiology review, the patient is not eligible for enrollment. Positron-emission tomography (PET) is not an evaluable imaging modality for this study.

2. Prior hormonal therapy. Neoadjuvant/adjuvant therapy to treat prostate cancer ≤36 months in duration and ≥9 months before randomization, or a single dose or a short course (≤6 months) of hormonal therapy given for rising PSA ≥9 months before randomization is allowed.

3. Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for prostate cancer.

4. Prior systemic biologic therapy, including immunotherapy, for prostate cancer.

5. Major surgery within 4 weeks before randomization date.

6. Treatment with 5-α reductase inhibitors (finasteride, dutasteride) within 4 weeks of randomization.

7. For patients who had a prior prostatectomy, a suitable candidate for salvage radiotherapy as determined by the investigator in consideration of appropriate guidelines (eg, American Society for Radiation Oncology/American Urological Association [ASTRO/AUA]; European Association of Urology [EAU]).

8. Participation in a clinical study of an investigational agent that inhibits the androgen receptor or androgen synthesis (eg, TAK-700, ARN-509, ODM-201); patients who received placebo are allowed.

9. Use of any other investigational agent within 4 weeks before randomization date.

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

11. History of another invasive cancer within 3 years before screening, with the exception of fully treated cancers with a remote probability of recurrence. The medical monitor and investigator must agree that the possibility of recurrence is remote.

12. Absolute neutrophil count <1500/μL, platelet count <100,000/μL, or hemoglobin <10 g/dL (6.2 mmol/L) at screening. NOTE: May not have received any growth factors or blood transfusions within 7 days before the hematology values obtained at screening.

13. Total bilirubin (TBili) ≥1.5-times the upper limit of normal (except patients with documented Gilbert's disease), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5-times the upper limit of normal at screening.

14. Creatinine >2 mg/dL (177 μmol/L) at screening.

15. Albumin <3.0 g/dL (30 g/L) at screening.

16. History of seizure or any condition that may predispose to seizure (eg, prior cortical stroke or significant brain trauma). History of loss of consciousness (unless of cardiac origin) or transient ischemic attack within 12 months before randomization.

17. Clinically significant cardiovascular disease including the following:

    - Myocardial infarction within 6 months before screening;
    - Unstable angina within 3 months before screening;
    - New York Heart Association class III or IV congestive heart failure or a history of New York Heart Association class III or IV congestive heart failure unless a screening echocardiogram or multigated acquisition scan performed within 3 months before the randomization date demonstrates a left ventricular ejection fraction ≥45%;
    - History of clinically significant ventricular arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes);
    - History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place;

- Hypotension as indicated by systolic blood pressure <86 mm Hg at screening;
- Bradycardia as indicated by a heart rate of ≤45 beats per minute on the screening electrocardiogram (ECG);
- Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg at screening.

18. Gastrointestinal disorder affecting absorption.
19. Hypersensitivity reaction to enzalutamide or any of the capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene.
20. Contraindication to the use of leuprolide, such as a previous hypersensitivity reaction to an LHRH analogue or any of the excipients in the leuprolide injection.
21. Ongoing drug or alcohol abuse as per investigator judgment.
22. Any concurrent disease, infection, or comorbid condition that interferes with the ability of the patient to participate in the study, which places the patient at undue risk, or complicates the interpretation of data, in the opinion of the investigator or medical monitor.

5. ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is also provided in the schedule of activities (Appendix 5). The interactive web response system (IWRS) user manual contains the information needed for registering patient status (eg, assigning screening and randomization numbers, indicating screen failure, temporary suspension of treatment, reinitiation of treatment, end of treatment).

5.1. Screening Period

The screening period will be from day -28 through day -1. Screening procedures are listed in Table 1. Radiographic assessments may be performed as early as day -42. Assessments not completed within the applicable screening window may be repeated and/or patients may rescreen if clinically appropriate.

For the purposes of this study, there will be no day 0.

5.1.1. Screening Identification Numbers

After obtaining informed consent, study site personnel will access the IWRS to assign a screening identification (ID) number to a potential study participant.

For patients who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent before randomization, study site personnel should document the screen failure in the patient's source documents. The documentation should include demographics

and medical history, the reason for screen failure, the eligibility criteria reviewed, procedures performed, etc.

5.1.2. Screening Visit Procedures

At the screening visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless the procedures are part of routine standard of care, and must document the informed consent process in the patient's source documents. Informed consent may be obtained before the screening period. Standard of care procedures must be clearly documented as such in the source in order to use for screening eligibility.

Screening procedures are listed in Table 1. The investigator will assess and confirm the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

After a patient is screened and the investigator determines the patient is eligible for randomization, study site personnel will complete a Randomization Authorization Form and fax or email it to the medical monitor or designee to approve the randomization in writing.

Table 1. Screening Procedures

Activity/Assessment/Timing	Comment
General	All screening procedures must be performed within the 28-day screening period, unless noted otherwise.
Informed consent	Must obtain informed consent before performing any study-specific procedures. May obtain before the screening period. Ensure consent is on the current version of the form approved by the ethics committee.
Screening number	Obtain from IWRS
Medical history	Review any time after obtaining informed consent.
Eligibility criteria	All inclusion criteria must be met and none of the exclusion criteria may apply per Section 4.
12-Lead ECG	Obtain per local practice and read locally to confirm eligibility.
Vital signs and complete physical examination	Measure blood pressure, heart rate, temperature, weight, and height. Assess systems per standard of care at the study site.
ECOG performance status	Refer to Table 13.
Serious adverse event review	Collect serious adverse event information from the time of signed informed consent Section 8.1.4. Record any serious adverse event for any patient who subsequently meets eligibility criteria and proceeds to randomization.
Concomitant medications review	Record all ongoing medications and those discontinued within 28 days before the visit. Record all prior hormonal therapy for prostate cancer treatment regardless of time period.

Table 1. Screening Procedures

Activity/Assessment/Timing	Comment
Central Laboratory Evaluations	Refer to the central laboratory manual for sample processing. Eligibility will be based on central laboratory assessment.
Serum chemistry, hematology	Refer to analytes listed in Table 12.
PSA, testosterone	
Central Radiology Evaluations	Submit all imaging results (bone scan, CT, MRI, or X-ray) for central radiology review to confirm absence of metastases before enrollment. Submit the clinical information form (CIF) if there is clinically relevant information available (such as biopsy results, trauma history, other medical diagnosis to inform the central readers that suspicious findings are not metastatic disease).
Radiographic assessments → ***Perform within 42 days (6 weeks) before randomization***	Includes posteroanterior and lateral chest x-ray or chest CT scan, abdominopelvic CT/MRI, and whole-body radionuclide bone scan to verify the absence of metastatic disease. PET is not an evaluable imaging modality for this study.
Randomization Authorization Form	Complete, sign, and fax or email the form with requested items to the medical monitor or designee at least 3 business days before the anticipated day 1 visit. The patient may proceed to the day 1 visit and randomize when the medical monitor or designee approves by signed form or email correspondence.

5.2. Treatment Period

Day 1 is the day of randomization, which is usually the day of the first dose of randomized study drug treatment. Patients will return to the study site at week 13 and every 12 weeks thereafter. Patients will also have a PSA assessment at week 36 to determine the course of study treatment at week 37 and be contacted by telephone at week 41 for assessment of adverse events.

The double-blind period has concluded and the open-label period is ongoing. The complete details for the conduct of the open-label period are provided in SUPPLEMENT 1: OPEN-LABEL STUDY PERIOD. The completed double-blind protocol has not changed.

5.2.1. Visit Windows

At each specified study visit, procedures will be performed according to the schedule of activities (Appendix 5).

A study visit may be scheduled on any day within a specified study week. For any given day within the study week, the visit window is ± 5 days (ie, 5 days before or after the given day) unless otherwise stated.

Study drug supplies must be taken into account when scheduling visits during windows. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

5.2.2. Week 1, Day 1

Study site personnel will access the IWRS to assign a randomization ID number to a study participant. This number will be used to identify the patient for the remainder of the study.

Day 1 procedures are listed in Table 2. Study site personnel should ensure that an approved Randomization Authorization Form is in the patient's file before proceeding with day 1 procedures.

The blood samples for central laboratory evaluations should be collected and the patient questionnaires should be completed before the first dose of study drug to establish baseline.

If study drug cannot be administered on the same day as randomization, the patient must come to the clinic within 3 business days after randomization for the required procedures and initiation of study treatment. Day 1 is the day of randomization regardless of the date of the first dose of study drug. Note that time of first dose will be recorded in the electronic data capture (EDC) system.

Table 2. Week 1, Day 1 Procedures

Activity/Assessment	**Comment**
Randomization	Access the IWRS to assign randomization ID number and study drug treatment. May occur up to 3 business days before the day of first dose.
General Activities	
Vital signs and brief physical examination	May skip these assessments if performed within prior 7 days. Measure blood pressure, heart rate, temperature, and weight. Perform symptom-directed examination and investigate any new abnormalities.
ECOG performance status	Refer to Table 13.
BPI-SF, FACT-P, EQ-5D-5L, and QLQ-PR25 questionnaires	Complete **BEFORE the first dose** of study drug. Refer to Appendix 1, Appendix 2, Appendix 3, and Appendix 4.
Adverse events review	Record adverse events that occurred in enrolled patients in the patient's source documents.
Concomitant medications review	Record any new medications or changes in ongoing medications.
Central Laboratory Evaluations	Collect blood samples **BEFORE the first dose** of study drug. Refer to the central laboratory manual for sample processing
Serum chemistry, hematology	Refer to analytes listed in Table 12.
PSA, testosterone	
Study Drugs Dosing/Dispensing	**As appropriate for treatment assignment.**
Leuprolide injection (if applicable)	**Single intramuscular or subcutaneous injection (22.5 mg).**

Table 2. Week 1, Day 1 Procedures

Activity/Assessment	Comment
Open-label enzalutamide dispensing (if applicable)	Provide the patient with a 12-week supply. Provide instructions for dosing, storage, and return of all study drug at future visits.
Blinded study drug dispensing (if applicable)	Provide the patient with a 12-week supply. Provide instructions for dosing, storage, and return of all study drug at future visits.

5.2.3. Week 13

The visit window is ± 5 days. Drug supply must be taken into account if a window is used to schedule the next visit.

Week 13 procedures are listed in Table 3.

Table 3. Week 13 Procedures

Activity/Assessment	Comment
General Activities	
Vital signs and brief physical examination	Measure blood pressure, heart rate, temperature, and weight. Perform symptom-directed examination and investigate any new abnormalities.
ECOG performance status	Refer to Table 13.
BPI-SF, FACT-P, EQ-5D-5L, and QLQ-PR25 questionnaires	Refer to Appendix 1, Appendix 2, Appendix 3, and Appendix 4.
Symptomatic skeletal events	Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain.
Adverse events review	Record any new or ongoing adverse events.
Concomitant medications review	Record any new medications or changes in ongoing medications.
Study Drugs Dosing/Dispensing	**As appropriate for treatment assignment.**
Leuprolide injection (if applicable)	Single intramuscular or subcutaneous injection (22.5 mg).
Open-label enzalutamide dispensing (if applicable)	Provide the patient with a 12-week supply. Confirm dosing instructions with patient.
Blinded study drug dispensing (if applicable)	Provide the patient with a 12-week supply. Confirm dosing instructions with patient.
Study drug accountability	Record study drug returned and remind patient to return all study drug at each future visit.

5.2.4. Week 25

The visit window is ± 5 days. Drug supply must be taken into account if a window is used to schedule the next visit.

Week 25 procedures are listed in Table 4.

Table 4. Week 25 Procedures

Activity/Assessment	Comment
General Activities	
Radiographic assessments	Includes abdominopelvic CT/MRI scan and whole-body radionuclide bone scan. Chest imaging is not required. PET is not an evaluable imaging modality for this study.
Vital signs and brief physical examination	Measure blood pressure, heart rate, temperature, and weight. Perform symptom-directed examination and investigate any new abnormalities.
ECOG performance status	Refer to Table 13.
BPI-SF, FACT-P, EQ-5D-5L, and QLQ-PR25 questionnaires	Refer to Appendix 117, Appendix 2, Appendix 3, and Appendix 4.
Symptomatic skeletal events	Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain.
Adverse events review	Record any new or ongoing adverse events.
Concomitant medications review	Record any new medications or changes in ongoing medications.
Study Drugs Dosing/Dispensing	**As appropriate for treatment assignment.**
Leuprolide injection (if applicable)	Single intramuscular or subcutaneous injection (22.5 mg).
Open-label enzalutamide dispensing (if applicable)	Provide the patient with a 12-week supply. Confirm dosing instructions with patient.
Blinded study drug dispensing (if applicable)	Provide the patient with a 12-week supply. Confirm dosing instructions with patient.
Study drug accountability	Record study drug returned and remind patient to return all study drug at each future visit.
Central Laboratory Evaluations	Refer to the central laboratory manual for sample processing.
Serum chemistry, hematology	Refer to analytes listed in Table 12.
PSA, testosterone	

5.2.5. Week 36

The visit window is ± 5 days. The purpose of this visit is to collect a blood sample for PSA determination by the central laboratory. The course of study treatment at week 37 will be based on this test result.

5.2.6. Week 37

The visit window is ± 5 days. Drug supply must be taken into account if a window is used to schedule the next visit.

The PSA value at week 36 (central laboratory result) will determine the course of each patient's study drug treatment as follows:

- For patients with detectable PSA (≥0.2 ng/mL), assigned study drug treatment will continue.
- For patients with undetectable PSA (<0.2 ng/mL), assigned study drug treatment will be suspended at week 37. Study visits will continue every 12 weeks. If subsequent PSA values increase to prespecified levels (Section 3.1), assigned study drug treatment should resume.

As PSA values will not be provided to study sites or patients, study sites will be notified whether or not PSA is undetectable to determine whether or not to suspend study drug treatment.

Week 37 procedures are listed in Table 5.

Table 5. Week 37 Procedures

Activity/Assessment	Comment
General Activities	
Vitals signs and brief physical examination	Measure blood pressure, heart rate, temperature, and weight. Perform symptom-directed examination and investigate any new abnormalities.
ECOG performance status	Refer to Table 13.
BPI-SF, FACT-P, EQ-5D-5L, and QLQ-PR25 questionnaires	Refer to Appendix 117, Appendix 2, Appendix 3, and Appendix 4.
Symptomatic skeletal events	Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain.
Adverse events review	Record any new or ongoing adverse events.
Concomitant medications review	Record any new medications or changes in ongoing medications.

Table 5. Week 37 Procedures

Activity/Assessment	Comment
Study Drugs Dosing/Dispensing	**As appropriate for treatment assignment and PSA value.** **The study sites will be notified whether or not PSA is undetectable to determine whether or not to continue or suspend study drug treatment. Register the week 37 visit in the IWRS (as either a suspension visit or IP dispensing visit, accordingly). Refer to the IWRS Site Manual.**
Leuprolide injection (if applicable)	Single intramuscular or subcutaneous injection (22.5 mg). Continued dosing depends on PSA value; see above.
Blinded study drug dispensing (if applicable)	Provide the patient with a 12-week supply. Confirm dosing instructions with patient. Continued dosing depends on PSA value; see above.
Open-label enzalutamide dispensing (if applicable)	Provide the patient with a 12-week supply. Confirm dosing instructions with patient. Continued dosing depends on PSA value; see above.
Study drug accountability	Record study drug returned and remind patient to return all study drug at each future visit (if applicable).
Central Laboratory Evaluations	Refer to the central laboratory manual for sample processing.
Serum chemistry, hematology	Refer to analytes listed in Table 12.
PSA, testosterone	

5.2.7. Week 41

The week 41 (± 5 days) telephone contact will be a telephone call to all patients to collect adverse event information only.

5.2.8. Week 49 and Repeating Every 12 Weeks

Visits repeat every 12 weeks (± 5 days) until criteria are met for permanent treatment discontinuation (Section 5.3). Drug supply must be taken into account if a window is used to schedule the next visit.

Week 49 and repeating every 12 weeks procedures are listed in Table 6.

Table 6. Week 49 and Repeating Every 12 Weeks Procedures

Activity/Assessment/Timing	Comment
General Activities	
Radiographic assessments → ***Perform at week 49 and at 24-week intervals thereafter***	Includes abdominopelvic CT/MRI and whole-body radionuclide bone scan. Chest imaging is not required. PET is not an evaluable imaging modality for this study.
Vital signs and brief physical examination	Measure blood pressure, heart rate, temperature, and weight. Perform symptom-directed examination and investigate any new abnormalities.
ECOG performance status	Refer to Table 13.
BPI-SF, FACT-P, EQ-5D-5L, and QLQ-PR25 questionnaires	Refer to Appendix 117, Appendix 2, Appendix 3, and Appendix 4.
Symptomatic skeletal events	Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain.
Adverse events review	Record any new or ongoing adverse events.
Concomitant medications review	Record any new medications or changes in ongoing medications.
Study Drugs Dosing/Dispensing	**As appropriate for treatment assignment and PSA value.** **The study sites will be notified if the PSA value meets the threshold specified for reinitiation of study drug treatment.** **If a PSA value requires treatment reinitiation, ask the patient to return to the study site as soon as possible for study drug dispensing.**
Leuprolide injection (if applicable)	Single intramuscular or subcutaneous injection (22.5 mg).
Open-label enzalutamide dispensing (if applicable)	Provide the patient with a 12-week supply. Confirm dosing instructions with patient.
Blinded study drug dispensing (if applicable)	Provide the patient with a 12-week supply. Confirm dosing instructions with patient.
Study drug accountability (if applicable)	Record study drug returned and remind patient to return all study drug at each future visit.
Central Laboratory Evaluations	Refer to the central laboratory manual for sample processing.
Serum chemistry, hematology	Refer to analytes listed in Table 12.
PSA, testosterone	

5.2.9. Unscheduled Visits

Unscheduled visits may be performed anytime to assess or follow-up adverse events, to perform scans, to dispense study drug, at the patient's request, or at the investigator's request. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on investigator assessment as appropriate.

Unscheduled visit procedures are listed in Table 7.

Table 7. Unscheduled Visit Procedures

Activity/Assessment	Comment
General Activities	
Radiographic assessments	If disease progression is suspected, protocol specified imaging should be obtained and sent to the central reader with a request for an expedited read.
Vital signs and brief physical examination	Measure blood pressure, heart rate, temperature, and weight. Perform symptom-directed examination and investigate any new abnormalities.
ECOG performance status	Refer to Table 13.
Symptomatic skeletal events	Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain.
Adverse events review	Record any new or ongoing adverse events.
Concomitant medications review	Record any new medications or changes in ongoing medications.
Study Drugs Dosing/Dispensing (eg, for patients resuming treatment following suspension at week 37)	**As appropriate for treatment assignment and PSA value.**
Leuprolide injection (if applicable)	Single intramuscular or subcutaneous injection (22.5 mg).
Open-label enzalutamide dispensing (if applicable)	Provide the patient with a 12-week supply. Confirm dosing instructions with patient.
Blinded study drug dispensing (if applicable)	Provide the patient with a 12-week supply. Confirm dosing instructions with patient.
Central Laboratory Evaluations	Refer to the central laboratory manual for sample processing.
Serum chemistry, hematology	Refer to analytes listed in Table 12.
PSA, testosterone	If missed during a regularly scheduled visit.

5.3. Permanent Treatment Discontinuation

Permanent treatment discontinuation is defined as cessation of randomized study drug treatment administration. Safety follow-up will be performed per Section 5.4. Information on study discontinuation related to COVID-19 is provided in Appendix 6.

Temporary treatment interruption (eg, due to an adverse event) is not considered permanent discontinuation.

Suspension of study drug treatment due to undetectable PSA is discussed in Section 5.2.6.

The primary reasons that require patients to *permanently discontinue* randomized study drug treatment are as follows:

- Adverse event or intercurrent illness: Any intolerable adverse event that cannot be ameliorated by the use of adequate medical intervention or that in the opinion of the investigator or medical monitor would lead to undue risk if study treatment were continued. Refer to Section 8.
- Gross noncompliance with protocol: The medical monitor or investigator and/or study management may request permanent treatment discontinuation in the event of a major protocol deviation, lack of cooperation, or noncompliance.
- Development of radiographic progression confirmed by central review after initial local read.
- Administration of prohibited concomitant therapy: Refer to Section 7.2.
  NOTE: Patients who discontinue due to administration of a prohibited concomitant therapy will remain in the study and complete safety follow-up assessments per Section 5.4, then begin long-term follow-up per Section 5.5.
- Laboratory abnormality defined by protocol as follows:

  Creatinine >354 µmol/L (>4.0 mg/dL);

  AST, ALT, or TBili >5 times the upper limit of normal;

  Absolute neutrophil count ≤750/µL.
- Platelet count <50,000/µL.
- Seizure: Regardless of resolution of any identified etiology. Refer to Section 8.5.5.1.
- Death: Refer to Section 8.5.5.2.
- Loss to follow-up: Refer to Section 5.6.
- Investigator conclusion that it is in the patient's best interest to discontinue therapy (eg, poor compliance with either protocol monitoring or with taking the study medications, etc.).
- Sponsor discontinuation of study: The sponsor reserves the right to terminate the study anytime as described in Section 13.6. The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.

- Patient decision : Patients may permanently discontinue randomized study drug treatment anytime for any reason. Following permanent treatment discontinuation, patients should have protocol-required safety follow-up assessments approximately 30 days after the last dose of randomized study drug treatment (enzalutamide plus leuprolide, enzalutamide monotherapy, or placebo plus leuprolide), unless the patient specifically declines further follow-up. Study site personnel must document the patient's decision in the source documents. Patients are strongly encouraged to continue in long-term follow-up as described in Section 5.5, even if they choose to permanently discontinue study drug treatment.

5.4. Safety Follow-Up

All patients will have safety follow-up after permanent discontinuation of randomized study drug treatment (enzalutamide plus leuprolide, enzalutamide monotherapy, or placebo plus leuprolide). Safety follow-up should occur approximately 30 days after the last dose of randomized study drug treatment.

In the event that antineoplastic treatment is initiated before safety follow-up occurs (eg, a physician not associated with protocol MDV3100-13(C3431004) initiates the treatment, and study site personnel are not aware of the treatment until afterward), safety follow-up should be scheduled as soon as possible.

If treatment is discontinued due to an adverse event or serious adverse event, the event(s) must be followed up as described in Section 8.5.6. Patients who discontinue study drugs due to adverse events are encouraged to continue long-term follow-up in the clinic (Section 5.5).

For patients who refuse further clinic study visits, telephone contact should be attempted and documented to review for adverse events through approximately 30 days after the last dose of randomized study drug treatment. If the patient does not respond to or refuses telephone contact, the patient's medical records from the treating physician may be reviewed. If all methods fail, the procedures for loss to follow-up in Section 5.6 should be followed.

Safety follow-up procedures are listed in Table 8. The visit window is -3 to +10 days from the last dose of randomized study drug treatment. For patients who permanently discontinue study treatment during the suspension period, the safety follow-up visit may be scheduled any time after 28 days post the last dose of randomized study drug treatment.

Table 8. Safety Follow-Up Procedures

Activity/Assessment	Comment
General Activities	
Vital signs and complete physical examination	Measure blood pressure, heart rate, temperature, and weight. Assess systems per standard of care at the study site and as clinically indicated by symptoms.
ECOG performance status	Refer to Table 13.
BPI-SF, FACT-P, EQ-5D-5L, and QLQ-PR25 questionnaires	Refer to Appendix 117, Appendix 2, Appendix 3, and Appendix 4.
Symptomatic skeletal events	Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain.
Adverse events review	Record any new or ongoing adverse events.
Concomitant medications review	Record any new medications or changes in ongoing medications.
Study drug accountability (if applicable)	Record study drug returned and remind patient to return all study drug.
Central Laboratory Evaluations	Refer to the central laboratory manual for sample processing.
Serum chemistry, hematology	Refer to analytes listed in Table 12.
PSA, testosterone	

5.5. Long-Term Follow-Up

Long-term follow up begins after safety follow-up. Visits repeat every 12 weeks (± 7 days) based on the 12-week visit schedule determined at randomization. For patients who permanently discontinue randomized study drug treatment before radiographic progression is documented and confirmed by central review, radiographic assessments will continue until radiographic progression is identified and confirmed by independent central radiology review per protocol.

For all patients in long-term follow-up, the site should make every effort to collect information on prostate cancer related treatments and investigator assessed disease progression.

For patients who refuse to return to the clinic for long-term follow-up, long-term follow-up may be conducted by telephone call. If the patient does not respond to or refuses telephone contact, alternate contacts are permissible (eg, primary care providers, treating physicians, relatives). The patient's medical records may be retrieved from the treating physician for review of medical, treatment, and survival information.

Long-term follow-up procedures are listed in Table 9.

Table 9. Long-Term Follow-Up Procedures

Activity/Assessment/Timing	Comment
General Activities	
BPI-SF, FACT-P, EQ-5D-5L, and QLQ-PR25 questionnaires	Refer to Appendix 1, Appendix 2, Appendix 3, and Appendix 4. Not applicable if patient does not return to the study clinic.
Symptomatic skeletal events	Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain.
Other information	Survival status. Subsequent therapies for prostate cancer, including opiate medication to treat bone pain. Dates of investigator assessed progression on first subsequent therapy, including clinical, radiographic or PSA progression.
Radiographic assessments → ***Perform at 24-week intervals (± 14 days)***	Includes abdominopelvic CT/MRI and whole-body radionuclide bone scan for patients who have not yet had radiographic progression. PET is not an evaluable imaging modality for this study. Standard of care scans will be accepted to meet the MFS endpoint for patients in long-term follow-up (LTFU).

5.6. Loss to Follow-Up

Every reasonable effort should be made to contact any patient apparently lost to follow-up during the course of the study to complete study-related assessments, record outstanding data, and retrieve study drug.

Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives). The patient's medical records may be retrieved from the treating physician for review of medical, treatment, and survival information. Such efforts should be documented in the patient's source documents.

If all efforts fail to establish contact, the patient will be considered lost to follow-up.

6. INVESTIGATIONAL PRODUCT INFORMATION

6.1. General Information

The study drugs include enzalutamide, placebo, and leuprolide (leuprorelin acetate). Xtandi (enzalutamide) is approved in the US and other regions to treat men with metastatic CRPC who have previously received docetaxel. Leuprolide is an LHRH agonist indicated for palliative treatment of advanced prostate cancer.[18],[19]

The sponsor will provide enzalutamide and placebo capsules. The sponsor will provide leuprolide.

6.2. Enzalutamide Product Characteristics

Enzalutamide, also known as MDV3100, has the chemical name 4-{3-[4-cyano-3-(trifluoromethyl) phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide . The drug substance is formulated in the surfactant caprylocaproyl polyoxylglycerides, or Labrasol. The product will be supplied as white to off-white gelatin capsules containing 40 mg of enzalutamide.[20] The chemical properties and list of excipients are presented in the investigator brochure.

The corresponding placebo consists of Labrasol and other excipients filled in matching capsules.

6.2.1. Packaging of Enzalutamide or Placebo

Enzalutamide or placebo study drug is packaged in bottles with induction-sealed child-resistant caps labeled with the study protocol number, contents, directions for use, storage directions, clinical trial statement, and sponsor name.

6.2.2. Storage of Enzalutamide or Placebo

Enzalutamide or placebo study drug should be handled and stored safely and properly in accordance with the study drug label.

6.2.3. Directions for Administration of Enzalutamide or Placebo

The daily dose of enzalutamide or placebo is 160 mg/day given in 4 capsules (40 mg each) by mouth.

Patients should self-administer enzalutamide or placebo by mouth once daily, with or without food. The capsules should be swallowed whole without chewing, dissolving, or opening them.

Patients should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed.

6.2.4. Directions for Dose Modification of Enzalutamide or Placebo

Patients who experience a grade 3 or higher toxicity that is attributed to enzalutamide or placebo and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with enzalutamide or placebo for 1 week or until the toxicity grade improves to grade 2 or lower severity. Subsequently, study drug dosing may be restarted at the original dose (4 capsules/day) or a reduced dose (3 or 2 capsules/day) in recommended consultation with the medical monitor.

If enzalutamide or placebo is coadministered with a strong CYP2C8 inhibitor, the dose of enzalutamide or placebo should be reduced to 80 mg once daily. If coadministration of the

strong CYP2C8 inhibitor is discontinued, the enzalutamide or placebo dose should return to the dose used before initiation of the strong CYP2C8 inhibitor.

6.3. Leuprolide Product Characteristics

Leuprolide acetate (leuprorelin acetate) is a synthetic nonapeptide analog of naturally occurring LHRH. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt).[18],[19] The chemical properties and a list of excipients are presented in the prescribing information.

6.3.1. Packaging of Leuprolide

Leuprolide acetate for depot suspension, 22.5 mg for 3-month administration, is packaged as a kit with a prefilled dual-chamber syringe for reconstitution before administration as an intramuscular injection.[18]

Leuprolide acetate suspension for subcutaneous injection, 22.5 mg for 3-month administration, is packaged as a single-use kit with a 2-syringe mixing system for constitution before administration.[19]

If leuprolide acetate, 22.5 mg for 3-month administration is not available, a suitable substitute may be allowed upon approval by the medical monitor.

6.3.2. Storage of Leuprolide

Leuprolide should be handled and stored safely and properly in accordance with the prescribing information.

6.3.3. Directions for Administration of Leuprolide

Leuprolide acetate for administration as a 22.5 mg injection once every 12 weeks formulated for either intramuscular or subcutaneous injection is allowed. Three injections will provide 36 weeks of treatment.

The leuprolide acetate formulation for intramuscular injection is supplied as sterile lyophilized microspheres along with an accompanying diluent. The microspheres are to be reconstituted as described in the prescribing information and administered as a single intramuscular injection of 22.5 mg once every 12 weeks.

The leuprolide acetate formulation for subcutaneous injection is supplied as sterile powder along with an accompanying liquid gel solution. The powder is to be mixed with the liquid as described in the prescribing information and administered in clinic by study site personnel as a single subcutaneous injection of 22.5 mg once every 12 weeks.

6.3.4. Directions for Dose Modification of Leuprolide

There are no provisions for dose modification of leuprolide on this study.

6.4. Treatment Compliance

Accountability for the study drug capsules (enzalutamide, placebo) will be performed to document compliance with the dosing regimens. Patients will be asked to bring all study drug including empty bottles to study visits. Study site personnel must make reasonable efforts to obtain study drug from patients who do not routinely return them at study site visits. Unreturned capsules will be considered to have been taken.

Compliance with leuprolide treatment will be determined by testosterone suppression.

7. PRIOR AND CONCOMITANT THERAPY

Prior and concomitant medications include all vitamins, herbal remedies, and over-the-counter and prescription medications.

7.1. Prior Therapy

Medications taken within 4 weeks before randomization, all prior hormonal therapies, and any medications prescribed for chronic or intermittent use during the study, or dose adjustments of these medications, must be recorded on the case report form and in the patient's source documents.

Per the study eligibility criteria, patients who received certain prior medications and therapies for prostate cancer are excluded from study participation.

7.2. Concomitant Therapy

Concomitant medications will be assessed at all clinic visits. All concomitant medications, including analgesic medications and opiates (including opioid-containing medications), must be recorded on the appropriate case report form. If the use of any medication during the study is due to an adverse event, the adverse event must be recorded on the adverse event case report form and in the patient's source documents.

Initiation of bisphosphonates or denosumab for the prevention of bone metastases is prohibited following randomization; however, treatment with these agents should continue at a stable dose if initiated at least 4 weeks before randomization. Initiation of bisphosphonates or denosumab at doses to treat osteoporosis is allowed if a diagnosis of osteoporosis is made during the study.

Patients are strongly encouraged to obtain an adequate intake of dietary calcium (at least 1000 mg per day, including supplements if necessary) and vitamin D (at least 800-1000 international units per day for adults 50 years of age and older) and to engage in regular exercise to maintain muscle strength and bone density.

Initiation of abiraterone or antiandrogen therapy is prohibited before radiographic disease progression.

Randomized study drug treatment must be permanently discontinued upon initiation of anti-cancer chemotherapy or antiandrogen therapy (eg, bicalutamide, nilutamide, or

flutamide). Note: Localized anticancer therapy (eg, topical treatment of non-melanoma skin malignancy, intravesical Bacillus Calmette-Guerin [BCG] treatment) may be acceptable upon prior Sponsor and Investigator agreement and written Sponsor approval.

Patients who discontinue study drug treatment due to initiation of any such therapy will remain in the study, complete safety follow-up per Section 5.4, and then begin long-term follow-up assessments every 12 weeks thereafter based on the 12-week visit schedule determined at randomization per Section 5.5.

The following treatments are allowed:

- Blood transfusions and growth factor support per standard of care and institutional guidelines;
- Corticosteroids for nonprostate cancer indication;
- Pain therapy per standard of care and institutional guidelines;
- Palliative procedures to treat skeletal-related events.

In addition, the administration of COVID-19 vaccine is permitted. Administration of COVID-19 vaccine should be recorded on the eCRF as a concomitant medication with applicable standard adverse event collection and reporting processes.

Deviation from these guidelines should occur only if absolutely necessary for the well-being of the patient, and the medical monitor is to be notified to determine the patient's suitability for continued treatment with study drug.

7.3. Potential Interactions Between the Test Products and Concomitant Medications

7.3.1. Enzalutamide

7.3.2. Effects of Enzalutamide on Exposure to Other Drugs

Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19 (Section 1.2.1). Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted at local laboratories.

7.3.2.1. Drugs That May Affect Exposure to Enzalutamide

7.3.2.1.1. Drugs That Inhibit or Induce CYP2C8

Coadministration of a strong CYP2C8 inhibitor (eg, gemfibrozil) increased the composite $AUC_{0-\infty}$ of enzalutamide plus its active metabolite in healthy volunteers by 2.2-fold (Section 1.2.1); therefore, coadministration of enzalutamide with strong CYP2C8 inhibitors

should be avoided if possible. If coadministration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, the enzalutamide dose should be reduced to 80 mg once daily. If coadministration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used before initiation of the strong CYP2C8 inhibitor.

The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated in vivo. Coadministration of enzalutamide with strong or moderate CYP2C8 inducers (eg, rifampin) may alter the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

7.3.2.1.2. Drugs That Induce CYP3A4

The effects of CYP3A4 inducers on the PK of enzalutamide have not been evaluated in vivo. Coadministration of enzalutamide with strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided if possible.

7.3.3. Leuprolide

Leuprolide is a nonapeptide that is metabolized by hydrolysis. No known CYP interactions have been elucidated and no interaction studies have been performed.[18],[19]

7.4. Precautions Regarding Concomitant Medications

Refer to the following websites for updated lists of CYP inhibitors, inducers, and substrates:

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency;
- http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

8. ADVERSE EVENT REPORTING

Study assessments of safety include adverse events, clinical laboratory tests, physical examinations, and vital signs.

In the following sections, the sponsor's safety monitoring procedures are described. Adverse events are discussed in detail in the context of patient management, study drug dose modification, emergency unblinding of treatment assignment, and safety reporting requirements, including follow-up procedures (Section 8.2, Section 8.3, and Section 8.5). Clinical laboratory safety tests are presented (Section 8.6). The study procedures for physical examinations, vital signs, and ECGs are also provided (Section 8.7).

The sponsor will periodically monitor safety data during the clinical study in addition to reviewing individual safety case reports, by examining the incidence and severity of adverse events and serious adverse events, changes in laboratory results, and other data (such as aggregate analysis of data from other enzalutamide studies). Any relevant safety concerns will be communicated to the investigators and regulatory agencies, as appropriate.

A Data Monitoring Committee will meet periodically during the study to monitor patient safety, identify potential safety signals and patterns, and perform benefit-risk assessments (Section 11).

8.1. Requirements

The table below summarizes the requirements for recording safety events on the Case Report Form and in the database for reporting safety events on the Clinical Trial Serious Adverse Event (CT SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) Serious Adverse Events (SAEs); (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the Case Report Form**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on

previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the case report form. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, case report form, laboratory data) are to be sent to Pfizer Safety ONLY upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious 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.

8.1.1. Additional Details On Recording Adverse Events on the Case Report Form

All events detailed in the table above will be recorded on the AE page(s) of the case report form. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the case report form. When the same data are collected, the forms 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 case report form and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the case report form all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the case report form.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the case report form and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above and Section 5.3.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 30 days after the last administration of the investigational product.

8.1.5. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient 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.

8.1.6. Recording Non-serious AEs and SAEs on the Case Report Form

During the active collection period, both non-serious AEs and SAEs are recorded on the case report form.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the case report form during the above-indicated active collection period.

8.1.7. Causality Assessment

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

The investigator will assess the relationship of an adverse event to study drug according to the criteria in Table 10 and document the relationship in the patient's source documents.

Adverse events considered in the relationship categories of "Possible" or "Probable" should be considered "adverse events whose relationship to the study drugs could not be ruled out."

Table 10. Criteria for Determining Causal Relationship to Study Drug

Relationship	Criteria
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable, and/or in which other drugs, chemicals, or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

8.1.8. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Special Safety Considerations

8.2.1. Study Drug Dose Modification Due to Adverse Event

The instructions for modifying the dose of study drug due to an adverse event are provided in Section 6.2.4 for enzalutamide or placebo. This study has no provisions for dose modification of leuprolide.

8.2.2. Emergency Procedure for Unblinding Treatment Assignment Due to Adverse Event

An emergency procedure for breaking the blind will be built into the randomization system (IWRS). Unblinding of treatment assignment at the study site should occur only if the knowledge will materially change the immediate clinical management of a patient in a medical emergency. When possible, the investigator should attempt to contact the medical monitor before unblinding a patient's treatment assignment.

To unblind a patient's treatment assignment, the investigator will access the unblinding module within the IWRS. The reason for breaking the blind must be documented in the source documents.

Patients whose treatment assignment has been unblinded will permanently discontinue randomized study drug treatment, have safety follow-up, and commence long-term follow-up.

8.2.3. Contraception

A patient must use a condom if having sex with a pregnant woman. Patients must not donate sperm from first dose of study drug through 3 months after the last dose of study drug.

The patient and his female partner of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method) from screening through 3 months after the last dose of study drug or per local guidelines where these require additional description of contraceptive methods. The 2 acceptable methods of birth control are as follows:

1. A condom (barrier method is required);

   AND

2. One of the following is required:

   Established and ongoing use of oral, injected, or implanted hormonal method by the female partner;

   Placement of an intrauterine device or intrauterine system by the female partner;

   Additional barrier method including contraceptive sponge or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner;

   Tubal ligation in the female partner performed at least 6 months before screening;

   Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy) performed at least 6 months before screening.

8.3. Definitions

8.3.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;

- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the case report form. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.3.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.3.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the case report form, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE version 4) grade 5 (see the Severity Assessment section).

8.3.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.4. Severity Assessment

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed in Table 11.

Table 11. Criteria for Determining the Severity (Intensity) of an Adverse Event

Grade	Intensity or Severity	Clinical Description
1	Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening	Life-threatening consequences; urgent intervention indicated
5	Death	Death related to adverse event

Source: Common Terminology Criteria for Adverse Events v4.0.

8.5. Special Situations

8.5.1. Protocol –Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.5.2. 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili 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 TBili 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 subject's individual baseline values and underlying conditions. Subjects 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:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST OR ALT OR TBili 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 TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili 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 subject 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.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/INR, total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. 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 (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, 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 and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (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.

8.5.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.5.3.1. Exposure During Pregnancy

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

  An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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 EDP supplemental form. 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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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 includes miscarriage and missed abortion;
- 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 investigational product.

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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.5.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.5.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported 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 does not pertain to a subject enrolled in the study, the information is not recorded on a case report form; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.5.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors and lack of efficacy.

Safety Event	Recorded on the Case Report Form	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.5.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the case report form, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the case report form and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the case report form.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form only when associated with an SAE.

8.5.4.1.1. Overdose of Enzalutamide

The medical monitor must be contacted in the event of a study drug overdose.

An overdose is defined as any dose greater than the protocol-specified dose of enzalutamide 160 mg once daily. In the event of an overdose, treatment with study drug should be stopped and general supportive measures initiated, taking into consideration the half-life is 5.8 days for enzalutamide. Patients may be at increased risk of seizures following an overdose of enzalutamide. There is no known antidote to overdose.

All overdose events are to be reported as special events of interest within 24 hours of awareness by the study site according to Section 8.5.5, whether or not the event meets adverse event criteria.

8.5.4.1.2. Overdose of Leuprolide

There is no experience with overdose of leuprolide in clinical trials. In rats, a single subcutaneous dose of 100 mg/kg (approximately 4000 times the estimated daily human dose based on body surface area) resulted in dyspnea, decreased activity, and excessive scratching. In early clinical studies with daily subcutaneous leuprolide acetate, doses as high as 20 mg/day for up to 2 years caused no adverse effects differing from those observed with the 1 mg/day dose.

8.5.5. Serious Adverse Event and Event of Special Interest Reporting

Study site personnel will collect serious adverse event information from the time the patient signs the informed consent form through screen failure and 30 days after the last dose of randomized study drug (permanent discontinuation).

Using a Pfizer CT SAE Report Form, all serious adverse events and events of special interest must be reported **within 24 hours** of the study site personnel's knowledge of the event to Pfizer Safety. All second malignancies (with the exception of uncomplicated nonmelanoma skin cancers) must be reported as a serious adverse event.

The initial report should include, at minimum, the following:

- Study number (MDV3100-13, C3431004);
- Country and site number;
- Investigator name;
- Patient number, sex, and age;
- Details of study drug administration;
- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event);

- Causal relationship to the study drug.

If the patient died, the report should include the cause of death as the event term (with fatal outcome) and whether or not the death was related to study drug.

Single patient unblinding may be required for reporting suspected unexpected serious adverse reactions (SUSARs) to certain regulatory authorities. Access to this information will be strictly limited and will not require unblinding at the study site.

8.5.5.1. Clarification in Reporting of Seizures

Any event of seizure is to be reported as serious adverse event.

8.5.5.2. Clarification in Reporting of Deaths

As overall survival is one of the study endpoints, all patients must be followed for survival status until death, and information relating to the death (eg, date and primary cause) should be obtained and recorded. Deaths due to prostate cancer should be recorded as such by the investigator to allow for determination of prostate cancer-specific survival.

Fatal events (regardless of relationship to study drug) should be reported as serious adverse events during the treatment-emergent safety reporting period (through 30 days after permanent treatment discontinuation).

Death is not an adverse event but is an outcome of an adverse event. For this protocol, reports of death without an adverse event will be managed as expedited reports (SUSARs) until the sponsor receives additional information.

8.5.6. Follow-Up of Serious and Nonserious Adverse Events

All adverse events reported during the study should be followed at appropriate intervals until resolution, or until the event has stabilized or reached a new baseline (all follow-up results are to be reported to the sponsor or designee).

Adverse events that remain unresolved at the conclusion of the study may continue to be monitored if warranted based on clinical assessment by the investigator and medical monitor.

Patients should be contacted by phone and written requests as appropriate for adverse event follow-up if they do not come to the clinic for safety follow-up as specified in Section 5.4.

8.6. Clinical Laboratory Safety Tests

Routine clinical laboratory safety tests (hematology, serum chemistry) will be performed according to the schedule of activities (Appendix 5), as will PSA and testosterone tests. Samples will be stored until the specified analyses are completed and then they will be destroyed in accordance with standard laboratory practice and applicable local regulations.

A list of the required routine clinical laboratory safety tests is provided in Table 12. All samples for laboratory analysis must be collected, prepared, labeled, and shipped according to laboratory requirements.

All clinical laboratory safety tests will be performed by the central laboratory specified in FDA 1572 or Investigator ICH GCP Attestation form Section 4. The central laboratory reference ranges will be used. Eligibility at screening will be based on central laboratory assessments.

For unscheduled visits or for urgent care, central laboratory kits should be used when possible; however, a different clinical laboratory may be used. Such laboratory data will not be entered into the study database and local laboratories will not be included on the FDA 1572 or Investigator ICH GCP Attestation form.

For protocol-specified safety laboratory evaluations that can be performed at a local laboratory because of the COVID-19 pandemic, refer to Appendix 6 Section A6-2.1.

Table 12. Clinical Laboratory Safety Tests

Hematology	Chemistry
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase
Mean corpuscular volume	ALT (alanine aminotransferase)
Platelet count	AST (aspartate aminotransferase)
Red blood cell count	Blood urea nitrogen and creatinine
White blood cell count with differential	Ca^{++}
	Creatine phosphokinase
	Glucose
	Lactate dehydrogenase
	Magnesium, phosphate
	Na^{+}, K^{+}, total CO_2 (bicarbonate), Cl^{-}
	Total bilirubin (TBili)
	Total protein

8.7. Physical Examinations, Vital Signs, and Electrocardiograms

The investigator will perform complete or brief physical examinations according to the schedule of activities (Appendix 5).

Complete physical examinations will be per standard care at the study site and may include dermatologic, cardiac, respiratory, lymphatic, gastrointestinal, musculoskeletal, and neurologic systems, and other systems if clinically indicated by symptoms. Weight will be measured as part of the examination. Height will be measured only at screening.

Brief physical examinations will be directed toward patient-reported symptoms and include investigating any new abnormalities. Weight will be measured as part of the examination.

Vital sign measurements will include blood pressure, heart rate, and temperature.

Standard 12-lead ECGs will be obtained and read locally for study eligibility purposes.

9. ASSESSMENT OF EFFICACY AND SAFETY ENDPOINTS

9.1. 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, testosterone, symptomatic skeletal events, pain scores, quality of life and PFS2.

9.1.1. Assessments for the Primary Efficacy Endpoint

On study assessments for the primary efficacy endpoint of MFS will include radiographic assessment of disease and monitoring of survival status.

9.1.2. Assessment of Radiographic Progression

Assessment for the primary efficacy endpoint of MFS will include radiographic assessment of soft tissue disease on CT or MRI, and bone disease on whole-body radionuclide bone scans. The determination of radiographic progression for the primary efficacy endpoint will be made by the independent, blinded central radiology reviewer.

Radiographic assessments will be obtained approximately every 6 months from the date of randomization until metastatic disease is observed. Scans may be obtained sooner if disease progression is clinically suspected. The study films (CT/MRI and bone scan) will be read at the local study site. 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. Study sites will be instructed to send the scans to a designated central facility.

9.1.2.1.1. Determination of Radiographic Progression in Soft Tissue

Soft tissue disease will be assessed using CT or MRI. Radiographic progression for soft tissue disease is defined by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) and in accordance with the central radiology reviewer agreement.[21] PET is not an evaluable imaging modality for this study. No confirmatory scans are required for soft tissue disease.

9.1.2.1.2. Determination of Radiographic Progression in Bone

Assessment of metastatic bone disease will be done by whole-body radionuclide bone scan. A bone scan will assess 5 regions of the skeleton, including skull, thorax, spine, pelvis, and extremities. Radiographic progression for bone disease is defined as the appearance of 1 or more metastatic lesions on bone scan. Confirmation with a second imaging modality (plain film, CT, or MRI) will be required when bone lesions are found in a single region on the bone scan. Appearance of metastatic lesions in 2 or more of the 5 regions on a bone scan will not require confirmation with a second imaging modality. PET is not an evaluable imaging modality for this study.

9.1.3. Assessments for the Secondary and Exploratory Efficacy Endpoints

On study assessments for the secondary and exploratory efficacy endpoints will include radiographic assessment of disease (Section 9.1.2), monitoring of survival status (Section 9.1.3.4), PSA, castration resistance (testosterone and PSA), resumption of any hormonal therapy, new antineoplastic therapy, and surgery/interventions for prostate cancer, symptomatic skeletal events, pain scores, quality of life, PFS2 therapy, and safety.

9.1.3.1. Assessment of PSA

PSA will be measured at the central laboratory throughout the study according to the schedule of activities (Appendix 5). With the exception of screening PSA values, PSA values will not be provided to study sites or patients. When PSA values are needed to make treatment decisions (such as the week 36 PSA value or subsequent PSA values for patients who are on study drug treatment suspension for undetectable PSA at week 36), study sites will be notified whether a patient's PSA value meets the specified threshold to determine whether or not to continue or suspend treatment at week 37, or whether to reinitiate study drug treatment.

Study sites will be notified when a suspended patient's central PSA meets the criteria for treatment reinitiation; suspended patients are to remain on treatment suspension until notified by the Sponsor to reinitiate study treatment.

If a central laboratory PSA value requires treatment reinitiation, the patient must return to the study site as soon as possible for study drug dispensing. The reinitiation must be registered in the IWRS to obtain study treatment assignment and provide a 12-week supply of study drug. (Refer to the IWRS Site Manual). Note after reinitiation dispensation, the patient will return to the clinic for their next expected study visit based on the 12-week visit schedule determined at randomization. Sites should attempt to bring in the patient after reinitiation notification as soon as possible, so that the treatment arm can be reinitiated immediately. If a patient is on the leuprolide arm, they will restart leuprolide and continue with their subsequent IP administration (including leuprolide as applicable) at their next study visit.

PSA values < 0.2 ng/mL will be considered undetectable for this study. Except for the week 36 PSA value (as described in the week 37 assessment in Section 5.2.6), study drug administration should continue regardless of PSA values until radiographic progression is confirmed by central imaging and the investigator considers continuing study drug not to be beneficial.

9.1.3.2. Assessment of Time to First Use of New Antineoplastic Therapy

The assessment of first use of new antineoplastic therapy will use the information collected on the case report forms for new and subsequent antineoplastic therapies used for prostate cancer after discontinuation of study drug treatment. This will include, medications used specifically for prostate cancer treatment including hormonal treatments, immunotherapy, chemotherapy and investigative agents.

9.1.3.3. Assessment of Time to Distant Metastasis

The assessment of distant metastasis in soft tissue and/or bone will be provided by the independent central radiology vendor. Soft tissue disease including lymph nodes above the aortic bifurcation and outside the pelvis and any bone metastases will be counted as distant metastases.

9.1.3.4. Assessment of Survival

The survival status of each patient will be monitored during study treatment, after suspension of study treatment at week 37 (if applicable), and after permanent treatment discontinuation for any reason. Survival status will be documented during long-term follow-up according to the schedule of activities (Appendix 5). The date and cause of death will be recorded for patients who die.

During the course of the study, the sponsor may request that a survival sweep be conducted to obtain an accurate number of deaths across the study. Blinded treatment assignments will remain blinded. The sponsor will provide instructions on these survival sweeps immediately before they commence as well as a timeline for contacting patients.

9.1.3.5. Assessment of Resumption of any Hormonal Therapy

The assessment of resumption of any hormonal therapy will use the information collected on the case report forms about hormonal therapies used for prostate cancer after treatment suspension at week 37 due to undetectable PSA.

9.1.3.6. Assessment of Symptomatic Skeletal Events

The assessment of symptomatic skeletal events will include monitoring 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain throughout the study. The assessment of opiate use will be based on questioning patients regarding their analgesic medication use. Opiate use for bone pain will be derived from the indication associated with the new use of an opiate.

9.1.3.7. Assessment of Castration Resistance

The assessment of castration resistance will include PSA and testosterone tests by the central laboratory, and assessments obtained in evaluation of radiographic progression and symptomatic skeletal events throughout the study according to the schedule of activities (Appendix 5). With the exception of screening PSA and testosterone values, castration-resistance status will not be provided to study sites or patients.

9.1.3.8. Assessment of Time to Symptomatic Progression

The assessment of time to symptomatic progression will be conducted using a composite of the assessments used in collecting time to development of symptomatic skeletal events, prostate cancer related pain, or worsening of disease-related symptoms requiring initiation of new systemic anti-cancer therapy, or development of adverse events or clinically significant signs and/or symptoms due to loco-regional tumor progression requiring opiate use, surgery/procedural intervention or radiation therapy, whichever occurs first.

9.1.3.9. Assessment of Pain

The assessment of pain progression will be conducted using the Brief Pain Inventory (Short Form). This questionnaire is a validated instrument that uses a self-reported scale assessing level of pain, its effect on activities of daily living, and analgesic medication use.

This study will use the short form containing 9 main questions related to pain. The primary question (paraphrased) is "On a scale of 0 to 10, please rate your pain at its worst in the last 24 hours."

The questionnaire is provided in Appendix 4. It is important that patients are fluent in reading the language used in the questionnaire and that they complete it at the beginning of their clinic visits and without influence of the investigator, study site staff, or anyone else. Patients who are illiterate, blind, or dyslexic; have motor deficit of their hands or difficulty working with electronic devices; or are otherwise unable to independently complete the questionnaires are not required to complete the electronic questionnaires.

9.1.3.10. Assessment of Quality of Life

The assessment of quality of life will include the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, the European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L), and the Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) module. Patients should complete the questionnaire information at the beginning of study visits, while alone. Patients who are illiterate, blind, or dyslexic; have motor deficit of their hands or difficulty working with electronic devices; or are otherwise unable to independently complete the questionnaires are not required to complete the electronic questionnaires.

The FACT-P questionnaire is a multidimensional, self-reported, quality-of-life instrument specifically designed for use in men with prostate cancer. The questionnaire contains 27 core items to assess function during the prior 7 days in the 4 domains of physical, social/family, emotional, and functional well-being; it also contains 12 site-specific items to assess 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 a global quality-of-life score, with higher scores representing better quality of life. The FACT-P questionnaire is provided in Appendix 1.

The EQ-5D-5L questionnaire is a standardized instrument that measures health-related quality of life for men with prostate cancer. Patients will self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression by choosing 1 of 5 possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. The questionnaire also includes a visual analog scale to self-rate general health state on a scale from "the worst health you can imagine" to "the best health you can imagine." The EQ-5D-5L questionnaire is provided in Appendix 2.

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-PR25, a module of the EORTC QLQ-30 questionnaire, was developed to assess the quality of life of patients with prostate cancer. Patients will self-rate their current state of pain as it relates to urination, ease and frequency of urination, and bowel and other problems during the past week. Patients will also answer 5 questions about weight loss/gain and sexual interest and 4 questions about sexual activity during the past 4 weeks. Patients will choose 1 of 4 possible responses that record level of intensity (not at all, a little, quite a bit, very much) within each dimension. The QLQ-PR25 module is provided in Appendix 3.

9.1.3.11. Assessment of PFS2

The assessment of PFS2 will use the information collected on the case report forms during long-term follow-up related to subsequent prostate cancer treatments and investigator assessed disease progression on the subsequent treatment. The date and cause of progression including, radiographic, clinical or PSA progression will be recorded.

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 occurred first, while the patient was receiving first subsequent therapy for prostate cancer. PFS2, an exploratory analysis, 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.

9.2. Assessment of Safety

Assessments of safety will include adverse events, clinical laboratory tests, physical examinations, and vital signs. The reason for permanent treatment discontinuation will also be collected. The procedures for the investigator assessment of adverse events are presented in detail in Section 8. The procedures for clinical laboratory safety tests are presented in Section 8.6, and for physical examinations, vital signs, and ECGs in Section 8.7.

If the safety of a study participant is at risk, because the participant cannot complete required evaluations or adhere to critical mitigation steps, the Sponsor should be consulted before the participant is discontinued from study treatment/intervention. If patient discontinuation is associated with the COVID-19 pandemic, and not related to any Adverse event, enter "COVID-19" in the "Other, specify" field of the eCRF.

9.3. ECOG Performance Status Assessments

ECOG performance status assessments are required to assess patient functional status for study eligibility purposes and will be performed throughout the study according to the schedule of activities (Appendix 5). Details of the assessment are shown in Table 13.

Table 13. ECOG Performance Status Assessments

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

Source: Oken et al (1982).[22]

10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

10.1. Statistical and Analytical Plans

A statistical analysis plan will present the detailed statistical methods and analyses for this study.

10.2. Randomization Methods

Central randomization will be used and treatment allocation to the 3 treatment groups will be 1:1:1. Randomization will be stratified by screening PSA ≤10 ng/mL versus >10 ng/mL, PSA doubling time ≤3 months versus >3 to ≤9 months, and prior hormonal therapy versus no prior hormonal therapy.

10.3. Analysis Populations

The intent-to-treat population (ITT) is defined as all patients randomly assigned to study treatment. The intent-to-treat population will be used for all efficacy analyses unless otherwise specified, and will be analyzed based on randomized treatment assignment.

The evaluable ITT population is defined as all patients in the ITT population who have confirmed nonmetastatic disease at baseline by independent central radiology review. This analysis population will be used for certain efficacy analyses as specified in the statistical analysis plan.

The safety population is defined as all patients who receive any amount of study drug. The safety population will be used for all safety analyses. The safety population will be analyzed based on the treatment received and not the treatment assigned.

10.4. Efficacy Analyses

All efficacy analyses will incorporate the randomization stratification by screening PSA ≤10 ng/mL versus >10 ng/mL, PSA doubling time ≤3 months versus >3 to ≤9 months, and by prior hormonal therapy versus no prior hormonal therapy, unless otherwise noted.

The analytical approach will be described in detail in the statistical analysis plan.

Patients who are randomized and later found to have metastatic disease at enrollment will be censored at randomization for time-to-event analyses. The statistical analysis plan will provide details for additional sensitivity analyses of selected endpoints.

10.4.1. Primary Efficacy Endpoint Analysis: Metastasis-Free Survival

For the primary endpoint, MFS, the stratified log-rank test will be used to compare enzalutamide plus leuprolide versus placebo plus leuprolide.

The primary efficacy endpoint is MFS using independent, central, blinded radiology reviewer assessment of radiographic progression as described in Section 9.1. MFS is defined as the duration of time in months between randomization and the earliest objective evidence of radiographic progression by central imaging or death. Emergent metastatic disease and deaths that occur while study drug treatment is suspended at week 37 due to undetectable PSA per protocol will be counted as MFS events regardless of their timing.

The primary endpoint analysis will be performed when at least 197 MFS events occur in the 3 treatment groups combined, at which time at least approximately 142 MFS events are expected to occur in the 2 blinded treatment groups combined for the primary hypothesis. A 2-sided stratified log-rank test will be used to compare enzalutamide plus leuprolide versus placebo plus leuprolide at 0.05 level of significance.

10.4.2. Key Secondary Efficacy Endpoint Analyses

Secondary endpoints will be evaluated using the ITT population. Kaplan-Meier methods will be used to describe the distributions of all time to event endpoints with inferential testing conducted using the stratified log rank test. Stratification factors at randomization will be included in the analyses as specified. Treatment group comparisons will be between the combination arm of enzalutamide plus leuprolide versus placebo plus leuprolide and between enzalutamide monotherapy therapy versus placebo plus leuprolide.

If the MFS test at the combination level is significant at the full alpha level of 0.05, the key secondary endpoints will be tested at alpha 0.02 utilizing a hierarchical approach to preserve the family-wise type I error rate for the combination arm. The remaining 0.03 alpha will be allocated to compare MFS as well as other key secondary endpoints for enzalutamide monotherapy versus placebo plus leuprolide.

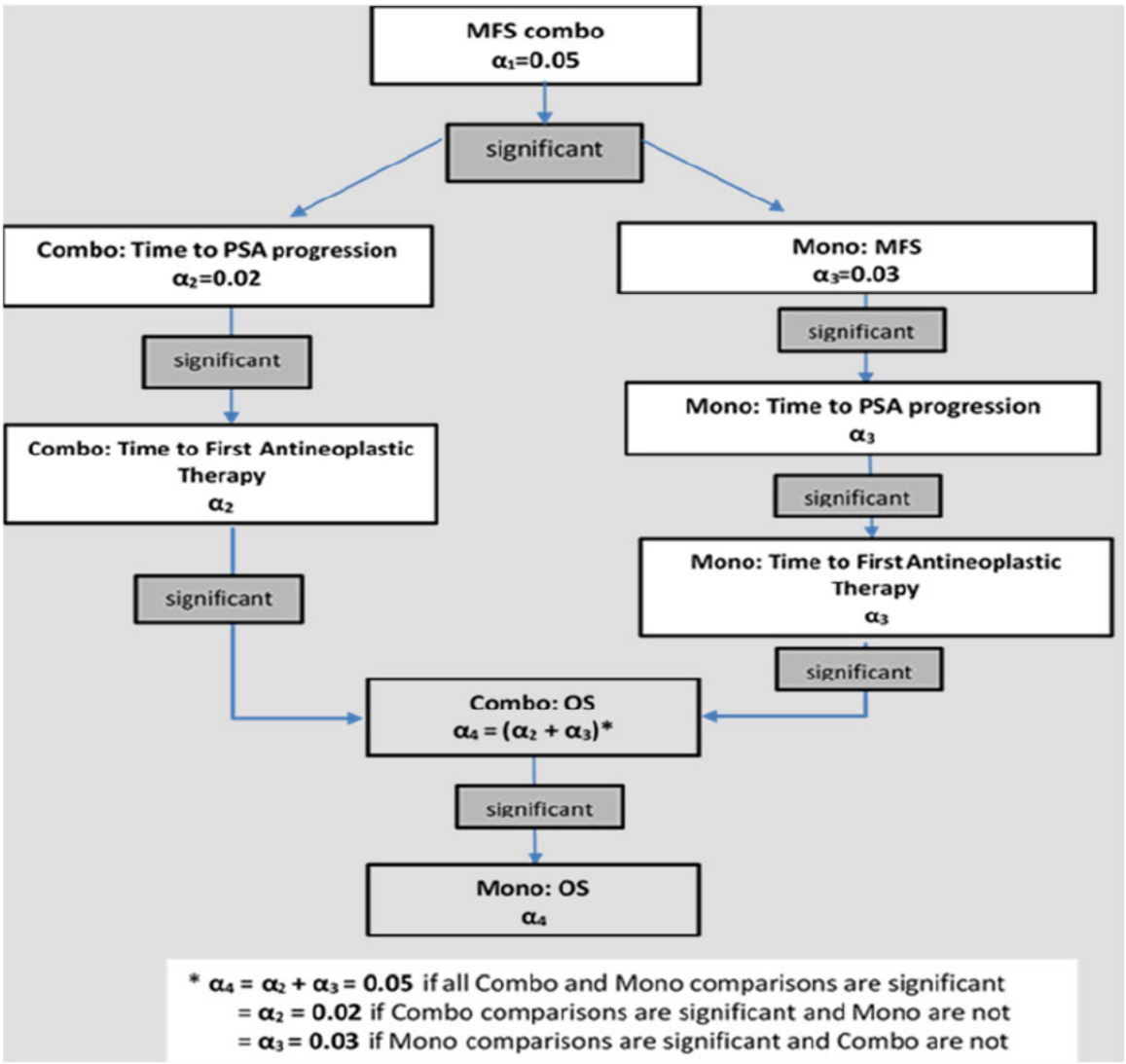
For the combination arm comparisons, if time to PSA progression is significant at the alpha level of 0.02, the alpha level is carried forward to test for the time to first use of antineoplastic therapy endpoint. If this is also significant at alpha level of 0.02, then the alpha level is carried forward to test the third endpoint of overall survival.

For the monotherapy comparison, if MFS test at the alpha level of 0.03 is significant, the key secondary endpoints will be tested in a similar hierarchical fashion for monotherapy as described above for combination therapy with an alpha level of 0.03.

If all key secondary comparisons for the combination arm comparisons are significant at the alpha level of 0.02, and for the monotherapy comparisons at the alpha level of 0.03, then OS for the combination arm will be tested at the alpha level of 0.05. Otherwise, only the alpha from the significant set of key secondary comparisons will be carried forward. OS for the monotherapy comparison will be tested in a hierarchical fashion at the same alpha level as the combination arm comparison if significant.

The methodology is described in Figure 2.

Figure 2. Testing Flowchart for Primary Endpoint and Key Secondary Endpoints of Combination Therapy and Monotherapy



10.4.2.1. 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 patients are on study treatment which is subsequently confirmed at least 3 weeks later.

In patients who DO NOT have treatment suspended due to undetectable PSA at week 36: Those with PSA decline at week 25, the PSA progression date is defined as the date that a ≥25% increase and an absolute increase of ≥2 μg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline by week 25).

For patients who have treatment suspended due to undetectable PSA at week 36: Following treatment suspension and reinitiation of study drug, the PSA progression date is defined as the date that a ≥25% increase and an absolute increase of ≥2 μg/L (2 ng/mL) above the nadir at week 36 is documented, which is confirmed by a second consecutive value obtained at a subsequent study visit. It will be compared between treatment groups using a 2-sided stratified log rank test.

10.4.2.2. Time to First Use 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 for prostate cancer. This will include medications used specifically for prostate cancer treatment including hormonal treatments, immunotherapy, chemotherapy and investigative agents. Patients 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.

10.4.2.3. Overall Survival

Overall survival is defined as the time between randomization and death of any cause. Overall survival will be compared between treatment groups using a 2-sided stratified log rank test. Long-term follow-up data (survival status, skeletal related events and new prostate cancer therapies) will be collected every 12 weeks up until the final analysis of OS.

10.4.3. Other Secondary Efficacy Endpoint Analyses

The following efficacy analyses will be performed for the ITT population. The resulting p-values will be considered descriptive and no adjustment will be made for multiplicity. Treatment group comparisons will be between the combination arms of enzalutamide plus leuprolide versus placebo plus leuprolide and between enzalutamide monotherapy therapy versus placebo plus leuprolide.

10.4.3.1. Time to Distant Metastasis

The time to distant metastasis is defined as the time in months from randomization to the earliest objective evidence of distant soft tissue metastases or metastatic bone disease by central imaging. Soft tissue disease including lymph nodes above the aortic bifurcation and

outside the pelvis and any bone metastases will be counted as distant metastases. It will be compared between treatment groups using a 2-sided stratified log rank test.

10.4.3.2. Proportion of Patients who Remain Treatment-Free at 2 Years After Suspension of Study Drug Treatment

The proportion of patients per group who remain treatment-free 2 years after suspension of study drug treatment at week 37 due to undetectable PSA will be compared between treatment groups using the stratified Cochran-Mantel-Haenszel test. Two-sided 95% CIs per group will be reported using the Clopper-Pearson method.

10.4.3.3. Proportion of Patients With Undetectable PSA at 2 Years

The proportion of patients per group with undetectable PSA 2 years after suspension of study drug treatment at week 37 due to undetectable PSA will be compared between treatment groups using the stratified Cochran-Mantel-Haenszel test. Two-sided 95% CIs per group will be reported using the Clopper-Pearson method.

10.4.3.4. Proportion of Patients With Undetectable PSA at 36 Weeks

The proportion of patients per group with undetectable PSA at 36 weeks will be compared between treatment groups using the stratified Cochran-Mantel-Haenszel test.

10.4.3.5. Time to Resumption of any Hormonal Therapy

The time to resumption of any hormonal therapy is defined as the time between the date of treatment suspension at week 37 due to undetectable PSA and the date that hormonal therapy is restarted. The time to resumption of any hormonal therapy will be compared between treatment groups using a 2-sided log-rank test.

10.4.3.6. Time to First Symptomatic Skeletal Event

The time to first symptomatic skeletal event is 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, or new use of opiate and/or systemic antineoplastic therapy due to bone pain, 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 overall survival analysis. The time to first symptomatic skeletal event will be compared between treatment groups using a 2-sided stratified log-rank test.

10.4.3.7. Time to Castration Resistance

Castration resistance applies only to patients receiving leuprolide treatment and is defined as the first occurrence of radiographic disease progression, PSA (as defined above) progression or symptomatic skeletal event with castrate levels of testosterone (<50 ng/dL). Time to castration resistance is defined as the time from randomization to the first castration-resistant event (radiographic disease progression, PSA progression or symptomatic skeletal event), whichever occurs first.

10.4.3.8. Time to Symptomatic Progression

Time to symptomatic progression is defined as the time from randomization to development of a skeletal-related event, worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy, or development of adverse events and clinically significant signs and/or symptoms due to loco-regional tumor progression requiring opiate use, surgical intervention or radiation therapy, whichever occurs first.

10.4.3.9. Time to Clinically Relevant Pain

Clinically relevant pain is defined as a 2-point increase from baseline on the Brief Pain Inventory (Short Form) question 3. The time to clinically relevant pain will be compared between treatment groups using a 2-sided log-rank test.

10.4.3.10. Quality of Life

Quality of life will be measured by time to a 10-point decline in global FACT-P score and assessed using the EQ-5D-5L and QLQ-PR25 questionnaires. The time to decline in global FACT-P score will be compared between treatment groups using a 2-sided log-rank test. FACT-P, EQ-5D-5L, and QLQ-PR25 data will be summarized descriptively by study visit.

10.4.4. Exploratory Analyses

10.4.5. 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 occurred first, while the patient 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.

10.5. Safety Analyses

All safety analyses will be performed using the safety population.

Safety analyses will be summarized by treatment. Safety will be evaluated by the incidence of serious adverse events, incidence and severity of adverse events, incidence of permanent treatment discontinuation due to adverse events, and incidence of new clinically significant changes in clinical laboratory values and vital signs.

The treatment-emergent period is defined as the duration of time from the date and time of the first dose of any randomized study drug treatment (enzalutamide plus leuprolide, enzalutamide monotherapy, or placebo plus leuprolide) through 30 days after the last dose of randomized study drug treatment (permanent treatment discontinuation). The treatment-emergent period will include the period from first dose through potential protocol-specified suspension and potential resumption of study drug treatment before permanent treatment discontinuation. Safety data collected following 30 days after study drug suspension and during the time off study drug treatment will be analyzed and described.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class and by preferred term within each system organ class. Tabular summaries will include the incidence overall (number and percentage of patients with treatment-emergent adverse events classified by system organ class and preferred term); incidence by intensity (severity graded according to the CTCAE, version 4), causality, seriousness, and outcome (eg, leading to discontinuation of study drug); and other presentations as appropriate.

Serious adverse events occurring before study treatment will be tabulated separately if considered related to study procedure.

Patients with the same adverse event reported more than once will be counted once at the maximum severity or strongest relationship to study drug.

Toxicity for laboratory parameters (hematology, serum chemistry) will be graded using the CTCAE, version 4 when applicable. Shift tables will be provided as appropriate for each parameter to summarize baseline toxicity grade versus postbaseline toxicity grade. For each laboratory parameter that is not gradable by the CTCAE, a shift table based on the normal range (low, normal, and high) will be provided to summarize baseline result versus postbaseline result. For each laboratory parameter, the baseline laboratory value is defined as the last laboratory value collected on or before the date of the first dose of study drug.

10.6. Other Analyses

Exposure: The dose and cumulative dose of enzalutamide (mg), placebo, and leuprolide (mg) will be summarized with descriptive statistics: n, mean, standard deviation, median, and range.

1. Summary of exposure during the time that patients actually receive protocol therapies (excludes days that study drug treatment is suspended due to undetectable PSA at week 36).

2. Summary of exposure during the entire study period (includes days that study drug treatment is suspended due to undetectable PSA at week 36).

Treatment compliance: For enzalutamide, will be measured by the number of capsules taken during the entire study divided by the expected number of capsules, multiplied by 100%.

10.7. Determination of Sample Size

The following assumptions were used in determining the sample size for this study:

- Overall type I error rate: 0.05;

- Patient accrual rate: Utilizing an adaptive enrollment rate, the following rate has been modified into two arms to fit into EAST v6.4 software from Cytel.

Period #	Starting at Time	Accrual Rate
1	0	6
2	12	17.3
3	24	16.6
4	27	19.3
5	30	28.3
6	34	22
7	38	30
8	42	33.3
9	44	28.7
10	48	33.3

- Randomization: 1:1:1;
- Median MFS for the control group: 55 months.

An observed 142 MFS events in the 2 blinded treatment groups will provide approximately 90% power to detect a target hazard ratio of 0.58 using a 2-sided log-rank test with a 0.05 level of significance. This target hazard ratio corresponds to a difference of approximately 40 months in median MFS assuming an exponential distribution in the duration of MFS and a constant hazard rate for each group. For the key secondary hypothesis of MFS between the monotherapy arm, the target effect size, and expected number of MFS events will be the same as the primary hypothesis in the combination arm. As the 2-sided alpha level will be 0.03 for the monotherapy arm comparison, the power for this analysis will be 86% with 142 MFS events observed. At the time of the final analysis, at least 197 MFS events total are required for the 3 treatment groups. An enrollment of approximately 1050 patients (350 in each group) is required to achieve the targeted total of 197 MFS events allowing for a 5% loss to follow-up, as outlined in the Statistical Analysis Plan.

An actual enrollment of 1068 patients will also allow for an assessment for the key secondary endpoint of OS, assuming a 5-year OS rate of 80% for the control arm and hazard ratio of 0.67.

The significance level associated with the test of OS, in blinded treatment arm and monotherapy arm comparisons, will depend on the outcome of the key secondary endpoints (see Figure 2). If both time to PSA progression and time to first use of antineoplastic therapy are statistically significant for the blinded treatment arms, then an alpha of 0.02 will be contributed to the comparison of OS according to the gatekeeping procedure. Similarly, if MFS, time to PSA progression, and time to first use of antineoplastic therapy are all statistically significant for the monotherapy treatment arm then an alpha of 0.03 will be contributed to the comparison of OS. With 191 deaths, the power to detect a hazard ratio of 0.67 is 79.0% (if all key secondary endpoints are significant for both the blinded arm and monotherapy arm comparisons), 72.3% (if the key secondary endpoints are significant for the monotherapy arm only) or 67.0% (if the key secondary endpoints are significant for the blinded arms only) using a 2-sided log-rank test at a significance level of 0.05, 0.03 or 0.02, respectively, and a 2-look group sequential design with a Haybittle-Peto efficacy boundary.

The data cut-off for the final MFS analysis will occur when at least 197 MFS events, based on independent central review, have occurred in the 3 treatment arms.

The data cut-off for the final OS analysis will occur after 271 OS events have occurred in the 3 treatment arms.

10.8. Interim Analysis

There will be no interim analysis for the primary endpoint (MFS). The interim and final analyses for the key secondary endpoint OS will be performed after the target number of events have occurred in the 3 treatment arms. A maximum of 2 distinct analysis cut-offs are planned according to the approximate number of events as described below:

- Final MFS and OS Interim: when at least 197 MFS events have occurred as assessed by the independent central radiology review have occurred in the 3 treatment groups;
- Final OS: when 271 deaths have occurred in the 3 treatment groups.

Table 14 shows the efficacy boundary associated with the final analysis of the primary endpoint of MFS between enzalutamide plus leuprolide and placebo plus leuprolide, according to independent central radiology review.

Table 14. MFS Based on Independent Review (2 blinded treatment arms) - Efficacy Boundary

Analysis	Analysis Cut-off Trigger	Number of MFS Events (2 blinded arms)[a]	Fraction of Required MFS Events	p-value (z-value) for Efficacy
Final MFS	197 MFS events in 3 arms	142	100%	⩽0.05 (-1.9600)

a. Number of events expected for MFS in blinded treatment arms assuming a hazard ratio of 0.58.

Table 15 shows the analysis triggers for OS as well the associated Haybittle-Peto efficacy boundaries. The significance level for the analyses of this key secondary endpoint is determined by the gatekeeping procedure.

Table 15. OS (2 blinded treatment arms) - Efficacy Boundaries

Analysis	Analysis Cut-off Trigger	Number of OS Events (2 blinded arms)[a]	Fraction of Required OS Events	p-value (z-value) for Efficacy[b]
IA OS	197 MFS events in 3 arms	82	43%	≤0.0001 (-3.89059)
Final OS	271 OS events in 3 arms	191	100%	≤0.04999 (-1.96001)

a. Number of events expected for OS in blinded treatment arms assuming a hazard ratio of 0.67.
b. The p-values and z-values noted for OS are those associated with the scenario where all the key secondary endpoints for the blinded treatment arms and the monotherapy arm are statistically significant (α=0.05).

Safety data will be summarized as described in Section 10.5. The timing and details of the E-DMC review are described in Section 11. The Statistical Analysis Plan (SAP) will describe the planned interim analysis in greater detail.

11. STUDY COMMITTEES AND COMMUNICATIONS

The independent E-DMC consisting of experts in prostate cancer, clinical trial safety monitoring, and statistics will evaluate safety data on a periodic basis for this study. Approximately every 6 months after the first 50 patients are enrolled and have reached their week 13 assessment, the E-DMC will review all available safety data and survival data. A separate charter will outline the details for the composition and responsibility of the E-DMC.

12. LABORATORY REQUIREMENTS

A central laboratory will analyze the clinical laboratory safety samples (hematology, serum chemistry) as well as the samples for PSA and testosterone for this study, as described in Section 8.6. The laboratory manual for this study provides details regarding sample collection procedures and laboratory tests.

13. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

Before initiating the study, the investigator must provide the following documents to the sponsor or designee:

- Fully executed and signed Form FDA 1572, or Investigator ICH GCP Attestation Form (as appropriate) ;
- Fully executed clinical trial agreement;
- Current curriculum vitae (also applies to all subinvestigators listed on the Form FDA 1572 or Investigator ICH GCP Attestation Form);

- Financial disclosure (also applies to all subinvestigators listed on the Form FDA 1572 or Investigator ICH GCP Attestation Form);
- Signed protocol signature page;
- Signed acknowledgment of receipt of the current Enzalutamide Investigator Brochure;
- Signed acknowledgment of receipt of the prescribing information for leuprolide;
- Ethics committee (EC) approval letter;
- EC-approved informed consent form;
- Additional documents as necessary per local requirements.

If an investigator changes during the course of the study, the sponsor and any local regulatory authorities, as applicable, must first approve the change of investigator and the new investigator must provide the sponsor all of the documents listed above.

The sponsor personnel or representatives may visit the study site, if necessary, before initiation of the study to review information with study site personnel about protocol requirements pertaining to the study drug, case report forms, monitoring, serious adverse event reporting, and other relevant information.

13.1. 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 Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

13.1.1. 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.

13.1.2. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative 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 or their legally authorized representative (if allowed by local regulations) 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 or their legally authorized representative 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 or their legally authorized representative 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 or their legally authorized representative.

The participant or their legally authorized representative 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 or their legally authorized representative 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 or their legally authorized representative 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 or their legally authorized representative (if allowed by local regulations).

13.1.3. 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 data sets 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.

13.2. Data Quality Assurance

13.2.1. Data Management

Clinical data management will be performed by the sponsor or designee according to procedures described in a comprehensive data management plan. The data management plan will include procedures for processing the data from this study, and will describe the responsibilities of the sponsor and designee when clinical data management is provided by an external vendor. In particular, the data management plan will include a list of the standard operating procedures that apply to this study.

Adverse events and medications will be coded using MedDRA and the World Health Organization Drug Dictionary (WHO-DD), respectively. The dictionary versions will be named in the data management plan.

13.2.2. Case Report Forms

The study will use an electronic data capture system. All electronic case report forms will be designed and provided electronically to the site by the sponsor or designee and electronic data capture system vendor. All case report form books are to be filled out completely, reviewed, and signed by the investigator or subinvestigators listed on the Form FDA 1572 or other appropriate local health authority documents. 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.

13.2.3. Study Monitoring

The sponsor or designee will monitor this study in accordance with current GCP guidelines. By signing this protocol, the investigator grants permission to the sponsor or designee and appropriate regulatory authorities to conduct onsite monitoring of all appropriate study documentation. To ensure the accuracy of data collected on the case report forms, it is mandatory that sponsor representatives (eg, study monitor) have direct access to original source documents (eg, paper or electronic patient records, patient charts, and laboratory reports) needed to verify the entries on case report forms. During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality.

A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various original medical records (paper or electronic) related to the study. The study monitor will be responsible for inspecting the case report forms at regular intervals throughout the study, to verify the adherence to the protocol and the completeness and correctness of all case report form entries. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2.4. Study Audits

During the course of the study and after study completion, it is likely that one or more quality assurance audits will be undertaken by authorized sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed upon time. By signing this protocol, the investigator grants permission to the sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

13.3. Investigational Product Accountability

The investigator must maintain accurate records (including dates, quantities, and identification numbers) of all study drug supplies received. All records must be made available to the sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

Current ICH GCP guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (eg, pharmacist), and the following:

- That such deliveries are recorded, for example, on the sponsor's drug accountability log or other sponsor-approved pharmacy log;
- That study drug is handled and stored safely and properly in accordance with the label and the study protocol;
- That study drug is only dispensed to study patients in accordance with the protocol;
- That any used or unused drug is returned by the patient at each required visit;
- That any unused study drug is returned to the sponsor-designated facility or standard procedures for the alternative disposition of unused study drug are followed and only after approval by the sponsor representative.

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drug to any persons except the patients in this study.
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions as required by the study drug label, accessible only to those authorized by the investigator to dispense these study drugs.

- The investigator/pharmacist will maintain a study drug inventory. The inventory will include details of material received and a clear record of when they were dispensed and to which patient.

- The investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the drug accountability record at the conclusion or termination of this study. It must be possible to reconcile delivery records with those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.

- Used or unused study drug may be destroyed at the study site according to standard institutional procedures if the sponsor agrees with the procedure, and after drug accountability has been conducted by the sponsor or representative, unless otherwise approved. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the sponsor or designee upon request for review and approval before the first onsite destruction. Unused study drug not destroyed at the site must be returned to the sponsor-designated facility at the end of the study or upon expiration.

13.4. Compensation, Insurance, and Indemnity

In the event of a side effect or injury, appropriate medical care as determined by the investigator or designated alternate will be provided.

If bodily injury is sustained, resulting directly from the use of the study drug or by required study procedures, the sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury that is not covered by the patient's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and study staff. No other compensation of any type will be provided by the sponsor. Financial compensation for lost wages, disability, or discomfort due to the study participation or procedures is not available.

13.5. Retention of Records

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.

13.6. Study Termination

The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.

The sponsor reserves the right to terminate the study anytime. When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may terminate the study and send a written notice of the termination along with the reasons to the investigator.

If an investigator or the investigator's EC intends to terminate participation in the study, the investigator must immediately inform the sponsor and provide the reason for it.

13.7. 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.

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.

13.8. Publication Policy

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of Medivation and Astellas (sponsors), regardless of the outcome of the trial. The data generated in this clinical trial are the exclusive property of the sponsors and are confidential. Written approval from the sponsors is required before disclosing any information related to this clinical trial, and no publications initiated by investigators may be published until all protocol-defined primary and secondary endpoints are published in a manuscript. Every attempt will be made to minimize the interval between the completion of data analysis and publication of the study results. Recommendations for the timing of presentation of trial endpoint data and the publication venues (congresses/journals) will be given by the sponsor's Publications Steering Committee.

The primary publication will be a joint publication developed by the investigator and sponsors 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.

Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsors prior to submission. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy.

The investigator will provide the sponsors 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 the sponsors 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 the sponsors. This allows the sponsors 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 sponsor-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. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement.

In accord with standard editorial and ethical practice, the sponsors will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator and lead author will be designated by mutual agreement. 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.

For all publications relating to the study, the investigator and the sponsors 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 the sponsors and any relevant potential conflicts of interest, including any financial or personal relationship with the sponsors, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication. The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

Any formal publication of the study in which input of sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate sponsor personnel. Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts or stricter local criteria.[23] The sponsors do not compensate for authorship of a publication. The sponsors 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. All authors will be required to disclose, as part of the publication submission, any potential conflicts of interest, including pertinent financial or personal relationships with the sponsors or related entities, including sponsors of competing products that might be perceived to be a source of bias. Authorship is decided on an individual basis and the sponsor's Publications Steering Committee and sponsor representatives will mutually determine authors and their sequence on individual publications based on the relative contribution of each author to the study and/or publication.

Investigators in this study agree to have their name listed as an investigator in any publication reporting results from this study, whether or not they are an author on the publication.

Professional medical writing support is permissible, and any writing support will be acknowledged in each applicable publication, explaining the role the professional writer had in the drafting of the publication. Medical writing and publications support funded by the sponsors on behalf of investigator authors will be considered as a transfer of value under the reporting requirements of the Patient Protection Affordable Care Act: Physician Payment Sunshine Provision.[24] Transfer of value will be allocated to authors following sponsor guidelines.

14. USE OF STUDY INFORMATION AND PUBLICATION

See Sections 13.7 and 13.8.

15. REFERENCES

1. Scher, H.I. and G. Heller, *Clinical states in prostate cancer: toward a dynamic model of disease progression.* Urology, 2000. **55**(3): p. 323-7.
2. Cooperberg, M.R., J.M. Broering, and P.R. Carroll, *Time trends and local variation in primary treatment of localized prostate cancer.* J Clin Oncol, 2010. **28**(7): p. 1117-23.
3. Han, M., et al., *Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience.* Urol Clin North Am, 2001. **28**(3): p. 555-65.
4. Deguchi, T., et al., *Detection of micrometastatic prostate cancer cells in the bone marrow of patients with prostate cancer.* Br J Cancer, 1997. **75**(5): p. 634-8.
5. Pound, C.R., et al., *Natural history of progression after PSA elevation following radical prostatectomy.* JAMA, 1999. **281**(17): p. 1591-7.
6. Freedland, S.J., et al., *Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy.* JAMA, 2005. **294**(4): p. 433-9.
7. Antonarakis, E.S., et al., *The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up.* BJU Int, 2012. **109**(1): p. 32-9.
8. Freedland, S.J., et al., *Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality.* J Clin Oncol, 2007. **25**(13): p. 1765-71.
9. Hussain, M., et al., *Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer.* N Engl J Med, 2018. **378**(26): p. 2465-2474.
10. Smith, M.R., et al., *Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer.* N Engl J Med, 2018. **378**(15): p. 1408-1418.
11. James, N.D., et al., *Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy.* N Engl J Med, 2017. **377**(4): p. 338-351.
12. Scher, H.I., et al., *Increased survival with enzalutamide in prostate cancer after chemotherapy.* N Engl J Med, 2012. **367**(13): p. 1187-97.
13. XTANDI® [United States Package Insert], *Northbrook (IL): Astellas Pharma US, Inc.; 2012 Aug. Package insert.*
14. XTANDI [Summary of Product Characteristics], *The Netherlands: Astellas Pharma Europe BV; 2018*.
15. Pantel, K., et al., *Immunocytochemical monitoring of micrometastatic disease: reduction of prostate cancer cells in bone marrow by androgen deprivation.* Int J Cancer, 1997. **71**(4): p. 521-5.
16. Smith MR, B.M., Rathenborg P, Werbrouck P, Van Poppel H, Heidenreiche A, et al, *Efficacy and safety of enzalutamide (ENZA) monotherapy in hormone naive prostate cancer (HNPC) [abstract].* J Clin Oncol 2013;31(Suppl):5001.
17. Arlen, P.M., et al., *Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time.* J Urol, 2008. **179**(6): p. 2181-5; discussion 2185-6.
18. Lupron Depot (leuprolide acetate) for depot suspension, *North Chicago (IL): AbbVie Inc.; 2013 Jul. Package insert.*

19. Eligard (leuprolide acetate) suspension for subcutaneous injection, *Bridgewater (NJ): sanofi aventis U.S. LLC; 2013 Feb. Package insert.*
20. XTANDI (enzalutamide) capsules, *Northbrook (IL): Astellas Pharma US, Inc.; 2012 Aug. Package insert*.
21. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.
22. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* Am J Clin Oncol, 1982. **5**(6): p. 649-55.
23. *International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals [Internet]. 2013 Aug [cited 2014 Jul 15]*.
24. *111th Congress. HR 3590-Patient Protection and Affordable Care Act. Section 6002: Physician payment sunshine provision. In: gpo.gov [Internet]. 2010 [cited 2014 Jul 21]*.
25. Memorial Sloan Kettering Cancer Center (MSKCC), *Prostate Cancer Nomograms: PSA Doubling Time*.

16. INVESTIGATOR SIGNATURE

The Investigator Signature page will be provided separately.

17. APPENDICES

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix 5. Study Schedule of Activities

Study Period or Visit	Screening	Treatment							Unsched [1]	Safety FU [2]	LTFU [3]
Study Week	-4 to -1	1	13	25	36	37	41	49 [3]	Varies	Varies	Every 12
Study Day	-28 to -1	1	85	169	246	253	281	337	na	na	Every 84
Window (Days) [4]	na	na	±5	±5	±5	±5	±5	±5	na	-3 to +10	±7
General Activities											
Informed consent, screen number [5]	X										
Medical history	X										
Eligibility criteria	X										
12-Lead ECG (local read)	X										
Chest x-ray or CT scan	X										
Abdominopelvic CT/MRI; bone scan	X [6]			X				X [7]	X [1]		X [8]
Randomization authorization form [9]	X										
Randomization		X									
Vital signs (temperature, BP, heart rate)	X	X [10]	X	X		X		X	X	X	
Complete physical examination [11]	X									X	
Brief physical examination [12]		X [10]	X	X		X		X	X		
ECOG performance status	X	X	X	X		X		X	X	X	
Brief Pain Inventory (Short Form) [13]		X [14]	X	X		X		X		X	X [15]
FACT-P, EQ-5D-5L, QLQ-PR25 questionnaires [13]		X [14]	X	X		X		X		X	X [15]
Symptomatic skeletal events [16]			X	X		X		X	X	X	X
Adverse events review [17]	X	X	X	X		X	X [18]	X	X	X	
Concomitant medications review	X	X	X	X		X		X	X	X	
Leuprolide injection [19]		X	X	X		√ PSA [20]		√ PSA [20]	X [21]		
Open-label enzalutamide dispensing [19]		X	X	X		√ PSA [20]		√ PSA [20]	X [21]		

Study Period or Visit	Screening	Treatment							Unsched [1]	Safety FU [2]	LTFU [3]
Study Week	**-4 to -1**	**1**	**13**	**25**	**36**	**37**	**41**	**49 [3]**	**Varies**	**Varies**	**Every 12**
Study Day	**-28 to -1**	**1**	**85**	**169**	**246**	**253**	**281**	**337**	**na**	**na**	**Every 84**
Window (Days) [4]	**na**	**na**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**na**	**-3 to +10**	**±7**
General Activities											
Blinded study drug dispensing [19]		X	X	X		√ PSA [20]		√ PSA [20]	X [21]		
Study drug accountability			X	X		X		X		X	
Long-term follow-up assessments [22]											X
Serum chemistry, hematology	X	X [14]		X		X		X	X	X	
Testosterone	X	X [14]		X		X		X	X [24]	X	
Prostate-specific antigen	X	X [14]		X	X	X		X [25]	X [24]	X	

[1] Anytime necessary to assess or follow-up adverse events, to resume study drug treatment after suspension, at the patient's request, or per investigator decision. Perform imaging as appropriate if disease progression is suspected.

[2] Approximately 30 days after permanent treatment discontinuation. Patients that discontinue from the study during the suspension period can schedule the follow-up visit any time after 28 days post the last dose.

[3] Visits repeat every 12 weeks based on the 12-week visit schedule determined at randomization.

[4] Drug supply must be taken into account when scheduling visits during windows. Visit procedures may be split across the window to allow for drug resupply and completion of study procedures.

[5] Must be before any study specific procedures. May obtain before the screening window. Ensure consent is on the current version of the form.

[6] Must be within 42 days (6 weeks) before randomization.

[7] Perform at week 49 and at 24-week intervals thereafter until radiographic progression is identified and confirmed by independent central radiology review per protocol.

[8] For patients who permanently discontinue randomized study drug treatment before radiographic progression is identified and confirmed by independent central radiology review per protocol, continue radiographic assessments every 24 weeks (± 14 days) until radiographic progression is identified and confirmed by independent central radiology review per protocol.

[9] Complete, sign, and fax or email the form with requested items to the medical monitor or designee at least 3 business days before the anticipated day 1 visit. Patient may proceed to day 1 visit and randomize when medical monitor or designee approves by signed form or email correspondence.

[10] May skip if performed within prior 7 days.

[11] Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes weight (height at screening only).

[12] Symptom-directed; includes investigating any new abnormalities and weight.

[13] Patients who are illiterate, blind, or dyslexic; have motor deficit of their hands or difficulty working with electronic devices; or are otherwise unable to independently complete the questionnaires are not required to complete the electronic questionnaires.

[14] Collect blood samples and have the patient complete the questionnaires before the first dose of study drug.

[15] Questionnaires will be completed for patients who come to the clinic.

Study Period or Visit	Screening	Treatment							Unsched [1]	Safety FU [2]	LTFU [3]
Study Week	-4 to -1	1	13	25	36	37	41	49 [3]	Varies	Varies	Every 12
Study Day	-28 to -1	1	85	169	246	253	281	337	na	na	Every 84
Window (Days) [4]	na	na	±5	±5	±5	±5	±5	±5	na	-3 to +10	±7
General Activities											

[16] Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain.

[17] Collect serious and nonserious adverse event information from the time of signed informed consent through and including a minimum of 30 days after the last administration of investigational product. Phone patients for follow-up if they do not come to the clinic.

[18] Telephone call to collect adverse event information.

[19] Specific study drug treatment (ie, leuprolide, open-label enzalutamide monotherapy, or blinded enzalutamide/placebo) is based on randomized treatment assignment.

[20] PSA values will not be provided to study sites or patients. The study sites will be notified at treatment decision points whether the PSA value meets the specified threshold to determine whether or not to continue or suspend treatment at week 37, or whether to reinitiate study drug treatment.

[21] For patients resuming study drug after treatment suspension.

[22] May obtain at clinic visits, by phone contact, chart review, etc. Includes survival status, subsequent therapies for prostate cancer, including opiate medication to treat bone pain, and dates of investigator assessed progression on first subsequent therapy, including clinical, radiographic or PSA progression.

[23] Refer to the central laboratory instruction manual for sample processing and for estimated turnaround time for PSA results.

[24] If missed during a regularly scheduled visit.

[25] If a PSA value requires treatment reinitiation, ask the patient to return for an unscheduled visit as soon as possible for study drug dispensing. If PSA values meet the criteria of PSA progression with PSADT ≤10m, the investigator for the patient will be notified.

√ PSA, check prostate specific-antigen; BP, blood pressure; CT/MRI, computed tomography/magnetic resonance imaging; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, European Quality of Life 5-Dimensions 5-Levels Health Questionnaire; FACT-P, Functional Assessment of Cancer Therapy-Prostate; FU, follow-up; lab, laboratory; LTFU, long-term follow-up; na, not applicable; PSA, prostate-specific antigen; QLQ-PR25, Quality of Life Questionnaire-Prostate 25; unsched, unscheduled.

Appendix 6. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic (as dictated by applicable governing laws of study site locations) and will become effective for other public emergencies only upon written notification from Pfizer. For patients who have missing data as local or site guidance during the public emergency (eg, COVID-19) has resulted in a change in study visit schedules, missed study visits, or missed study evaluations, the reason for the missing data and the relationship to the public emergency should be reported in the source documents and relevant CRFs.

Use of these alternative study measures are expected to cease upon the return of business-as-usual circumstances (including the lifting of any quarantines and travel bans/advisories).

A6-1. Telehealth/Remote 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 Schedule of Activities or unscheduled visits. Telehealth (ie, remote) visits may be used to continue 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.

Telehealth/remote visits should be recorded as COVID-19-related protocol deviations.

The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications (including COVID-19 vaccine) or changes in concomitant medications since the last contact.
- Review and record contraceptive method. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 8.2.3 for acceptable methods of contraception.

In addition, every effort should be made to administer the ERT Clinical ePRO questionnaires (FACT-P, EQ-5D-5L, QLQ-PR25, BPI-SF) at all scheduled study visits per protocol. The ERT Clinical ePRO questionnaires may be administered remotely via telephone by delegated site staff using the study provisioned device in the event that an in-clinic study visit cannot be conducted due to the COVID-19 pandemic. ERT Clinical ePRO questionnaires should be administered prior to gathering any other study information. Study staff will read the

questionnaire questions to the participant and record participant answers on the study site tablet. Any questionnaires administered via telephone should be indicated as such in the EDC system.

Study participants must be reminded to promptly notify site staff about any change in their health status.

A6-2. Alternative Facilities for Safety Assessments

A6-2.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing (except PSA tests) may be conducted at a local laboratory if permitted by local regulations. The 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. Any abnormal laboratory results from the local laboratory report should be recorded on the CRF as an AE.

Protocol-specified laboratory safety testing (hematology, serum chemistry, testosterone) that is performed at a local laboratory because the study participant was unable to visit the study site because of COVID-19, should be recorded as a COVID-19-related protocol deviation.

For participants with missed or delayed central PSA tests, as PSA results are blinded, all PSA study testing should be handled by the central laboratory. Investigators and study participants should make every effort to follow the protocol required schedule for PSA testing.

A6-2.2. Imaging

If the participant is unable to visit the study site for protocol-required CT/MRI, the participant may visit an alternative facility to have the CT/MRI performed. CT/MRI scans, regardless of where they are obtained, must be sent to the central reader as outlined in the Site Operations Manual.

Patient protocol-specified laboratory that was performed at a at a location other than the study site should be recorded as a COVID-19-related protocol deviation.

A6-2.3. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

A6-3. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Study drugs (enzalutamide open label or enzalutamide/placebo) assigned to the participant via IWRS may be shipped by courier to study participants if permitted by local regulations and in accordance with applicable storage and transportation requirements. Participants must provide verbal consent (and written informed consent if required by local regulatory authorities) for providing their contact details for shipping purposes. The verbal consent should be documented in the source document. If required by local regulatory authorities, verbal consent will be followed up by consent via a short form informed consent document (ICD) amendment. The amount of study drug shipped via courier should correspond to the amount of study drug that is dispensed at the specific study visit. The tracking record of shipments and the chain of custody of study drug must be kept in the participant's source documents/medical records. If the total transport time of study drug shipped to the participant is less than 36 hours than temperature monitoring is not mandated; however, for total transport time is 36 hours or more, temperature monitoring should be used.

Delivery of study drugs to the participant at a location other than the study site should be recorded as a COVID-19-related protocol deviation.

The following is recommended for the continued administration of study drug for participants who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV-2 infection:

- For symptomatic participants with active SARS-CoV-2 infection, study drug should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV-2 infection.

- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV-2-related symptoms should have recovered to Grade ≤1 for a minimum of 72 hours. Notify the study team when treatment is restarted.

- Continue to consider potential drug-drug interactions as described in Section 7.3 for any concomitant medication administered for treatment of SARS-CoV-2 infection.

A6-4. Adverse Events and Serious Adverse Events

If a participant has reported symptoms of COVID-19 or has tested positive for SARS-CoV-2 during the study, this should be reported as an adverse event (AE) or serious adverse event (SAE) and appropriate medical intervention provided.

For confirmed COVID-19 cases, defined as laboratory confirmation of COVID-19 infection irrespective of clinical signs and symptoms, the result of the SARS-CoV-2 test should be recorded in the AE CRF. "Positive SARS-CoV-2 infection" should be entered in the AE description field and, if known, the type of assay (eg, PCR or Antibody). The remainder of the AE form should be completed in the usual manner.

For participants who currently report or who have reported signs and symptoms indicative of COVID-19 infection, but who have not received a SARS-CoV-2 test, "Unconfirmed COVID-19 infection" should be entered in the AE description field. The remainder of the AE form should be completed in the usual manner.

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

For participants who are discontinuing the study due to COVID-19-related reasons, the most appropriate status for discontinuation should be promptly reported in the CRF.

- For End of Treatment, if treatment discontinuation is associated with the current COVID-19 pandemic, and not related to any AE, record "COVID-19" in the "Other, specify" field on the discontinuation electronic CRF (eCRF). If treatment discontinuation was due to COVID-19 infection, record the primary reason for study drug discontinuation of COVID-19 infection as an AE.

- For End of Survival Follow-up, if discontinuation of follow-up is associated with the current COVID-19 pandemic, record "COVID-19" in the "Other, specify" field on the EOS form under the primary reason patient is no longer followed for survival.

Appendix 7. Abbreviations

Abbreviation	Definition
ADT	Androgen deprivation therapy
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the curve from time zero to infinity
BCG	Bacillus Calmette-Guerin
BICR	Blinded independent central reviewer
BPI-SF	Brief Pain Inventory (Short Form)
BUN	Blood urea nitrogen
Ca	Calcium
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CIF	Clinical information form
CK	Creatine kinase
Cl	Chlorine
C_{max}	Maximum plasma concentration
CO2	Carbon dioxide
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
CT SAE	Clinical trial serious adverse event
C_{trough}	Predose trough plasma concentration
CYP	Cytochrome P450
DIL	Dear Investigator Letter
DILI	Drug-induced liver injury
EC	Ethics committee (global term including institutional review boards, independent ethics committees, research ethics committees, and the like)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
E-DMC	External data monitoring committee
EDP	Exposure during pregnancy
EMBARK	Safety and Efficacy Study of Enzalutamide Plus Leuprolide in Patients With Nonmetastatic Prostate Cancer
EORTC	European Organization for Research and Treatment of Cancer
ePRO	Electronic patient-reported outcome
EQ-5D-5L	European Quality of Life 5-Dimensions 5-Levels Health Questionnaire
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice

Abbreviation	Definition
GGT	Gamma-glutamyl transferase
HR	Hazard ratio
IA	Interim analysis
IB	Investigator's Brochure
ICD	Informed consent document
ICH	International Council for Harmonisation
ID	Identification
INR	International normalized ratio
IP	Investigational Product
IPCW	Inverse probability of censoring weighting
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
K	Potassium
LFT	Liver function test
LHRH	Luteinizing hormone-releasing hormone
LT	Long term
LTFU	Long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-free survival
Mo	Months
MRI	Magnetic resonance imaging
na	not applicable
Na	Sodium
OL	Open-label
OS	Overall Survival
PACL	Protocol Administrative Change Letter
PCD	Protocol completion date
PCR	Polymerase chain reaction
PET	Positron-emission tomography
PFS2	Progression-free survival on first subsequent therapy
PK	Pharmacokinetic
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
PSA	Prostate-specific antigen
PSADT	Prostate-specific antigen doubling time
PT	Prothrombin time
q	Every
QLQ-PR25	Quality of Life Questionnaire-Prostate 25 module
RPSFTM	Rank-preserving structural failure time model
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOA	Schedule of activities
SOC	Standard of care
SOP	Standard operating procedure
SPARTAN	A Study of Apalutamide (ARN-509) in Men With Non-Metastatic Castration-Resistant Prostate Cancer
SRSD	Single reference safety document
STAMPEDE	Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation	Definition
TBili	Total bilirubin
ULN	Upper limit of normal
US	United States
Wk	Week

18. SUPPLEMENT 1: OPEN-LABEL STUDY PERIOD

NOTE: This supplement contains cross-references to the main protocol text where study procedures are to be performed in the same manner.

18.1. Rationale and Treatment Plan

Primary endpoint analyses demonstrated that the primary efficacy endpoint of metastasis free survival (MFS) was established and the safety profile of enzalutamide was confirmed, therefore, the treatment codes for all patients will be unblinded and an open-label treatment period is being implemented. The final analysis of the key secondary endpoint for overall survival (OS) will be performed as planned. Patients will continue to receive their originally assigned study treatment in this open-label (OL) study period. Patients assigned to the placebo plus leuprolide arm will no longer take the placebo capsules. No crossover treatment will be implemented.

For patients whose cancer has not progressed radiographically, locally (change was effective as of 31-Mar-2023) performed scans (CT/MRI and bone scan) will be conducted until the patient's cancer progresses radiographically. Scans read centrally by blinded independent central reviewer (BICR) ceased as of 31-Mar-2023. Prostate-specific antigen (PSA) levels will also be done at a local lab and monitored by the investigator per standard of care (SOC) effective date of 31-May-2023. Patients who are in treatment suspension (due to prior undetectable PSA at study Week 36) will continue to have their PSA values, done at the local lab, evaluated by the investigator every 3 months for possible treatment reinitiation per protocol criteria. For details, refer to Table 16.

Patients who discontinue study treatment or withdraw consent for further treatment will continue safety follow-up and long-term follow-up assessments per protocol (see Section 18.8). Long-term follow-up data including survival status, documentation of new antineoplastic therapies for prostate cancer, skeletal-related events, and progression on first subsequent therapy (PFS2) will be collected every 12 weeks until the final OS analysis. The associated endpoints will be summarized descriptively at the time of the final OS analysis.

Patients who receive any treatment other than their assigned study treatment for prostate cancer after unblinding will not be eligible for this OL period. All patients who permanently discontinue study drug treatment will remain in the study, complete safety follow-up, and subsequently commence long-term follow-up.

Randomized study drug treatment must be permanently discontinued upon initiation of systemic anti-prostate cancer therapy (eg, bicalutamide, nilutamide, or flutamide).

The Brief Pain Inventory (Short Form) (BPI-SF) and quality of life measurements including the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L), and the Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) module are no longer required as of 31-Mar-2023.

Table 16. Supplement Table 1: Study Schedule of Activities (Open-Label Period)

Study Period or Visit Abbreviations used in this table may be found in Appendix 7	**Treatment**			**Un-scheduled**	**Safety FU**	**Long-Term FU**
Study Week	**1**	**Wk 13 & Every 12 wks**	**Wk 25 & Every 6 months**	**Varies [2]**	**Varies [3]**	**Every 12 wks**
Study Day	**1 [1]**	**85**	**169**	**na**	**na**	**Every 84 days**
Windows [4]	**na**	**±5**	**±7**	**na**	**±7**	**±7**
General Activities						
Informed consent **[5]**	X					
Brief physical examination **[6]**	X	X	X	X	X	
Radiographic assessments CT/MRI, Bone Scan (local) **[7]**			X	X		X **[8]**
Symptomatic skeletal events **[9]**		X	X	X	X	X
Serious and non-serious AE monitoring **[10]**		X		X	X	
Concomitant medications review **[11]** and contraceptive check [12].	X	X	X	X	X	X
Enzalutamide dispensing (via IWRS) [13]	X	X		X [14]		
Leuprolide injection [15]	X	X		X [14]		
Study drug accountability		X			X	
Local laboratory evaluation [16]	X	X	X	X	X	
Prostate Specific Antigen (PSA) [18]	X	X		X [17]		
Safety and Long-Term Follow-up Assessments [19]	X				X	X

1. OL Day 1 will be the next regularly scheduled visit following approval and activation of this protocol amendment at the study site.
2. Anytime necessary to assess or follow-up adverse events, at the patient's request, or per investigator decision.
3. Approximately 30 days after the last dose of study drug. If a new antineoplastic treatment is initiated before 30 days after the last dose of study drug, then safety follow-up will occur immediately before starting the new treatment.
4. Drug supply must be taken into account if a window is used to schedule the next visit. Visits may be split across the window to allow for drug resupply and completion of study procedures.
5. Must obtain informed consent before performing any study specific procedures. This is applicable for all patients participating in the Open-Label Period regardless of those on treatment.
6. Symptom directed and includes investigating any new abnormalities and assessment of vital signs per Institution's SOC.
7. Per Institution's SOC, refer to Section 18.3.3 for radiographic assessments (CT Scan/MRI/Bone scan).
8. For patients who permanently discontinue randomized study drug treatment before radiographic progression is identified and confirmed by local radiology review per protocol, continue radiographic assessments every 24 weeks (± 14 days) until radiographic progression is identified and confirmed by local radiology review per protocol. Refer to Section 18.3.3.
9. Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain. Refer to Section 9.1.3.6.
10. Collect serious and nonserious adverse event information from the time of signing of informed consent through safety follow-up. If no safety follow-up, collect adverse event information through 30 days after the last dose of study drug. Contact patients for survival follow-up if they do not come to the clinic per Section 8.
11. Only new concomitant medications for prostate cancer, hormonal, antineoplastic therapies and opiates

Table 16. Supplement Table 1: Study Schedule of Activities (Open-Label Period)

Study Period or Visit Abbreviations used in this table may be found in Appendix 7	**Treatment**			**Un-scheduled**	**Safety FU**	**Long-Term FU**
Study Week	**1**	**Wk 13 & Every 12 wks**	**Wk 25 & Every 6 months**	**Varies [2]**	**Varies [3]**	**Every 12 wks**
Study Day	**1 [1]**	**85**	**169**	**na**	**na**	**Every 84 days**
Windows [4]	**na**	**±5**	**±7**	**na**	**±7**	**±7**

should be reported per Section 18.6.

12. Contraceptive review per Section 8.2.3 applicable through 3 months after the last dose of study drug or per local guidelines.
13. Specific study drug treatment (ie, enzalutamide, enzalutamide plus leuprolide, or leuprolide) is based on randomized treatment assignment.
14. For patients resuming study drug after treatment suspension, if applicable.
15. Leuprolide acetate (leuprorelin acetate), 22.5 mg will be given as a single intramuscular or subcutaneous injection once every 12 weeks.
16. Performed, collected and assessed locally per Institution's SOC. Hematology and serum chemistry. Report any clinically significant abnormalities as adverse events per CTCAE v4 criteria. PSA levels for patients in treatment suspension should be entered into the study database.
17. If missed during regularly scheduled visit.
18. Perform and assess PSA locally. Evaluate if PSA value meets threshold for treatment reinitiation in patients on treatment suspension, if so study drug dispensing should be arranged. The investigator to monitor PSA values for PSA progression. Refer to Section 18.3.4.
19. May obtain at clinic visits, by telephone contact, chart review, etc. Includes survival status, new antineoplastic therapies for prostate cancer, skeletal-related events, and PFS2 up to final OS analysis.

18.1.1. Blinding

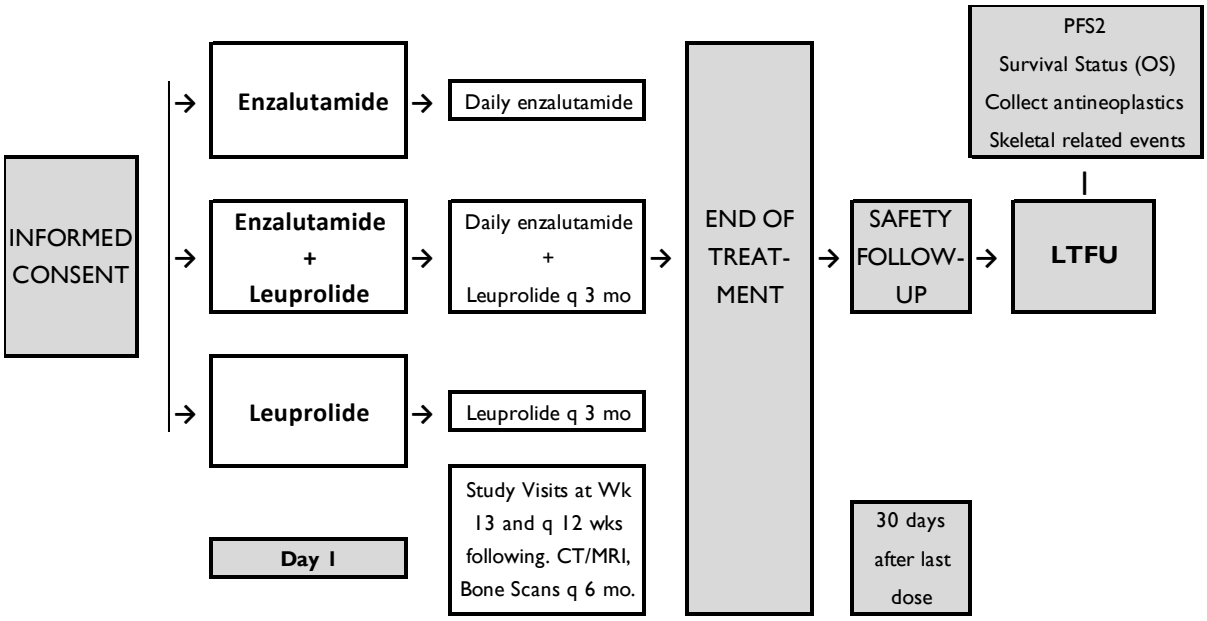
Participants will be unblinded to their assigned study intervention at the start of this OL study period. Investigators and other site staff will be unblinded to participants' assigned study intervention. Sponsor staff will be unblinded to participants' assigned study intervention.

18.2. Open-Label Study Period

Day 1 of the OL period will occur after consent is signed and eligibility is verified. Patients will continue their assigned treatment, return for safety follow-up within approximately 30 days after last dose, and will enter long-term follow-up.

Sites must have all OL Day 1 visits completed within 16 weeks after IRB/EC approval of this protocol amendment (see Figure 3).

Figure 3. Schematic – Open-Label Treatment Period



18.3. Study Procedures and Assessments

Patients will sign informed consent on OL Day 1 (their next regular scheduled visit following approval and activation of this amendment at the study site). All patients must have their OL Day 1 visit within 16 weeks after the approval and activation of this protocol at the study site. The enrollment period will end after this time. For detailed procedures see the Schedule of Activities (Table 16).

Study participants must be reminded to promptly notify site staff about any change in their health status. In addition to the protocol-specified visits, participants should attend clinic visits whenever clinically indicated or needed.

During the OL Period, study assessments will include monitoring as clinically indicated for adverse events, clinical laboratory tests, brief physical examinations including vital signs and drug accountability. For patients whose cancer has not progressed radiographically, scans (CT/MRI and bone scan) will be performed every 6 months until the patient's cancer progresses radiographically by local determination.

The following laboratory values are recommended to be evaluated throughout the study in accordance with the schedule of activities (SOA). These evaluations are to take place locally, per each Institution's SOC:

- Hematology: hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differential, and absolute neutrophil count must be obtained, or be able to be calculated.

- Comprehensive chemistry panel: albumin, alkaline phosphatase, ALT, AST, creatinine, blood urea nitrogen (BUN), Ca++, total CO2 (bicarbonate), glucose, Na+, K+, Cl-, total bilirubin, and testosterone.

- PSA.

Patients in survival follow-up will be followed for their survival status, new anti-prostate cancer therapies and scans every 6 months until they progress on the first anti-prostate cancer follow-up therapy.

18.3.1. Telehealth 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, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.

- Review and record any AEs and SAEs since the last contact (see Section 8).

- Review and record any new concomitant medications or changes in concomitant medications since the last contact per Section 18.6.

- Review for presence of symptomatic skeletal events.

- Review and record contraceptive method. Confirm that the participant is adhering to the contraception method(s) required in the protocol (see Section 8.2.3).

18.3.2. Safety Assessments

Safety data will continue to be collected in the OL period through 30 days after the last dose (ie, permanent discontinuation) of study drug including the period following protocol-specified treatment suspension (due to prior undetectable PSA at study Week 36) and resumption of study drug treatment through permanent treatment discontinuation per Protocol Section 8. Assessments of safety will include all adverse events, clinical laboratory tests (hematology, serum chemistry), physical examinations and vital signs according to the Schedule of Activities for the OL treatment period (Table 16). Local clinical laboratory test results will no longer be required to be entered into the clinical database with the exception of the PSA levels collected for patients who are in treatment suspension. All second primary malignancies (with the exception of uncomplicated nonmelanoma skin cancers) must be reported as a serious adverse event (see Section 8).

18.3.3. Radiographic Assessments

For patients entering the OL treatment period whose cancer has not progressed radiographically, scans (CT/MRI and bone scan) will be performed locally every 6 months according to the Schedule of Activities (Table 16) until progression is identified radiographically. The study Investigator will review and assess the radiographic scans for disease progression. Study treatment will be stopped upon disease progression as assessed by the investigator. Patients who do not participate in the OL treatment period or withdraw consent for further treatment will continue long-term follow-up assessments per protocol (Table 18).

18.3.4. Monitoring PSA Progression

PSA levels will be measured and monitored by the investigator locally to make decisions during the OL study period. For details, refer to Schedule of Activities (Table 16).

Time to PSA progression is defined in Section 10.4.2.1.

For patients who have been in treatment suspension since Week 37 for undetectable (<0.2 ng/ml) PSA values at Week 36, the study investigator will directly monitor and assess the patient's locally obtained PSA levels. Open-labeled treatment will be reinitiated if subsequent local laboratory PSA values increase to ≥2.0 ng/mL for patients with prior prostatectomy, or ≥5.0 ng/mL for patients who had prior radiation therapy. If laboratory PSA values meet the requirement for treatment reinitiation, the patient should return to the study site as soon as possible for drug dispensing and reinitiation of study treatment.

Treatment reinitiation must be registered in the IWRS to obtain the enzalutamide treatment for patients on the enzalutamide treatment arms and provision of a 12 week supply of study drug for resumption of treatment. (Refer to the IWRS Site Manual). If a patient is on the leuprolide arm, they will restart leuprolide and continue with their subsequent IP administration (including leuprolide as applicable) at their next study visit. Study drug administration should continue regardless of PSA values until radiographic progression is confirmed by local imaging (CT/MRI) per investigator's assessment and the investigator considers continuing study drug not to be beneficial.

A prostate cancer nomogram will be provided to investigational sites for uniform calculation of the PSA doubling time.[25]

18.4. Investigational Product

18.4.1. Enzalutamide Administration, Storage, and Accountability

All patients will self-administer four 40-mg soft gelatin enzalutamide capsules (160 mg/day) by mouth once daily with or without food, unless they were receiving a reduced dose during double-blind treatment (open-labeled treatment will continue at the reduced dose). Patients should return all study drug bottles, including unused study drug to the site as indicated in the study drug accountability visits (Table 16).

Enzalutamide should be handled and stored safely and properly in accordance with the study drug label. Study site personnel must make all reasonable efforts to obtain all bottles and unused study drug from patients who do not routinely return the bottles at study site visits.

18.4.2. Leuprolide Administration, Storage, and Accountability

For patients receiving leuprolide acetate (leuprorelin acetate), 22.5 mg will be given as a single intramuscular or subcutaneous injection once every 12 weeks.

The leuprolide acetate formulation for intramuscular injection is supplied as sterile lyophilized microspheres along with an accompanying diluent. The microspheres are to be reconstituted as described in the prescribing information and administered as a single intramuscular injection of 22.5 mg once every 12 weeks.

The leuprolide acetate formulation for subcutaneous injection is supplied as sterile powder along with an accompanying liquid gel solution. The powder is to be mixed with the liquid as described in the prescribing information and administered in clinic by study site personnel as a single subcutaneous injection of 22.5 mg once every 12 weeks.

Leuprolide should be handled and stored safely and properly in accordance with the prescribing information. Pfizer does not permit the shipment of leuprolide by mail.

18.4.3. Shipment of Enzalutamide to Study Participants

Enzalutamide may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for enzalutamide. The tracking record of shipments, including temperature monitoring data, and the chain of custody of enzalutamide must be kept in the participant's source documents/medical records.

18.5. Duration of Treatment and Dose Modification

Open-label study treatment administration may continue for patients whose prostate cancer has not progressed radiographically.

Enzalutamide dose modification: patients who experience a grade 3 or higher toxicity that cannot be ameliorated by the use of adequate medical intervention may interrupt treatment for 1 week or until the toxicity grade improves to grade 2 or lower severity. Subsequently, study drug dosing may be restarted at the original dose (4 capsules/day [160 mg/day]) or a reduced dose (3 or 2 capsules/day [120 or 80 mg/day]) in consultation with the medical monitor.

There are no provisions for dose modification of leuprolide on this study. If enzalutamide is coadministered with a strong CYP2C8 inhibitor (eg, gemfibrozil), the dose of enzalutamide should be reduced to 80 mg once daily. If coadministration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.

18.6. Concomitant Medications – Follow-up Anticancer Medications

Concomitant medications will be assessed at all clinic visits. Record only concomitant medications given for prostate cancer, hormonal therapies, antineoplastic therapies, and opioids on the concomitant medication CRF. All other concomitant medications do not need to be added to the concomitant medication CRF in this OL study period. Additionally, the use of any medication given during the study that is due to an adverse event is no longer required to be entered in the concomitant medication CRF but, the adverse event for which the drug was prescribed should be recorded on the adverse event CRF and in the patient's clinical record.

The use of concurrent cytotoxic chemotherapy or investigational anticancer agents while on study treatment is prohibited. Initiation of bisphosphonates or denosumab for bone health is now allowed and SOC supplementation with calcium and vitamin D is encouraged.

18.7. Treatment Interruption and Discontinuation

Patients whose treatment is interrupted due to an adverse event and restarted will continue to have regularly scheduled study visits based on their enrollment date in the OL period.

Permanent treatment discontinuation is defined as cessation of randomized study drug treatment administration. *Temporary* treatment interruption (eg, due to an adverse event) is not considered permanent discontinuation. For more details, refer to Section 5.3. Safety follow-up will be performed per Table 17. Information on study discontinuation related to COVID-19 is provided in Appendix 6.

Sponsor discontinuation of study: The sponsor has the right to terminate the study anytime. However, the sponsor will ensure that study treatment will be available to all patients who participate in the OL period for as long as they are deriving clinical benefit.

Patients who discontinue study treatment (with exception of patients who withdraw consent) will have safety follow-up approximately 30 days after the last dose or before initiating treatment with a cytotoxic chemotherapy or investigational agent for prostate cancer. If a new cytotoxic or investigational anti-cancer treatment is initiated before 30 days after the last dose of enzalutamide/leuprolide, then safety follow-up should occur immediately before starting the new treatment. Long-term follow-up will commence after completion of safety follow-up. For more details, refer to Section 18.8.

18.7.1. Loss to Follow-Up

Every reasonable effort should be made to contact patients apparently lost to follow-up to complete study-related assessments, record outstanding data, and retrieve study drug. Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives). Such efforts should be documented in the patient's source documents. If all efforts fail to establish contact, the patient will be considered lost to follow-up.

18.8. Safety Follow-up and Long-Term Follow-Up

Patients are to have a safety follow-up approximately 30 days after the last dose of OL study treatment. If a new antineoplastic or investigational anticancer treatment is initiated before 30 days after the last dose, then safety follow-up should occur immediately before starting any new treatment (Table 17).

Table 17. Safety Follow-Up Procedures (Open-Label Period)

Activity/Assessment	Comment
General Activities	
Vital signs and physical examination	As clinically indicated, measure blood pressure, heart rate, temperature and weight. Assess body systems per institution's SOC at the study site and as clinically indicated by symptoms.
ECOG performance status	Refer to Table 13.
Symptomatic skeletal events	Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain.
Adverse events review	Record any new or ongoing adverse events.
Concomitant medications review/contraceptive check	Record any new medications for prostate cancer, hormonal, antineoplastic therapies, and opiates.
Study drug accountability (if applicable)	Record study drug returned and remind patient to return all study drug.
Local Laboratory Evaluations	
Serum chemistry, hematology	Performed per SOC, refer to analytes listed in Section 18.3

Long-term follow-up data will be collected every 12 weeks. The information collected will include survival status, new antineoplastic therapies for prostate cancer, skeletal-related events, and PFS2 (Table 18).

Table 18. Long-Term Follow-Up Procedures (Open-Label Period)

Activity/Assessment/Timing	Comment
General Activities	
Symptomatic skeletal events	Record 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, and use of opiate and/or systemic antineoplastic therapy due to bone pain.

Table 18. Long-Term Follow-Up Procedures (Open-Label Period)

Activity/Assessment/Timing	Comment
Other information	Survival status. Subsequent therapies for prostate cancer, including opiate medication to treat bone pain. Dates of investigator assessed progression on first subsequent therapy, including clinical, radiographic or PSA progression.
Radiographic assessments → ***Perform at 24-week intervals (± 14 days)***	Includes abdominopelvic CT/MRI and whole-body radionuclide bone scan for patients who have not yet had radiographic progression.

18.9. Statistical Methods

The final analysis of overall survival is planned after approximately 271 deaths occur across the 3 arms. Analyses will be performed using a stratified log-rank test to compare OS for enzalutamide plus leuprolide versus placebo plus leuprolide and for enzalutamide monotherapy versus placebo plus leuprolide on ITT population respectively.

The final analysis of the key secondary endpoint OS will be performed as planned (Section 10.4.2). Based on the planned testing procedure in Section 10.4.2 and the actual results from tests for the primary endpoint and key secondary endpoint at the time of final analysis for primary endpoint, the analysis of OS for the combination arm will be tested at the alpha level of 0.05. The analysis of OS for the monotherapy comparison will be tested hierarchically as planned at the same alpha level as the combination arm comparison if significant (Figure 2 and Table 15).

In the final OS analysis, the significance level will be adjusted for the interim OS analysis following the specified Haybittle-Peto efficacy boundaries (Section 10.8 and Table 15).

The analysis of OS in the aforementioned final analyses will be based on an ITT approach, and will be performed as the SAP. An additional confounding factor for the OS analysis may come from patients who choose to access commercial enzalutamide, combination of enzalutamide and leuprolide and other commercially available treatments for the patients. The sponsors may explore the effect of crossover and post-study systemic anticancer therapy using rank-preserving structural failure time model (RPSFTM), and the inverse probability of censoring weighting (IPCW) method if appropriate. Justifications, limitations and assumptions of RPFSTM and IPCW methods will be provided with further details in SAP.

At the time of final analysis of OS, updated results from following secondary endpoints including time to first use of new antineoplastic therapy, time to first symptomatic skeletal event and progression free survival on first subsequent therapy will be summarized descriptively and provided as exploratory analysis. No other efficacy endpoints will be formally tested.

All exploratory efficacy analyses will be performed in ITT population.

Safety analyses will include all patients who receive 1 dose or partial dose of study drug (safety population). Safety data for the patients treated in OL stage will be summarized by double blinded stage and OL stage separately.

Safety will be evaluated by the frequency of serious adverse events, frequency and severity of adverse events, frequency of study drug discontinuation due to adverse events, and frequency of new clinically significant changes in clinical laboratory values and vital signs.

All adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and severity. Descriptive statistics will be used. For more details, refer to Section 10.5.

Central laboratory values (from the double-blind portion study) will be classified for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4. Descriptive statistics will be used to analyze the laboratory data.