**Medivation, Inc.**

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| **Study Title:** | PROSPER: A Multinational, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer |
| **Protocol Identifier:** | MDV3100-14 (C3431005) |
| **Phase:** | 3 |
| **Investigational Product:** | Enzalutamide (formerly MDV3100) |
| **Indication:** | Prostate Cancer |
| **Sponsor:** | Medivation, Inc., a wholly owned subsidiary of Pfizer Inc<br>525 Market Street, 36th Floor<br>San Francisco, CA 94105<br>Telephone: +1 (415) 543-3470<br>Fax: +1 (415) 543-3411<br>Medivation and Astellas Pharma Global Development, Inc. are in a partnership to codevelop enzalutamide for the treatment of cancer |
| **Reference Numbers:** | United States CCI [redacted]<br>EudraCT 2012-005665-12 |
| **Sponsor Medical Monitor:** | PPD MD, PhD<br>Telephone: PPD<br>Email: PPD |
| **Original Protocol:** | v1.0 – 29 Mar 2013 |
| **Amendment 1:** | v2.0 – 16 May 2013 |
| **Amendment 2:** | v3.0 – 31 May 2017 |
| **Amendment 3:** | v4.0 – 11 Aug 2017 |
| **Amendment 4:** | v5 – 26 Jan 2018 |

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.

## SYNOPSIS

**Title of Study:** PROSPER: A Multinational, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

**Protocol Identifier:** MDV3100-14 (C3431005)

**Phase of Development:** 3

**Number of Patients:** Approximately 1440 (960 enzalutamide and 480 placebo)

**Study Centers:** Approximately 250 (global)

**Study Objectives:**

Primary:

- To determine the efficacy of enzalutamide compared with placebo as assessed by metastasis-free survival (MFS).

Secondary:

- To evaluate the benefit of enzalutamide compared with placebo as measured by the following:
  - Time to prostate-specific antigen (PSA) progression;
  - Time to first use of new antineoplastic therapy;
  - Overall survival;
  - Time to pain progression;
  - Time to first use of cytotoxic chemotherapy;
  - Chemotherapy-free disease-specific survival;
  - Chemotherapy-free survival;
  - PSA response rates;
  - Quality of life as assessed by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) health questionnaire, and Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) module.
- To evaluate safety.

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| **OPEN-LABEL PERIOD** | As the study met the primary efficacy endpoint of metastatis-free survival and the established safety profile of enzalutamide was confirmed, all patients will be unblinded. Eligible patients will be offered enzalutamide at the discretion of the investigator. For patients that have not progressed radiographically, scans (CT (computed tomography)/MRI (magnetic resonance imaging) and bone scan) will be performed per investigator discretion until patient has progressed radiographically. Continuation of treatment on the open-label period after radiographic progression will be at the discretion of the investigator. Patients who do not participate in the open-label period or withdraw consent for further treatment will continue long-term follow-up assessments per protocol. Treatment with open-labeled Enzalutamide will be stopped upon disease progression when in the opinion of the Investigator, there is no added clinical benefit to continue treatment with Enzalutamide.<br><br>Long-term follow-up data (Includes survival status, new antineoplastic therapies for prostate cancer, skeletal-related events, and interventions due to locoregional progression) will be collected every 16 weeks. |

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| | Day 1 of the open-label period will occur after consent is signed and eligibility is verified. Patients who choose not to continue in the open-label period will discontinue treatment and return for safety follow-up within approximately 30 days after last dose.<br><br>Sites must have all open-label day 1 visits completed within 16 weeks after IRB (Institutional Review Board)/EC (Ethics Committee) approval of this protocol amendment.<br><br>Patients who will receive any other treatment for prostate cancer after unblinding will not be eligible for an open label enzalutamide extension.<br><br>The complete details for the conduct of the open-label period are provided in Supplement 1: Open-Label Period. |
| **DOUBLE-BLIND** | The completed double-blind protocol remains unchanged. The double-blind period has concluded and the open-label period is ongoing. |

**Methods:** This multinational, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study will evaluate enzalutamide (formerly MDV3100) versus placebo in approximately 1440 men with nonmetastatic castration-resistant prostate cancer (CRPC). All patients will be required to maintain androgen deprivation during the study, either using a gonadotropin-releasing hormone (GnRH) agonist/antagonist or having a history of bilateral orchiectomy.

Central randomization to enzalutamide or placebo treatments (2:1) will be stratified by the following factors:

- PSA doubling time (< 6 months vs ≥ 6 months);
- Baseline use of a bone-targeting agent (yes vs no).

Enzalutamide (160 mg/day) will be administered as four 40-mg soft gelatin capsules by mouth once daily with or without food. Placebo capsules, identical in appearance to enzalutamide capsules, will be administered to patients in the control arm in the same manner.

Study drug administration should continue until radiographic progression as specified in the protocol. Investigators are discouraged from obtaining PSA assessments at their local laboratories during the study and from discontinuing a patient's study drug treatment due to PSA rise alone. Initiation of new therapy for prostate cancer (with the exception of cytotoxic chemotherapy, androgen receptor inhibitors, and investigational agents) at the time of radiographic progression will not mandate discontinuation of study drug if the investigator considers continuing study drug to be beneficial. Patients will continue with Enzalutamide after radiographic progression, if continuation of treatment with Enzalutamide seems clinically beneficial.

Initiation of bisphosphonates or other bone-targeting agents for bone health, such as denosumab, is not allowed during the study prior to development of bone metastasis; however, treatment with these agents should continue if initiated at least 4 weeks before enrollment. Standard of care supplementation with calcium and vitamin D is encouraged.

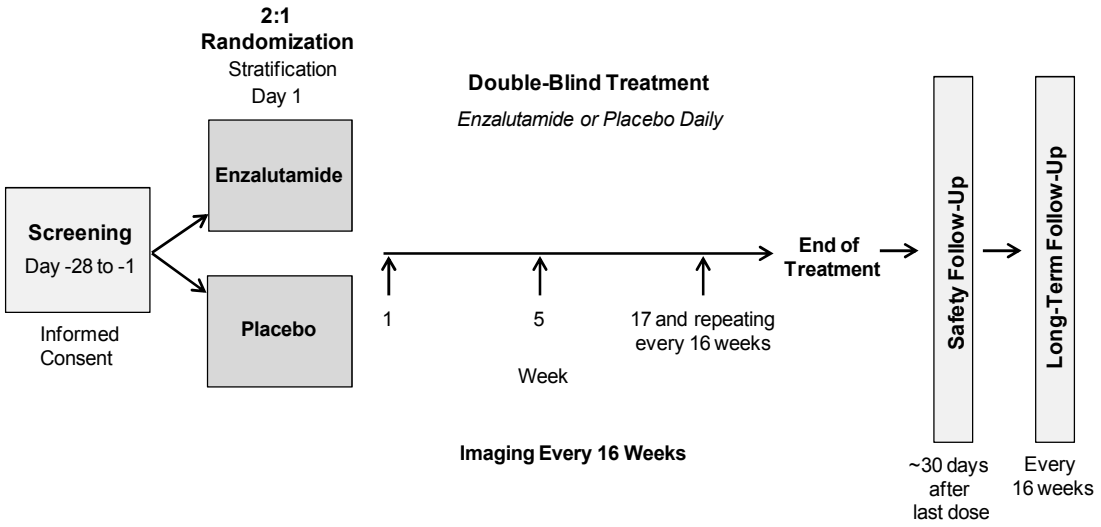
The primary efficacy endpoint is MFS assessed by blinded independent central radiology review, defined as the time from randomization to radiographic progression or death on study (death within 112 days of treatment discontinuation without evidence of radiographic progression), whichever occurs first. Assessment of bone disease will be done by whole-body radionuclide bone scan. A bone scan will consist of 5 regions 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. When bone lesions are found in a single region on the bone scan, confirmation with a second imaging modality (plain film, CT, or MRI) will be required. 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 done 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) (Eisenhauer et al, 2009).[1]

All study films should be read locally at the study site and submitted to the central imaging unit for independent central radiology review. Each study site should designate a radiologist or investigator as the primary imaging reviewer to ensure that all images are read consistently as specified by the protocol. Radiographic assessments will be approximately every 16 weeks, but images may be obtained sooner if progression is clinically suspected. Radiographic imaging will not be required after radiographic progression is confirmed by independent central radiology review according to protocol specifications.

In addition to imaging, the following assessments of prostate cancer status will be made during the course of the study: survival status, pain intensity and interference using the Brief Pain Inventory Short Form (BPI-SF), PSA values, and quality of life as assessed by the FACT-P, EQ-5D-5L and QLQ-PR25 questionnaires. Assessments of safety will include adverse events, clinical laboratory tests, physical examinations, and vital signs. An independent Data Monitoring Committee will periodically monitor the safety data.

Patients will have safety follow-up 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. Long-term follow-up assessments will include monitoring for survival status, new antineoplastic therapies for prostate cancer, opiate medications, skeletal-related events, and interventions due to locoregional progression (eg, radiation, transurethral resection of the prostate, nephrostomy tube placement).

**Study Schematic:**




**Key Eligibility Criteria:**

The patients to be included in this study must have nonmetastatic CRPC progressing on androgen deprivation therapy with no prior or present evidence of metastatic disease as assessed by whole-body radionuclide bone scan for bone disease and CT/MRI for soft tissue disease. Presence of progressive disease will be based on rising PSA ≥ 2 ng/mL (most recent value in a series of at least 3 measurements at ≥ 1-week intervals). The PSA doubling time must be ≤ 10 months and testosterone ≤ 50 ng/dL. Patients must agree to use androgen deprivation therapy with a GnRH agonist/antagonist for the duration of the study or must have had prior bilateral orchiectomy. No prior cytotoxic chemotherapy for prostate cancer is allowed. Those who received prior androgen receptor inhibitor therapy must have progression by rising PSA criteria after withdrawal ≥ 4 weeks. The Eastern Cooperative Oncology Group score must be 0 or 1 and life expectancy ≥ 12 months. Patients with soft tissue pelvic disease may be eligible if lesions do not qualify as target lesions (eg, lymph nodes below aortic bifurcation are permissible if the short axis of the largest lymph node is < 15 mm).

**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.

**Reference Therapy, Dose and Mode of Administration:**

Placebo capsules, identical in appearance to enzalutamide capsules, will be administered in the same manner as enzalutamide.

**Duration of Treatment:**

Study drug administration should continue until radiographic progression as specified in the protocol. Investigators are discouraged from obtaining PSA assessments at their local laboratories during the study and from discontinuing a patient's study drug treatment due to PSA rise alone. Initiation of new therapy for prostate cancer (with the exception of cytotoxic chemotherapy, androgen receptor inhibitors, and investigational agents) at the time of radiographic progression will not mandate discontinuation of study drug if the investigator considers continuing study drug to be beneficial. Patients will continue with Enzalutamide after radiographic progression, if continuation of treatment with Enzalutamide seems clinically beneficial.

**Statistical Methods:**

The primary efficacy analysis of MFS will be conducted using an intent-to-treat population defined as all patients randomly assigned to study treatment. Randomization will be central and treatment allocation will be 2:1. Stratification will be as described in the Methods section. All efficacy analyses will use the intent-to-treat population and incorporate the stratification used at randomization unless otherwise noted. Patients who are randomized and later found to have metastatic disease at enrollment will be censored for time-to-event analyses, and those who receive study drug will be included in all safety analyses.

The single MFS analysis will be performed after approximately 440 MFS events occur. All secondary endpoints will be evaluated for efficacy at this time. This will include the single analysis of time to PSA progression and time to first use of new antineoplastic therapy as well as the first interim analysis of overall survival. Approximately 135 death events are expected at the time of this analysis. Two additional interim analyses and the final analysis of overall survival are planned after approximately 285, 440, and 596 deaths occur, respectively. A multiplicity adjusted inferential procedure will be used to maintain the family-wise 2-sided type I error rate at 0.05. No additional analyses of other efficacy endpoints are planned at the time of the additional interim and final analyses of overall survival. If an interim analysis of overall survival is statistically significant, it will be reported as the final analysis and no subsequent analyses will be performed.

Primary Efficacy Endpoint:

The primary efficacy endpoint of MFS is defined as the time from randomization to radiographic progression or death on study (death within 112 days of treatment discontinuation without evidence of radiographic progression), whichever occurs first. Assessment of bone and soft tissue disease will be as described in the Methods section. Assessment of images for determination of progression will be made by an independent, central, blinded radiology reviewer.

A stratified log-rank test will be used to compare the treatment groups using a 2-sided test at the 0.05 level of significance.

Secondary Efficacy Endpoints:

The following key secondary endpoints will be tested utilizing methodology to preserve the family-wise 2-sided type I error rate at 5%. This methodology and the secondary endpoints to which it applies will be described in detail in the statistical analysis plan. A stratified log-rank test will be used to compare the treatment groups unless otherwise noted.

- 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, which is subsequently confirmed. For patients with PSA decline at week 17, 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 17) is documented, which is confirmed by a second consecutive value obtained at least 3 weeks later.

- Time to First Use of New Antineoplastic Therapy: Time to first use of new antineoplastic therapy is defined as the time from randomization to the first use of new antineoplastic therapy for prostate cancer.

- Overall Survival: Overall survival is defined as the time from randomization to death due to any cause.

Additional secondary endpoints are as follows:

- Time to Pain Progression: Pain will be assessed using the BPI-SF. Pain progression is defined as a 2-point or more increase from baseline in the question 3 pain score. Time to this event is defined as the time from randomization to onset of pain progression;

- Time to First Use of Cytotoxic Chemotherapy: Time to first use of cytotoxic chemotherapy is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer;

- Chemotherapy-Free Disease-Specific Survival: Chemotherapy-free disease-specific survival is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer as assessed by the investigator;

- Chemotherapy-Free Survival: Chemotherapy-free survival is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer or death due to any cause;

- PSA Response: PSA response will be calculated as a decline from baseline in PSA (ng/mL) to the maximal PSA response with thresholds at 50% and 90%. Additionally, PSA response will be assessed as a decline to undetectable levels, where undetectable is defined as below the limit of quantification of the centrally assessed PSA results. A PSA response must be confirmed by a second consecutive value at least 3 weeks later. A stratified Cochran-Mantel-Haenszel mean score test will be used to compare response rates between treatment groups;

- Quality of Life as Assessed by the FACT-P questionnaire, EQ-5D-5L Health Questionnaire, and QLQ-PR25 Module: FACT-P, EQ-5D-5L, and QLQ-PR25 quality-of-life data will be summarized descriptively by study visit.

Safety analyses will include all patients who receive 1 dose or partial dose of study drug (safety population).

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.

Central laboratory values 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.

**Sample Size Considerations:**

The following assumptions were used in determining the sample size for the MFS endpoint:

- 2:1 enzalutamide to placebo treatment allocation;
- Target hazard ratio of 0.72 at the 5% significance level with 90% power. The targeted difference in Kaplan-Meier estimated medians is 9 months (24 months vs 33 months). The median MFS of 24 months for the placebo arm is based on published data from a similar clinical trial (Nelson et al, 2008).[2]

A minimum of 440 events provides 90% power to detect a target hazard ratio of 0.72 based on a 2-sided log-rank test at an overall significance level of 0.05. A sample size of approximately 1305 patients will achieve 440 MFS events within approximately 43 months. It is assumed that a number of patients will be lost to follow-up, will be found to have metastatic disease at enrollment, or will have events censored due to required analytical methods. To account for this anticipated loss in contribution of events to the primary and secondary endpoint analyses, an additional 135 patients (approximately 10% of 1305) will be enrolled to achieve a final sample size of 1440 patients (960 enzalutamide and 480 placebo).

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## LIST OF ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| AUC0-∞ | Area under the curve from time zero to infinity |
| BPI-SF | Brief Pain Inventory Short Form |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CK | |
| Cmax | Maximum plasma concentration |
| Ctrough | Predose trough plasma concentration |
| CRPC | Castration-resistant prostate cancer |
| CRF | Case Report Form |
| CT | Computed tomography |
| CT | Clinical Trial |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | Cytochrome P450 |
| 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 |
| EDP | Exposure during pregnancy |
| EORTC | European Organization for Research and Treatment of Cancer |
| EQ-5D-5L | European Quality of Life-5 Dimensions-5 Levels health questionnaire |
| FACT-P | Functional Assessment of Cancer Therapy-Prostate |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GGT | Gamma Glutamyl Transferase |
| GnRH | Gonadotropin-releasing hormone |
| ICH | International Council for Harmonisation |
| ID | Identification |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| IXRS | Interactive voice / web recognition system |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFS | Metastasis-free survival |
| MRI | Magnetic resonance imaging |
| PFS | Progression-free survival |
| PK | Pharmacokinetic |
| PRES | Posterior reversible encephalopathy syndrome |
| PSA | Prostate-specific antigen |
| QLQ-PR25 | Quality of Life Questionnaire-Prostate 25 module |
| RECIST 1.1 | Response Evaluation Criteria in Solid Tumors, version 1.1 |
| SAE | Serious Adverse Even |
| SUSAR | Suspected unexpected serious adverse reaction |
| TBili | Total bilirubin |
| ULN | Upper limit of normal |
| US | United States |

# 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.[3] Following the initial evaluation and diagnosis of prostate cancer, approximately 90% of men undergo primary localized treatment with curative intent.[4] After initiation of androgen deprivation therapy in men with rising prostate-specific antigen (PSA) after primary therapy, the next clinical state in the current model of prostate cancer progression is that of castration-resistant prostate cancer (CRPC), defined as progression despite castrate hormone levels (testosterone ≤ 50 ng/dL). CRPC is present in 10% to 20% of all men with prostate cancer, and is associated with a high risk of bone metastases, bone pain, pathologic fractures, spinal cord compression, decreased quality of life, and death from prostate cancer.

PSA doubling time and baseline PSA are useful for identifying the subset of men who are at high risk for morbidity and mortality from CRPC. For example, an analysis of 201 patients with nonmetastatic CRPC randomized to the placebo arm in an aborted randomized controlled trial of zoledronic acid showed that PSA doubling time and baseline PSA independently predicted risk of time to first bone metastases, overall survival, and metastasis-free survival (MFS).[5] The relative risk of a shorter time to first bone metastases for patients with a PSA greater than 10 ng/mL was 3.18 (95% confidence interval [CI]: 1.74, 5.8) and the relative risk for a 0.01 increase in PSA velocity was 4.34 (95% CI: 2.30, 8.21).

Currently, although continued use of androgen deprivation therapy is part of clinical practice, no medicine is approved for treatment of patients with nonmetastatic CRPC or for prevention of metastasis, and the results of several studies designed to address these needs have been disappointing.[2,5,6,7] Therefore, no standard of care is defined for nonmetastatic CRPC and accordingly, patients are encouraged to participate in clinical trials.[8]

The androgen receptor remains the main driver of prostate cancer progression in CRPC. Enzalutamide is a potent androgen receptor inhibitor that significantly prolonged overall survival in men with metastatic CRPC previously treated with docetaxel.[9] Patients with nonmetastatic CRPC at high risk for metastatic disease may therefore also derive significant benefit from treatment with enzalutamide. The phase 3 study described herein is designed to address this unmet medical need.

## 1.2. Summary of Relevant Clinical Experience With Enzalutamide

The United States (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.[9]

The current enzalutamide investigator brochure provides the most up-to-date information on clinical studies evaluating enzalutamide in men with prostate cancer. The key clinical studies evaluating enzalutamide in men with prostate cancer are described briefly as follows:

S-3100-1-01: The pharmacokinetics (PK), tolerability, and antitumor activity of enzalutamide (then known as MDV3100) were first studied in a multicenter, open-label, first-in-human, dose-escalation study in 140 patients with CRPC.[10] Patients who were chemotherapy-naïve or who had previous docetaxel-based chemotherapy failure were treated with enzalutamide at doses of 30 to 600 mg/day until disease progression or intolerable side effects developed. The maximum tolerated dose was determined to be 240 mg daily. After review of the safety and efficacy data available from S-3100-1-01, the optimal dose of enzalutamide for evaluation in phase 3 clinical trials was determined to be 160 mg/day.

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.[9] The primary endpoint was overall survival. The first FDA approval of enzalutamide was based on the results of this study.

MDV3100-03 (PREVAIL): A multinational, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in chemotherapy-naïve patients with progressive metastatic after failure of 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 (PFS). The prespecified interim analysis at the time of 540 death events demonstrated statistically significant improvements in overall survival and radiographic PFS 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 PFS (hazard ratio 0.19 [95% CI: 0.15, 0.23]; $p < 0.0001$). Results of an updated survival analysis performed when 784 deaths were observed was consistent with the interim analysis (hazard ratio 0.77 [95% CI: 0.67, 0.88]).

9785-CL-0222 (TERRAIN): A phase 2, randomized, bicalutamide-controlled efficacy and safety study in 375 patients with chemotherapy-naïve metastatic CRPC. Patients were randomized to enzalutamide or bicalutamide. A significant improvement in radiographic PFS was demonstrated in patients treated with enzalutamide versus bicalutamide with an observed hazard ratio of 0.60 (95% CI: 0.43, 0.83).

MDV3100-09 (STRIVE): A phase 2, randomized, bicalutamide-controlled efficacy and safety study in 396 patients with chemotherapy-naïve metastatic (N = 257) or nonmetastatic (N = 139) CRPC. Patients were randomized to enzalutamide or bicalutamide. A significant improvement in radiographic PFS was demonstrated in the overall population with an observed hazard ratio of 0.30 (95% CI: 0.21, 0.44) and in the nonmetastatic subgroup with an observed hazard ratio of 0.24 (95% CI: 0.10, 0.56).

Across these studies, clinically meaningful and statistically significant improvements were demonstrated for the secondary endpoints. In the CRPC2 and MDV3100-03 studies comparing enzalutamide versus placebo, enzalutamide treatment was associated with a delay in median time to PSA progression of 5.4 months (8.3 months enzalutamide vs 2.9 months placebo; hazard ratio 0.25 [95% CI: 0.20, 0.30]) and 8.4 months (11.2 vs 2.8 months; hazard ratio 0.17 [95% CI: 0.15, 0.20]), respectively. In MDV3100-03, enzalutamide treatment was also associated with a delay of 17.2 months in median time to initiation of a subsequent cytotoxic chemotherapy (28.0 vs 10.8 months; hazard ratio 0.35 [95% CI: 0.30, 0.40]) and a delay of 15.4 months in median time to first postbaseline use of any antineoplastic therapy (cytotoxic, hormonal, or investigational) (22.8 vs 7.4 months; hazard ratio 0.27 [95% CI: 0.24, 0.31]).

Enzalutamide treatment was also associated with a statistically significant reduction in the risk of PSA progression compared with bicalutamide treatment. In 9785-CL-0222, the delay in median time to PSA progression was 13.6 months (19.4 months enzalutamide vs 5.8 months bicalutamide; hazard ratio 0.28 [95% CI: 0.20, 0.39]). In MDV3100-09, the median time to PSA progression was not reached in the enzalutamide group versus a median of 8.3 months in the bicalutamide group (hazard ratio 0.19 [95% CI: 0.14, 0.26]) for the overall population. In the metastatic subgroup, the delay in median time to PSA progression was 19.2 months (24.9 months enzalutamide vs 5.7 months bicalutamide; hazard ratio 0.19 [95% CI: 0.13, 0.28]). In the nonmetastatic subgroup, time to PFS progression was not reached in the enzalutamide group versus a median of 11.1 months in the bicalutamide group (hazard ratio 0.18 [95% CI: 0.10, 0.34]).

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

More than 10,000 subjects and patients have been enrolled and treated worldwide in completed and ongoing clinical trials evaluating enzalutamide. The current enzalutamide investigator brochure provides the most up to date information on enzalutamide exposure.

The most common adverse reactions (≥10%) that occurred more commonly (≥2% over placebo) in enzalutamide-treated patients from the 2 phase 3, randomized, placebo-controlled clinical studies (CRPC2, MDV3100-03) were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

In clinical studies, seizure occurred in 0.5% of patients receiving enzalutamide. Because of the risk of seizure associated with enzalutamide use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Enzalutamide should be permanently discontinued in patients who develop a seizure during treatment. Posterior reversible encephalopathy syndrome (PRES), a neurologic disorder that can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurologic disturbances, with or without associated hypertension, has been reported in patients receiving enzalutamide in

the postmarketing setting. Enzalutamide should be permanently discontinued in patients who develop PRES during treatment.

Additional information on the clinical experience with enzalutamide is provided in the enzalutamide investigator brochure.

### 1.2.1. Pharmacokinetics and Drug Metabolism

The current enzalutamide investigator brochure provides the most up to date information on enzalutamide PK and drug metabolism. In 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. No major deviations from dose proportionality were observed over the dose range 30 mg to 600 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 $\leq 25\%$. 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) 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). 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 prior to initiation of the strong CYP2C8 inhibitor. The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated in vivo (Section 7.4).

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 7.4).

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

The current enzalutamide investigator brochure provides the most up to date nonclinical information on 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 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 toxicology studies tested enzalutamide formulated in Labrasol, the same excipient used in clinical studies and in the commercial product marketed for CRPC.

Long-term animal studies are being conducted to evaluate the carcinogenic potential of enzalutamide.

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.

Based on nonclinical findings in repeat-dose toxicology 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).

Additional toxicology studies are ongoing and planned. Additional information on the nonclinical experience with enzalutamide is provided in the enzalutamide investigator brochure.

### 1.4. Enzalutamide Benefits and Risks Assessment

The current enzalutamide investigator brochure provides the most up to date information on the benefits and risks of enzalutamide treatment. As stated in Section 1.2, more than 10,000 subjects and patients have been enrolled and treated worldwide in completed and ongoing clinical trials evaluating enzalutamide.

In the randomized, placebo-controlled phase 3 study CRPC2 (AFFIRM), the prespecified interim analysis at the time of 520 events demonstrated a statistically significant improvement in overall survival in patients with metastatic CRPC treated with enzalutamide versus placebo (hazard ratio = 0.631; 95% CI: 0.529, 0.752, $p < 0.0001$).[9] The median survival was 18.4 months in the enzalutamide arm and 13.6 months in the placebo arm ($\Delta = 4.8$ months). The overall survival benefit was consistent across all subgroups, including age, baseline pain intensity, geographic region, and type of disease progression at entry. Enzalutamide treatment was superior to placebo for all secondary endpoints including the proportion of patients with a reduction in PSA level by 50% or more (54% vs 2%, $p < 0.001$), soft tissue response rate (29% vs 4%, $p < 0.001$), quality-of-life response rate (43% vs 18%, $p < 0.001$), time to PSA progression (8.3 vs 3.0 months; hazard ratio 0.25, $p < 0.001$), radiographic PFS (8.3 vs 2.9 months; hazard ratio 0.40, $p < 0.001$), and time to first skeletal-related event (16.7 vs 13.3 months; hazard ratio 0.69, $p < 0.001$). Based on the AFFIRM data, the US FDA approved enzalutamide in August 2012 for men with metastatic CRPC who previously received docetaxel therapy.

In the pivotal phase 3 study MDV3100-03 in patients with chemotherapy-naïve metastatic CRPC, the prespecified interim analysis at the time of 540 death events demonstrated statistically significant improvements in overall survival and radiographic PFS in patients treated with enzalutamide versus placebo. Data from this study resulted in a label extension for enzalutamide to include all patients with metastatic CRPC.

In the phase 2 study 9785-CL-0222, which was also conducted in patients with chemotherapy-naïve metastatic CRPC, patients were randomized to enzalutamide or bicalutamide. A significant improvement in radiographic PFS was demonstrated in patients treated with enzalutamide versus bicalutamide with an observed hazard ratio of 0.60 (95% CI: 0.43, 0.83). In the phase 2 study MDV3100-09, patients with chemotherapy-naïve metastatic or nonmetastatic CRPC were randomized to enzalutamide or bicalutamide. A significant improvement in radiographic PFS was demonstrated in the overall population with an observed hazard ratio of 0.30 (95% CI: 0.21, 0.44) and in the nonmetastatic subgroup with an observed hazard ratio of 0.24 (95% CI: 0.10, 0.56).

In the 2 phase 3, randomized, placebo-controlled studies (CRPC2, MDV3100-03), the most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in enzalutamide-treated patients were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral

edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo. The important identified risks for enzalutamide, identified as important adverse events for which there is adequate evidence of a causal association with enzalutamide, include seizure, PRES, hypertension, fall, nonpathological fracture, neutrophil count decreased, and cognitive/memory impairment. Additionally, the important identified interactions associated with enzalutamide treatment include interactions with strong inhibitors or inducers of CYP2C8 and interactions with medicinal products that are substrates of CYP3A4, CYP2C9, or CYP2C19.

The totality of the efficacy and safety data suggests a positive benefit-risk assessment for the use of enzalutamide in men with CRPC, and for the continued investigation of enzalutamide in men with earlier stage prostate cancer.

## 2. STUDY OBJECTIVES

### 2.1. Primary Objective

The primary objective is to determine the efficacy of enzalutamide compared with placebo as assessed by MFS.

### 2.2. Secondary Objectives

- To evaluate the benefit of enzalutamide compared with placebo as measured by the following:
    - Time to PSA progression;
    - Time to first use of new antineoplastic therapy;
    - Overall survival;
    - Time to pain progression;
    - Time to first use of cytotoxic chemotherapy;
    - Chemotherapy-free disease-specific survival;
    - Chemotherapy-free survival;
    - PSA response rates;
    - Quality of life as assessed by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) health questionnaire, and Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) module.
- To evaluate safety.

# 3. INVESTIGATIONAL PLAN

## 3.1. Overall Study Design and Plan:Description

This multinational, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study will assess the efficacy and safety of enzalutamide versus placebo in approximately 1440 men with nonmetastatic CRPC at approximately 250 study centers. All patients will be required to maintain androgen deprivation during the study, either using a gonadotropin-releasing hormone (GnRH) agonist/antagonist or having a history of bilateral orchiectomy.

Central randomization to enzalutamide or placebo treatments (2:1) will be stratified by the following factors:

- PSA doubling time (< 6 months vs ≥6 months);
- Baseline use of a bone-targeting agent (yes vs no).

Enzalutamide (160 mg/day) will be administered as four 40-mg soft gelatin capsules by mouth once daily with or without food. Placebo capsules, identical in appearance to enzalutamide capsules, will be administered to patients in the control arm in the same manner.

Study drug administration should continue until radiographic progression. Investigators are discouraged from obtaining PSA assessments at their local laboratories during the study and from discontinuing a patient's study drug treatment due to PSA rise alone. Initiation of new therapy for prostate cancer (with the exception of cytotoxic chemotherapy, androgen receptor inhibitors, and investigational agents) at the time of radiographic progression will not mandate discontinuation of study drug if the investigator considers continuing study drug to be beneficial. Patients will continue with Enzalutamide after radiographic progression, if continuation of treatment with Enzalutamide seems clinically beneficial. Prostate cancer is a multiclonal disease, and a patient with confirmed disease progression may have other clones/foci that may benefit from continued treatment with study drug. In the ongoing, blinded, phase 3 PREVAIL study, approximately 34 of 1715 treated patients (2%) received study drug and antiandrogen or abiraterone after radiographic disease progression.

Initiation of bisphosphonates or other bone-targeting agents for bone health, such as denosumab, is not allowed during the study prior to development of bone metastasis; however, treatment with these agents should continue if initiated at least 4 weeks before enrollment. Standard of care supplementation with calcium and vitamin D is encouraged.

The primary efficacy endpoint is MFS assessed by blinded independent central radiology review, defined as the time from randomization to radiographic progression or death on study (death within 112 days of treatment discontinuation without evidence of radiographic progression), whichever occurs first. Assessment of bone disease will be done by whole-body radionuclide bone scan. A bone scan will consist of 5 regions 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, computed tomography [CT], or magnetic resonance imaging [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 done 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).[1]

All study films should be read locally at the study site and submitted to the central imaging unit for independent central radiology review. Each study site should designate a radiologist or investigator as the primary imaging reviewer to ensure that all images are read consistently as specified in Section 9.1. Radiographic assessments will be approximately every 16 weeks, but images may be obtained sooner if progression is clinically suspected. Radiographic imaging will not be required after radiographic progression is confirmed by independent central radiology review according to protocol specifications.

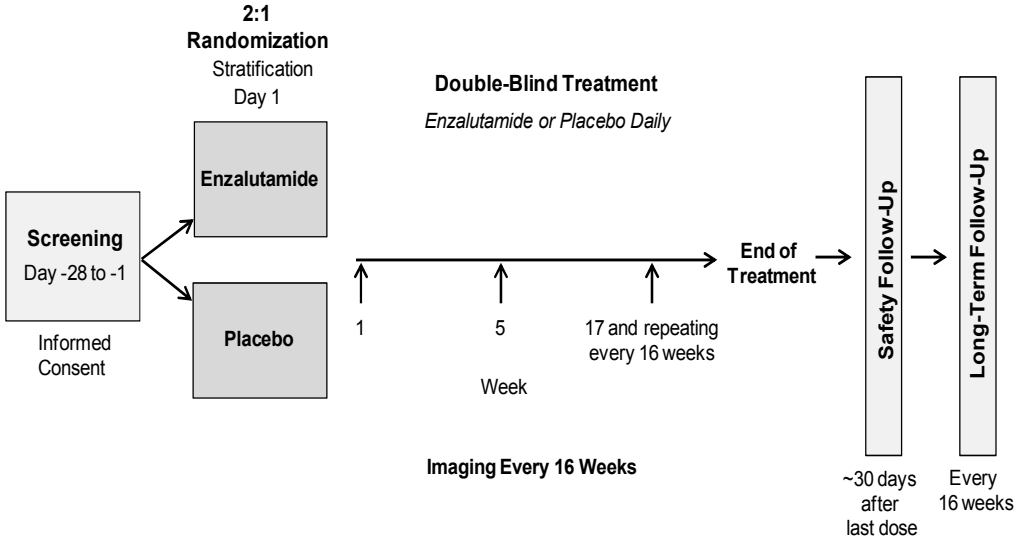
In addition to imaging, the following assessments of prostate cancer status will be made during the course of the study: survival status, pain intensity and interference using the Brief Pain Inventory Short Form (BPI-SF) (Appendix 1), PSA values, and quality of life as assessed by the FACT-P (Appendix 2), EQ-5D-5L (Appendix 3), and QLQ-PR25 (Appendix 4) questionnaires. Assessments of safety will include adverse events, clinical laboratory tests, physical examinations, and vital signs. An independent Data Monitoring Committee will periodically monitor the safety data.

Patients will have safety follow-up 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. Long-term follow-up assessments will include monitoring for survival status, new antineoplastic therapies for prostate cancer, opiate medications, skeletal-related events, and interventions due to locoregional progression (eg, radiation, transurethral resection of the prostate, nephrostomy tube placement).

As the study met the primary efficacy endpoint of metastatis-free survival and the established safety profile of enzalutamide was confirmed, all patients will be unblinded. The complete details for the conduct of the open-label period are provided in Supplement 1: Open-Label Period.

## 3.2. Study Schematic

**Figure 1: Study Schematic**




## 3.3. Blinding

All patients, study site personnel (including investigators), and sponsor staff and its representatives will be blinded to treatment assignment.

The blinded control for this study will be placebo capsules (placebo) 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 total duration of this study will be determined at the patient level and will depend on individual response to treatment. Patients are expected to receive study treatment until radiographic progression as specified in the protocol, have a safety follow-up visit, and then have long-term follow-up until the patient dies.

The primary analysis of MFS will be performed when approximately 440 MFS events based on independent central radiology review are observed.

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

This study is designed to demonstrate the efficacy and safety of enzalutamide in the treatment of patients with nonmetastatic CRPC. The primary efficacy endpoint is MFS.

Androgen deprivation therapy will be continued for all patients on study as its use is common in clinical practice for the treatment of patients with CRPC. Enzalutamide at a dose of 160 mg/day will be compared with placebo. A placebo-controlled trial is considered appropriate and ethical because there is no approved or standard treatment for patients with nonmetastatic CRPC.

An independent Data Monitoring Committee will be used for safety oversight in this study.

## 4. SELECTION OF STUDY POPULATION

The selected study population will have nonmetastatic CRPC with a rapid PSA doubling time. 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 without neuroendocrine differentiation, signet cell, or small cell features.

3. Ongoing androgen deprivation therapy with a GnRH agonist/antagonist or prior bilateral orchiectomy (medical or surgical castration).

4. Testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening.

5. For patients receiving bisphosphonates or denosumab, dose must be stable for at least 4 weeks before randomization.

6. Progressive disease on androgen deprivation therapy at enrollment defined as a minimum of 3 rising PSA values (PSA1 <PSA2 <PSA3) assessed by a local laboratory (local PSA) with an interval of ≥1 week between each determination.

7. The most recent local PSA and the screening PSA assessed by the central laboratory (central PSA) should be ≥2 µg/L (2 ng/mL). In the event of prior androgen receptor inhibitor use, the most recent local PSA and the central PSA assessed at screening must be obtained at least 4 weeks after the last dose of the androgen receptor inhibitor.

8. PSA doubling time ≤10 months calculated by the sponsor using the method of Pound et al, 1999.[11]

9. No prior or present evidence of metastatic disease as assessed by CT/MRI for soft tissue disease and whole-body radionuclide bone scan for bone disease. 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, the patient is not eligible for enrollment. Patients with soft tissue pelvic disease may be eligible if lesions do not qualify as target lesions (eg, lymph nodes below aortic bifurcation are permissible if the short axis of the largest lymph node is <15 mm).

10. Asymptomatic prostate cancer.

11. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

12. Estimated life expectancy ≥12 months.

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

14. Male 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) starting at screening and continuing throughout the study period and for 3 months after final study drug administration. Two acceptable methods of birth control thus include the following:

    - Condom (barrier method of contraception);

      AND

    - One of the following is required:

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

      - Placement of an intrauterine device (IUD) or intrauterine system (IUS) by the female partner;

      - Additional barrier method: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository in the female partner;

      - Tubal ligation in the female partner;

      - Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy), for more than 6 months.

15. Male patient must use a condom if having sex with a pregnant woman.

### 4.2. Exclusion Criteria

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

1. Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for the treatment of prostate cancer or participation in a clinical trial of an investigational agent that inhibits the androgen receptor or androgen synthesis (unless treatment was placebo).

2. Treatment with hormonal therapy (eg, androgen receptor inhibitors, estrogens, 5-alpha reductase inhibitors) or biologic therapy for prostate cancer (other than approved bone-targeting agents and GnRH agonist/antagonist therapy) within 4 weeks of randomization.

3. Use of an investigational agent within 4 weeks of randomization.

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

5. History of another invasive cancer within 3 years of randomization, with the exception of fully treated cancers with a remote probability of recurrence in the opinion of both the medical monitor and investigator.

6. Absolute neutrophil count <1000/μL, platelet count <100,000/μL, or hemoglobin <10 g/dL (6.2 mmol/L) at screening. NOTE: may not have received growth factors or blood transfusions within 7 days before obtaining the hematology values at screening.

7. Total bilirubin ≥1.5 times the upper limit of normal (ULN) (except patients with a diagnosis of Gilbert's disease); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times ULN at screening.

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

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

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

11. Clinically significant cardiovascular disease including the following:

    - Myocardial infarction within 6 months before screening;
    - Uncontrolled angina within 3 months before screening;
    - Congestive heart failure New York Heart Association class 3 or 4, or a history of congestive heart failure New York Heart Association class 3 or 4, unless a screening echocardiogram or multigated acquisition scan performed within 3 months before randomization demonstrates a left ventricular ejection fraction ≥ 50%;
    - 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 millimeters of mercury (mm Hg) at screening;
    - Bradycardia as indicated by a heart rate of <45 beats per minute on the screening electrocardiogram (ECG) and on physical examination;

- Uncontrolled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood pressure >105 mm Hg at screening.

12. Gastrointestinal disorder affecting absorption (eg, gastrectomy, active peptic ulcer disease within 3 months before randomization).

13. Major surgery within 4 weeks of randomization.

14. Hypersensitivity reaction to the active pharmaceutical ingredient or any of the capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene.

15. Any concurrent disease, infection, or comorbid condition that interferes with the ability of the patient to participate in the trial, 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

Enrollment and study procedures are summarized in the following subsections. The timing of all study procedures is provided in the schedule of activities (Appendix 5).

### 5.1. Screening Period

The screening period will be from day -28 through day -1. Screening procedures are listed in Table 1. Certain assessments may be performed as early as day -42. Assessments not completed within the appropriate interval must be repeated.

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

#### 5.1.1. Screening Identification Numbers

Study site personnel will access the interactive voice/web recognition system (IXRS) 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, study site personnel should ensure that the source record includes documentation for the screen failure, such as demographics, medical history, eligibility criteria reviewed, procedures performed, etc.

Patient ID numbers will be assigned to eligible patients at randomization as described in Section 5.2.2.

#### 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 clinical record.

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 enrollment, study site personnel will complete a randomization authorization form and fax it to the medical monitor or designee to approve the enrollment in writing. Patients approved for enrollment will be randomly assigned to treatment on day 1 according to the procedures described in Section 5.2.2.

**Table 1. Screening Procedures**

| Activity / Assessment | Interval (Days) | | Comment |
|---|---|---|---|
| | -42 to -1 | -28 to -1 | |
| **General** | | | |
| Informed consent; obtain screening number from IXRS | Must obtain informed consent before performing any study-specific procedures. | | |
| Medical history | | X | |
| Eligibility criteria | | X | All inclusion criteria must be met and none of the exclusion criteria may apply. |
| 12-lead electrocardiogram | | X | Obtain per local practice and read to confirm eligibility. |
| Radiographic assessments | X | | Includes whole-body radionuclide bone scan, abdominopelvic CT/MRI, and posteroanterior and lateral chest x-ray or chest CT scan.<br>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) excludes bone metastasis. If the imaging results are equivocal or consistent with metastasis, the patient is not eligible for enrollment.<br>Use the same imaging modality for all subsequent scans. |
| Complete physical examination | | X | Measure vital signs (temperature, blood pressure, and heart rate), weight, and height. Assess systems such as dermatologic, cardiac, respiratory, lymphatic, gastrointestinal, musculoskeletal, and neurologic per standard of care at the study site. Assess other systems if clinically indicated by symptoms. |

**Table 1. Screening Procedures**

| Activity / Assessment | Interval (Days) | | Comment |
|---|---|---|---|
| | -42 to -1 | -28 to -1 | |
| Assess ECOG performance status | | | ECOG Status<br>Score: Criterion<br>0: Normal activity<br>1: Symptoms but ambulatory<br>2: In bed < 50% of time<br>3: In bed > 50% of time<br>4: 100% bedridden<br>5: Dead<br>Source: Based on Oken 1982.[12] |
| Concomitant medications | | X | Record all ongoing medications and those discontinued within 28 days before the visit. |
| Serious adverse events | X | | Collect and report serious adverse event information from the time of the signed informed consent through screen failure or safety follow-up. Record any serious adverse event occurring during the screening period on the medical history case report form and in the patient's clinical record for any patient who subsequently meets eligibility criteria and proceeds to randomization. |
| **Central Laboratory** | | | Refer to the laboratory manual for sample processing. |
| Hematology, serum chemistry | | X | Eligibility will be based on central laboratory assessments.<br>Refer to analytes listed in Table 8. |
| Testosterone | | X | Eligibility will be based on central laboratory assessments. |
| Prostate-specific antigen | | X | |
| Randomization Authorization Form | | X | Complete, sign, and fax the form to the medical monitor at the number provided on the form at least 2 business days before the day 1 visit. In addition, fax copies of the items requested on the form. If approved by the medical monitor (signed form or email correspondence), the patient may proceed to the day 1 visit. |

## 5.2. Treatment Period

Day 1 is the day of randomization. While on study drug treatment, patients will return to the study site at weeks 5, 17, and every 16 weeks thereafter.

### 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 or ±7 days, a 10- or 14-day period (ie, the 5- or 7-day period before or after the given day).

Drug supplies must be taken into account when scheduling visits during windows. Visits may be split across the window to allow for drug resupply and completion of study procedures.

### 5.2.2. Day 1 (Randomization)

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 randomization and day 1 procedures.

Study site personnel will access the IXRS to randomly assign patients to blinded study treatment after receiving approval by the medical monitor (signed randomization authorization form or email correspondence).

The IXRS will assign a patient ID number to each patient who proceeds to randomization. This number will identify the patient for the duration of the study.

The IXRS will assign a blinded study drug bottle number according to the randomization code. Patients will be randomly assigned to enzalutamide or placebo treatment. If study drug administration is not logistically feasible on the same day as randomization, the patient must come to the clinic within 3 days of randomization for the required procedures and initiation of treatment. Day 1 will be defined as the day of randomization regardless of the first dose date.

**Table 2. Day 1 Procedures**

| Activity / Assessment | Comment |
|---|---|
| **General Activities** | |
| Brief physical examination | Measure vital signs (temperature, blood pressure, and heart rate).<br>Perform symptom-directed examination. |
| Assess ECOG performance status | ECOG Status Score / Criterion:<br>0 Normal activity<br>1 Symptoms but ambulatory<br>2 In bed < 50% of time<br>3 In bed > 50% of time<br>4 100% bedridden<br>5 Dead<br>Source: Based on Oken 1982.[12] |
| BPI-SF, FACT-P, EQ-5D-5L, and QLQ-PR25 questionnaires | Patient to complete these assessments in the clinic. |
| Adverse events review | Record any new adverse events on the medical history case report form and in the patient's clinical record. |
| Concomitant medications review | Record any new medications or changes in ongoing medications. |
| Randomization (interactive voice/web recognition system, IXRS) | Assignment to blinded treatment group (blinded study drug bottle number). |
| Study drug dispensing | Provide the patient with 4 bottles (124-count each) for a 16-week supply. Provide instructions for dosing, storage, and return of all bottles (used and unused) of study drug at future visits. |
| **Central Laboratory Evaluations** | Refer to the laboratory manual for sample processing. |
| Hematology, serum chemistry | Refer to analytes listed in Table 8. |
| Prostate-specific antigen | |

### 5.2.3. Treatment Guidelines

Dosing with blinded study drug should continue until radiographic progression. Investigators are discouraged from obtaining PSA assessments at their local laboratories during the study and from discontinuing a patient's study drug treatment due to PSA rise alone. Initiation of new therapy for prostate cancer (with the exception of cytotoxic chemotherapy, androgen receptor inhibitors, and investigational agents) at the time of radiographic progression will not mandate discontinuation of study drug if the investigator considers continuing study drug to be beneficial.

### 5.2.4. Week 5

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

Week 5 procedures are listed in Table 3.

**Table 3. Week 5 Procedures**

| Activity / Assessment | Comment |
|---|---|
| **General Activities** | |
| Brief physical examination | Measure vital signs (temperature, blood pressure, and heart rate).<br><br>Perform symptom-directed examination. |
| Assess ECOG performance status | ECOG Status Score — Criterion<br>0 — Normal activity<br>1 — Symptoms but ambulatory<br>2 — In bed < 50% of time<br>3 — In bed > 50% of time<br>4 — 100% bedridden<br>5 — Dead<br>Source: Based on Oken 1982.[12] |
| Adverse events review | Record any new or ongoing adverse events. |
| Concomitant medications review | Record any new medications or changes in ongoing medications. |
| Drug accountability | Record study drug returned and remind patient to return all bottles (used and unused) of study drug at each future visit.<br><br>Confirm dosing instructions with patient (4 capsules by mouth once daily). |

### 5.2.5. Week 17 and Repeating Every 16 Weeks

The same procedures are performed at week 17 and repeating every 16 weeks until treatment discontinuation (Section 5.3). Visit windows are ±5 days. Drug supply must be taken into account if a window is used to schedule the next visit. Week 17 and repeating every 16 weeks procedures are listed in Table 4.

**Table 4. Week 17 and Repeating Every 16 Weeks Procedures**

| Activity / Assessment | Comment |
|---|---|
| **General Activities** | |
| Radiographic assessments | Use the same imaging modality as at screening.<br>Perform radiographic assessments approximately every 16 weeks, but obtain images sooner if progression is clinically suspected. Radiographic imaging should be performed until radiographic progression is identified per Section 9.1.1.<br>A second imaging modality (plain film, CT, or MRI) will be required for confirmation of bone progression when bone lesions are found in a single region of the bone scan. Bone lesions in 2 or more of the 5 bone scan regions or soft tissue radiographic progression on the CT or MRI per RECIST 1.1 will not require confirmation.<br>Determination of radiographic progression should be confirmed by independent central radiology review before stopping radiographic imaging. |
| Brief physical examination | Measure vital signs (temperature, blood pressure, and heart rate).<br>Perform symptom-directed examination. |
| Assess ECOG performance status | ECOG Status Score / Criterion<br>0 Normal activity<br>1 Symptoms but ambulatory<br>2 In bed < 50% of time<br>3 In bed > 50% of time<br>4 100% bedridden<br>5 Dead<br>Source: Based on Oken 1982.[12] |
| BPI-SF, FACT-P, EQ-5D-5L, and QLQ-PR25 questionnaires | Patient to complete these assessments in the clinic. |
| Adverse events review | Record any new or ongoing adverse events. |
| Concomitant medications review | Record any new medications or changes in ongoing medications. |
| Drug accountability | Record study drug returned and remind patient to return all bottles (used and unused) of study drug at each future visit.<br>Confirm dosing instructions with patient (4 capsules by mouth once daily). |
| Study drug dispensing | Provide the patient with 4 bottles (124-count each) for a 16-week supply. |
| **Central Laboratory Evaluations** | Refer to the laboratory manual for sample processing. |
| Hematology, serum chemistry | Refer to analytes listed in Table 8. |
| Prostate-specific antigen | |

### 5.2.6. Unscheduled Visits

Unscheduled visit procedures are listed in Appendix 5.

Unscheduled visits may be performed anytime during the study to assess or follow-up adverse events, perform scans, at the patient's request, or at the request of the investigator. The date and reason for the unscheduled visit should be recorded in the source documentation. If an unscheduled visit is necessary to assess toxicity, then a symptom-directed physical examination, clinical laboratory evaluation, adverse events review, and concomitant medication assessment should be performed. If disease progression is suspected, perform disease assessments including imaging studies as appropriate.

## 5.3. Permanent Treatment Discontinuation

*Permanent* treatment discontinuation is defined as cessation of study drug administration. Safety follow-up (Section 5.4.1) and long-term follow-up (Section 5.4.2) will still be performed.

*Temporary* treatment interruption due to an adverse event is not considered permanent discontinuation. Patients whose treatment is interrupted due to an adverse event and restarted will continue to have regularly scheduled study visits based on their randomization date.

The primary reasons for permanent treatment discontinuation are listed in Table 5. Cross-references are provided to protocol sections with additional information.

## Table 5. Primary Reasons for Permanent Treatment Discontinuation

| Reason | Comment |
|---|---|
| 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 (violation) | The medical monitor or investigator may request permanent discontinuation of study drug treatment in the event of a major protocol deviation, lack of cooperation, or noncompliance. |
| Disease progression | Study drug treatment will be discontinued after development of radiographic progression if the investigator considers continuing study drug not to be beneficial.<br>Initiation of new therapy for prostate cancer (with the exception of cytotoxic chemotherapy, androgen receptor inhibitors, and investigational agents) at the time of radiographic progression will not mandate discontinuation of study drug if the investigator considers continuing study drug to be beneficial. |
| Laboratory abnormality defined by protocol | |
| Creatinine >354 µmol/L (4.0 mg/dL) | |
| AST, ALT, or total bilirubin >5 times the upper limit of normal (ULN)<br>AST or ALT > 3 times ULN and total bilirubin > 2 times ULN without findings of cholestasis | |
| Absolute neutrophil count ≤750/µL | |
| Platelet count <50,000/µL | |
| Seizure | Regardless of resolution of any identified etiology. Refer to Section 1.4. |
| Death | Refer to Section 1.1. |
| Loss to follow-up | Refer to Section 5.5. |
| 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 study treatment anytime for any reason. Following study drug discontinuation, patients should have protocol-required safety follow-up and long-term follow-up assessments unless the patient specifically declines further follow-up. |

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

## 5.4. Follow-Up After Permanent Treatment Discontinuation

### 5.4.1. Safety Follow-Up

All patients will have safety follow-up after permanent treatment discontinuation. Safety follow-up should occur approximately 30 days after the last dose of study drug. However, if a new antineoplastic treatment is initiated before 30 days after the last dose of study drug, then the safety follow-up visit will occur immediately before starting the new treatment.

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. 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 study drug.

Safety follow-up procedures are listed in Table 6.

**Table 6. Safety Follow Up Procedures**

| Activity / Assessment | Comment |
|---|---|
| **General Activities** | |
| Complete physical examination | Measure vital signs (temperature, blood pressure, and heart rate).<br>Assess systems such as dermatologic, cardiac, respiratory, lymphatic, gastrointestinal, musculoskeletal, and neurologic systems per standard of care at the study site. Assess other systems if clinically indicated by symptoms. |
| Assess ECOG performance status | ECOG Status Score – Criterion<br>0 – Normal activity<br>1 – Symptoms but ambulatory<br>2 – In bed < 50% of time<br>3 – In bed > 50% of time<br>4 – 100% bedridden<br>5 – Dead<br>Source: Based on Oken 1982.[12] |
| BPI-SF, FACT-P, EQ-5D-5L and QLQ-PR25 questionnaires | Patient to complete these assessments in the clinic. |
| Adverse events review | Record any new or ongoing adverse events. |
| Concomitant medications review | Record any new medications or changes in ongoing medications. |
| Drug accountability | If applicable. Patients must return all study drug bottles at this visit. |
| **Central Laboratory Evaluations** | Refer to the laboratory manual for sample processing. |
| Hematology, serum chemistry | Refer to analytes listed in Table 8. |
| Prostate-specific antigen | |

### 5.4.2. Long-Term Follow-Up

All patients who permanently discontinue study treatment must have long-term follow-up as continuation of their every 16 weeks study visit schedule. Every reasonable effort must be made to obtain the required information. The long-term follow-up windows are ±7 days.

Study site personnel may collect follow-up information by any means including telephone, during a patient's clinic visit, chart review, or by communicating with referring healthcare providers for patients who do not return to the study site for their subsequent care.

Long-term follow-up procedures are listed in Table 7.

**Table 7. Long Term Follow up Procedures**

| Activity / Assessment | Comment |
|---|---|
| **General Activities (All Patients)** | |
| Collect long-term follow-up information | Survival status.<br>New antineoplastic therapies for prostate cancer.<br>Opiate medications.<br>Skeletal-related events (radiation therapy or surgery to bone, clinically apparent pathologic bone fractures, and spinal cord compression).<br>Interventions due to locoregional progression (eg, radiation, transurethral resection of the prostate, nephrostomy tube placement). |
| **Additional Assessments for Patients Who Do Not Have Confirmed Radiographic Progression at Time of Study Drug Discontinuation** | |
| Radiographic assessments<br>→ *Obtain approximately every 16 weeks or sooner if progression is clinically suspected until radiographic progression*. | Use the same imaging modality as at screening.<br>Radiographic imaging should be performed until radiographic progression is identified per Section 9.1.1.<br>A second imaging modality (plain film, CT, or MRI) will be required for confirmation of bone progression when bone lesions are found in a single region of the bone scan. Bone lesions in 2 or more of the 5 bone scan regions or soft tissue radiographic progression on the CT or MRI per RECIST 1.1 will not require confirmation.<br>Determination of radiographic progression should be confirmed by independent central radiology review before stopping radiographic imaging. |
| BPI-SF, FACT-P, EQ-5D-5L and QLQ-PR25 questionnaires | Patient to complete these assessments if at the clinic. |

### 5.5. Loss to Follow-Up

Every reasonable effort should be made to contact any patient lost to follow-up during the course of the study to complete study-related assessments, record outstanding data, and retrieve study drug. In particular, survival status information is especially critical to the analyses of both primary and secondary efficacy endpoints, as described in Section 10.3.1 and Section 10.3.2.3.

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 source documents.

## 6. INVESTIGATIONAL PRODUCT INFORMATION

### 6.1. General Information

The study drugs include enzalutamide and placebo. Enzalutamide is approved in the US to treat men with metastatic CRPC who previously received docetaxel.

### 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.

The corresponding placebo consists of Labrasol filled in matching capsules. Both active and placebo formulations contain the same relative concentrations of the 2 preservatives, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT).

#### 6.2.1. Packaging

Blinded 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. Each bottle contains 124 capsules (31-day supply).

#### 6.2.2. Storage

Study drug should be handled and stored safely and properly in accordance with the study drug label.

#### 6.2.3. Directions for Administration

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

Patients should self-administer blinded study drug by mouth once daily, with or without food, starting on day 1. 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

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

If blinded study drug is coadministered with a strong CYP2C8 inhibitor, the dose of blinded study drug should be reduced to 80 mg once daily. If coadministration of the strong CYP2C8 inhibitor is discontinued, the blinded study drug dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.

### 6.2.5. Treatment Compliance

Study drug accountability will be performed to document compliance with the blinded dosing regimen. Patients will be asked to bring all used and unused blinded study drug, including packaging, to study visits. Unreturned capsules will be considered to have been taken.

## 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 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.

Treatment with bisphosphonates or denosumab is allowed if initiated at least 4 weeks before enrollment and should continue on study.

In addition to prior therapies that render a patient ineligible per the protocol eligibility criteria, the following medication classes are prohibited within 4 weeks before day 1:

- Hormonal therapy (eg, androgen receptor inhibitors, 5-alpha reductase inhibitors) or biologic therapy for prostate cancer;
- Investigational agents.

### 7.2. Concomitant Therapy

Concomitant medications will be assessed at screening and all clinic visits. All concomitant 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 clinical record.

Initiation of bisphosphonates or other bone-targeting agents for bone health, such as denosumab, is not allowed during the study prior to development of bone metastasis; however, treatment with these agents should continue if initiated at least 4 weeks before enrollment and the dose remains stable. Standard of care supplementation with calcium and vitamin D is encouraged.

Investigators are strongly discouraged from discontinuing a patient's study drug and/or initiating new treatments for prostate cancer before radiographic progression. Initiation of the following therapies will result in permanent treatment discontinuation (Section 5.3):

- Cytotoxic chemotherapy;
- Androgen receptor inhibitors;
- Investigational agents.

The concomitant use of medications known to lower the seizure threshold is allowed because the use of these medications is not restricted in the ongoing phase 3 PREVAIL study. In PREVAIL, 302 of 1715 treated patients received medications known to lower the seizure threshold, including selective serotonin reuptake inhibitors, certain antidepressants, antipsychotics, and antiasthmatics. As of May 2013, no seizures were reported for any of these patients. A single patient in PREVAIL was reported to have a seizure, and this patient was not receiving a medication known to lower the seizure threshold.

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

### 7.3. 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 narrow therapeutic index drugs 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, conduct additional INR monitoring.

### 7.4. Drugs That May Affect Exposure to Enzalutamide

#### 7.4.1. 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 (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 prior to 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.

### 7.4.2. 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.

## 7.5. 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 (Section 8). 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 and Section 8.3). Clinical laboratory safety tests are presented including estimates of blood volume to be collected during the study (Section 8.6). The study procedures for physical examinations and vital signs are also provided (Section 8.7).

The sponsor will periodically monitor blinded 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) as appropriate and per the sponsor's Safety Management Team Charter. Any relevant safety concerns will be communicated to the Data Monitoring Committee, investigators, and regulatory agencies, as appropriate.

## 8.1. Requirements

An independent Data Monitoring Committee will meet periodically during the study to monitor patient safety (Section 11).

The table below summarizes the requirements for recording safety events on the Case Report Form (CRF) and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) 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 CRF | 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 suspected causal relationship to the investigational product 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 CRF. 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, CRF, 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 CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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 CRF. 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 CRF 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 CRF 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 Events (see also the Subject Withdrawal section)

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 CRF.

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

### 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 calendar days; except as indicated below after the last administration of the investigational product.

If a patient begins a new anticancer therapy, the recording period for all AEs ends at the time the new treatment is started. However, the reporting of SAEs should continue beyond this period if the investigator believes there to be at least a reasonable possibility of the SAE being related to investigational product. Phone patients for follow up if they do not come to the clinic within the follow up period.

#### 8.1.4.1. 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.

#### 8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

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

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.

### 8.1.5. 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 in the study records. The criteria for determining causal relationship to study drug are presented in Table 8.

**Table 8. Criteria for Determining Causal Relationship to Study Drug**

| Relationship | Critera |
|---|---|
| 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). |

### 8.1.6. 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.

### 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 (IXRS). 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 IXRS. The reason for breaking the blind must be documented in the source documents.

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

Single patient unblinding may be required for reporting unexpected serious adverse events to certain regulatory authorities. Access to this information will be strictly limited.

### 8.2.3. Contraception

Male patients must use condoms if having sex with pregnant women.

Male patients and their female partners of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method) from the screening visit through 3 months after the last dose of study drug.

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 use of oral, injected, or implanted hormonal method;
   - Placement of an intrauterine device (IUD) or intrauterine system (IUS);

- Additional barrier method including contraceptive sponge or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
- Tubal ligation performed at least 6 months before screening;
- Vasectomy or other surgical castration at least 6 months before screening.

Patients must not donate sperm from first dose of study drug through 3 months after the last dose of study drug.

## 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 CRF. 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 CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) 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 9.

**Table 9. 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 aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (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)/international normalized ratio (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 coformulated 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 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 of 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

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (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 CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

### 8.5.4. Medical Errors and Lack of Efficacy

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 CRF | Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| Medication errors and lack of efficacy* | All (regardless of whether associated with an AE) | Only if associated with an SAE |

*For lack of efficacy (particularly for studies conducted with vaccines, contraceptives, and products used in the treatment of life-threatening diseases or conditions [eg, anti-infectives]), see the Lack of Efficacy section below.

#### 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 (other examples of concern may be added based on the investigational product administration, such as inadvertent exposure).

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 CRF, 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 CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

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

An overdose is defined as at least 2 daily doses of study drug taken the same calendar day. 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. The medical monitor must be contacted in the event of a study drug 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 8.5.4, whether or not the event meets adverse event criteria. Neither the effects of overdose of enzalutamide nor an antidote to overdose are known.

#### 8.5.4.2. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

### 8.6. Clinical Laboratory Safety Tests

Routine clinical laboratory safety tests (hematology, serum chemistry) will be performed at specified study visits according to the schedule of activities (Appendix 5) and at unscheduled visits if necessary.

A list of the required routine clinical laboratory safety tests is provided in Table 10. 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 Form FDA 1572 Section 4. The central laboratory reference ranges will be used. Eligibility at screening will be based on central laboratory assessments.

A different clinical laboratory may be used for unscheduled visits or for the care of a patient with an urgent adverse event. Such laboratory data will not be entered into the study database. The central laboratory should be used whenever possible.

**Table 10. Clinical Laboratory Safety Tests**

| Hematology | Chemistry |
|---|---|
| Hematocrit<br>Hemoglobin<br>Mean corpuscular volume<br>Platelet count<br>Red blood cell count<br>White blood cell count with differential | Albumin<br>Alkaline phosphatase<br>ALT (alanine aminotransferase)<br>AST (aspartate transaminase)<br>Blood urea nitrogen and creatinine<br>Ca++, total CO2 (bicarbonate)<br>Creatine phosphokinase<br>Glucose<br>Lactate dehydrogenase<br>Magnesium, phosphate<br>Na+, K+, Cl-<br>Total bilirubin<br>Total protein |

### 8.6.1. Estimated Blood Volume

Blood samples will be collected for standard safety evaluations (hematology, serum chemistry), for monitoring PSA, and for the screening testosterone test according to the schedule of activities (Appendix 5). 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.

The total blood volume to be collected at each study visit for safety evaluations and PSA is approximately 2.5 to 3 teaspoons (12-15 mL).

## 8.7. Physical Examinations, Vital Signs, and Electrocardiograms

The investigator will perform complete or brief physical examinations according to the schedule of activities in 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.

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

Standard 12-lead ECGs with rhythm strips will be obtained per local practice. The investigator or designee will be responsible for reading the ECG to assess eligibility.

# 9. ASSESSMENT OF EFFICACY AND SAFETY VARIABLES

## 9.1. Assessment of Efficacy

Study assessments of efficacy are measures of prostate cancer status. These will include MFS; overall survival; pain progression; first use of cytotoxic chemotherapy; first use of new antineoplastic therapy; PSA progression; PSA response rates; and quality of life as assessed by the FACT-P questionnaire, EQ-5D-5L health questionnaire, and QLQ-PR25 module.

### 9.1.1. Assessments for the Primary Efficacy Endpoint

Assessments for the primary efficacy endpoint of MFS will include radiographic assessment of bone disease by whole-body radionuclide scan and soft tissue disease by CT scan or MRI. The same imaging method should be used throughout the study.

Radiographic assessments will be done at screening and approximately every 16 weeks, but images may be obtained sooner if progression is clinically suspected. All study films should be read locally at the study site and submitted to the central imaging unit for independent central radiology review. Each study site should designate a radiologist or investigator as the primary imaging reviewer to ensure that all images are read consistently as specified by the protocol. Radiographic imaging will not be required after radiographic progression is confirmed by independent central radiology review according to the specifications in Section 9.1.1.1 and Section 9.1.1.2.

#### 9.1.1.1. Determination of Bone Metastasis

Assessment of bone disease will be done by whole-body radionuclide bone scan. A bone scan will consist of 5 regions 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.

#### 9.1.1.2. Determination of Soft Tissue Metastasis

Assessment of soft tissue disease will be done by CT or MRI. Radiographic progression for soft tissue disease is defined by RECIST 1.1.[1]

### 9.1.2. Assessments for the Secondary Efficacy Endpoints

#### 9.1.2.1. Assessment of Survival

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

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

#### 9.1.2.2. Assessment of Pain Progression

The assessment of pain progression will be conducted using the BPI-SF. The BPI-SF 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 and analgesic medication use. 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 1. Study site personnel will collect the questionnaire information at the study visits. It is important that patients are fluent in reading the language used in the questionnaire and that they complete it without influence of the investigator, study site staff, or anyone else.

#### 9.1.2.3. Assessment of New Cytotoxic Chemotherapy Use

The assessment of cytotoxic chemotherapy use will use the information collected on the case report forms about new cytotoxic chemotherapies initiated for prostate cancer after randomization.

#### 9.1.2.4. Assessment of New Antineoplastic Therapy Use

The assessment of first use of new antineoplastic therapy will use the information collected on the case report forms about new antineoplastic therapies initiated for prostate cancer after randomization.

#### 9.1.2.5. Assessment of PSA

PSA will be assessed at the central laboratory throughout the study according to the schedule of activities (Appendix 5). With the exception of the screening PSA values, PSA values will not be provided to study sites or patients.

PSA values considered undetectable for this study will be those below the limit of quantification of centrally assessed PSA results. Regardless of PSA values, study drug administration should continue until radiographic progression and the investigator considers continuing study drug not to be beneficial.

Throughout the study, PSA rise without evidence of radiographic progression is strongly discouraged as a criterion to start a new systemic antineoplastic therapy.

#### 9.1.2.6. Assessment of Quality of Life

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 in 4 domains during the prior 7 days: physical, social/family, emotional, and functional well-being, as well as 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 questionnaire is provided in Appendix 2. Study site personnel will collect the questionnaire information at the study visits.

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 questionnaire is provided in Appendix 3. Study site personnel will collect the questionnaire information at the study visits.

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 questionnaire is provided in Appendix 4. Study site personnel will collect the questionnaire information at the study visits.

### 9.2. Assessment of Safety

Assessments of safety will include adverse events, clinical laboratory tests, physical examinations, and vital signs. The reason for discontinuation of study drug 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 including estimates of blood volume are presented in Section 8.6, and for physical examinations, vital signs, and ECGs in Section 8.7.

## 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. Analysis Populations

The intent-to-treat population is defined as all patients randomly assigned to study treatment and is based on randomized treatment assignment regardless of whether or not treatment was administered. The intent-to-treat population will be used for all efficacy analyses unless otherwise specified in the statistical analysis plan.

The safety population is defined as all patients who receive 1 dose or partial dose 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.

Patients who are randomly assigned to study treatment and later found to have had metastatic disease at enrollment will be censored for time-to-event analyses, and those who receive study drug will be included in all safety analyses.

### 10.3. Efficacy Analyses

The statistical analysis plan will provide details on additional sensitivity analyses of selected endpoints.

All inferential efficacy analyses will incorporate PSA doubling time (< 6 months vs ≥ 6 months) and baseline use of a bone-targeting agent (yes vs no) as the only stratification factors, unless otherwise noted.

The single MFS analysis will be performed after approximately 440 MFS events occur. All secondary endpoints will be evaluated for efficacy at this time. This will include the single analysis of time to PSA progression and time to first use of new antineoplastic therapy as well as the first interim analysis of overall survival. Approximately 135 death events are expected at the time of this analysis. Two additional interim analyses and the final analysis of overall survival are planned after approximately 285, 440, and 596 death events occur, respectively. No additional analyses of other efficacy endpoints are planned at the time of the additional interim and final analyses of overall survival. If an interim analysis of overall survival is statistically significant, it will be reported as the final analysis and no subsequent analyses will be performed.

### 10.3.1. Primary Efficacy Endpoint Analysis: Metastasis-Free Survival

The primary efficacy endpoint is MFS using the assessment of radiographic progression by an independent, central, blinded radiology reviewer as described in Section 9.1.1 and defined as the time from randomization to radiographic progression or death on study (death within 112 days of treatment discontinuation without evidence of radiographic progression), whichever occurs first. Patients not known to have had an MFS event at the time of analysis will be right censored on the date of the last available scan before the analysis data cutoff date for the purposes of analysis. Both scheduled and unscheduled radiographic imaging will be considered in the determination of radiographic events. The detailed conventions for censoring for the primary analysis and sensitivity analyses that incorporate possible sources of competing risk for assessment of progression will be described in the statistical analysis plan.

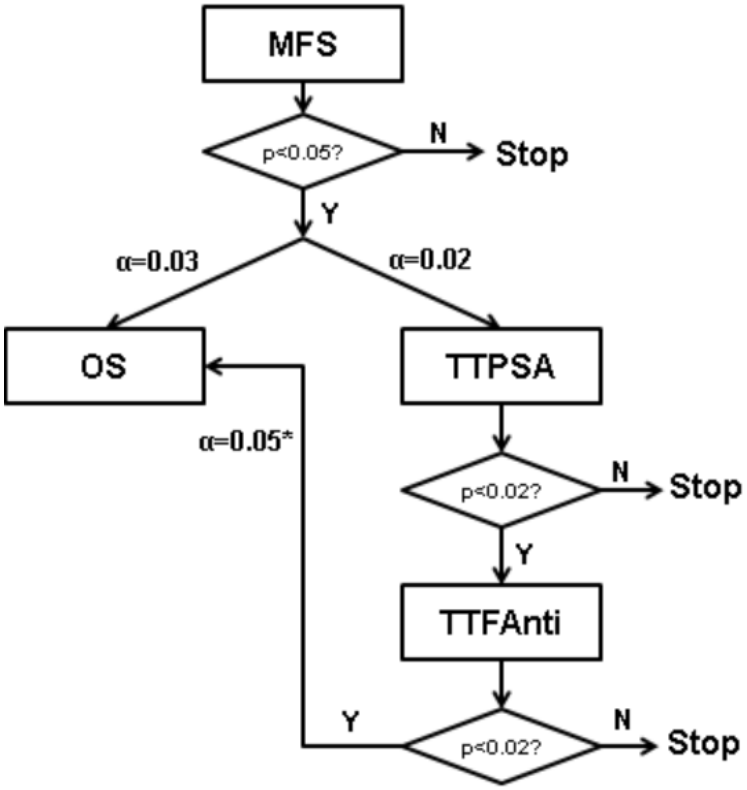
The MFS analysis will be performed when approximately 440 MFS events are observed. The primary endpoint analysis will be performed using a stratified log-rank test to compare the 2 treatment groups using a 2-sided test at the 0.05 level of significance.

### 10.3.2. Key Secondary Efficacy Endpoint Analyses

The following key secondary endpoints will be tested: time to PSA progression, time to first use of new antineoplastic therapy, and overall survival. All secondary endpoint analyses will be performed at the time of the single MFS analysis. To maintain the family-wise 2-sided type I error rate at 0.05, the following multiplicity adjusted inferential procedure will be performed.

The primary endpoint, MFS, will be tested at a 0.05 significance level. To maintain the family-wise 2-sided type I error rate at 0.05, a parallel testing strategy between overall survival (with allocated type I error rate 0.03) and remaining key secondary endpoints (time to PSA progression and time to first use of new antineoplastic therapy with allocated type I error rate 0.02) will be performed. The testing strategy for primary and key secondary endpoints is summarized in Figure 2.

**Figure 2: Testing Strategy for Primary and Key Secondary Endpoints**




MFS, metastasis-free survival; OS, overall survival; TTPSA, time to prostate-specific antigen progression; TTFAnti, time to first use of new antineoplastic therapy.
* Overall survival will be tested at 0.05 only if both time to PSA progression and time to first use of new antineoplastic therapy endpoints are significant. If either time to PSA progression or time to first use of new antineoplastic therapy endpoints fail to show significance, OS will be tested at 0.03.

Details of primary and key secondary endpoint testing as a step-by-step approach will be described in details in the Statistical Analysis Plan.

At the time of the single MFS analysis, an interim analysis of overall survival will be performed with a fixed 0.001 significance level. Approximately 135 death events are expected at the time of this analysis. Two additional interim analyses and the final analysis of overall survival are planned after approximately 285, 440, and 596 death events occur, respectively.

No additional analyses of other efficacy endpoints are planned at the time of the additional interim and final analyses of overall survival. If an interim analysis of overall survival is statistically significant, it will be reported as the final analysis and no subsequent analyses will be performed.

#### 10.3.2.1. Time to PSA Progression

PSA progression is defined according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) guidelines. Time to PSA progression is defined as the time from randomization to the date of the first PSA value demonstrating progression, which is subsequently confirmed. Patients without confirmed PSA progression at the time of analysis will be right censored on the date of the last PSA assessment before the analysis data cutoff date.

For patients with PSA decline at week 17, 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 is documented, which is confirmed by a second consecutive value obtained at least 3 weeks later.

For patients with no PSA decline at week 17, 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 baseline is documented, which is confirmed by a second consecutive value at least 3 weeks later.

Time to PSA progression will be compared between the 2 treatment groups using a stratified log-rank test.

#### 10.3.2.2. Time to First Use of New Antineoplastic Therapy

Time to first use of new antineoplastic therapy is defined as the time from randomization to the first use of new antineoplastic therapy for prostate cancer. Patients not starting treatment with a new antineoplastic therapy at the time of analysis will be right censored on the date of the last assessment before the analysis data cutoff date for the purposes of analysis.
A stratified log-rank test will be used to compare the 2 treatment groups.

#### 10.3.2.3. Overall Survival

Overall survival is defined as the time from randomization to death due to any cause. Patients not known to have died at the time of analysis will be right censored on the date at which they were last known to be alive before the analysis data cutoff date for the purposes of analysis.

Three interim and 1 final efficacy analyses of overall survival are planned. The first interim analysis will be performed at a 0.001 significance level at the time of the single MFS analysis. The number and percentage of death events in each treatment group will be summarized, along with Kaplan-Meier curves with the hazard ratio and its 95% CI. Two additional interim analyses and a final analysis of overall survival are planned after approximately 285, 440, and 596 deaths occur, respectively. The overall survival analyses will be performed using a stratified log-rank test to compare the 2 treatment groups. Depending on the outcome of time to PSA progression and time to first use of new antineoplastic therapy endpoints, the total type I error rate across the interim and final analyses will be controlled at 0.03 or 0.05 with the O'Brien-Fleming alpha spending function.[14] The significance level will be fixed at 0.001 for the first interim analysis. For the other overall survival analyses, the significance levels will be recalculated based on the actual number of events at each analysis using the O'Brien-Fleming method, using the

remaining type I error rate (0.029 or 0.049 depending on the outcome of time to PSA progression and time to first use of new antineoplastic therapy endpoints). If an interim analysis of overall survival is statistically significant, it will be reported as the final analysis and no subsequent analyses will be performed. The approximate number of events and corresponding significance level at each analysis based on this methodology are provided in Table 11. The interim analysis testing methodology will be described in detail in the statistical analysis plan.

**Table 11. Type I Error Spending for the Overall Survival Analyses**

| Analysis | Number of Death Events [1] | Significance Level | |
|---|---|---|---|
| | | Error Rate: 0.03 [2] | Error Rate: 0.05 [3] |
| First interim | 135 | 0.001 | 0.001 |
| Second interim | 285 | 0.001 | 0.002 |
| Third interim | 440 | 0.009 | 0.018 |
| Final | 596 | 0.026 | 0.044 |

1. Approximate number of targeted events.
2. Will be used if either time to PSA progression or time to first use of new antineoplastic therapy endpoint fails to show significance. The significance level will be fixed at 0.001 for the first interim analysis. For the other analyses, the significance levels will be recalculated based on the actual number of events at each analysis using the O'Brien-Fleming method.[14]
3. Will be used if both time to PSA progression and time to first use of new antineoplastic therapy endpoints show significance. The significance level will be fixed at 0.001 for the first interim analysis. For the other analyses, the significance levels will be recalculated based on the actual number of events at each analysis using the O'Brien-Fleming method.[14]

### 10.3.3. Additional Secondary Endpoint Analyses

#### 10.3.3.1. Time to Pain Progression

Pain will be assessed using the score from the BPI-SF question 3: "Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours." Time to this event is defined as the time from randomization to the onset of pain progression, where pain progression is defined as a 2-point or more increase from baseline in the question 3 pain score. Patients without observed pain progression at the time of analysis will be right censored on the date of the last pain assessment for the purposes of analysis. A stratified log-rank test will be used to compare the 2 treatment groups.

#### 10.3.3.2. Time to First Use of Cytotoxic Chemotherapy

Time to first use of cytotoxic chemotherapy is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer. Patients not starting treatment with a cytotoxic chemotherapy for prostate cancer at the time of analysis will be right censored on the date of the last assessment before the analysis data cutoff date for the purposes of analysis. A stratified log-rank test will be used to compare the 2 treatment groups.

#### 10.3.3.3. Chemotherapy-Free Disease-Specific Survival

Chemotherapy-free disease-specific survival is defined as the time from randomization to first use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer as assessed by the investigator. Patients not starting treatment with a cytotoxic chemotherapy or not know to have died due to prostate cancer at the time of analysis will be right censored at the date of last assessment before the analysis data cutoff date for the purposes of analysis. A stratified log-rank test will be used to compare the 2 treatment groups.

#### 10.3.3.4. Chemotherapy-Free Survival

Chemotherapy-free survival is defined as the time from randomization to first use of cytotoxic chemotherapy for prostate cancer or death due to any cause. Patients not starting treatment with a cytotoxic chemotherapy or not known to have died at the time of analysis will be right censored at the date of last assessment before the analysis data cutoff date for the purposes of analysis. A stratified log-rank test will be used to compare the 2 treatment groups.

#### 10.3.3.5. PSA Response

PSA response will be calculated as a decline from baseline PSA (ng/mL) to the maximal PSA response with thresholds at 50% and 90%. Additionally, PSA response will be assessed as a decline to undetectable levels, where undetectable is defined as below the limit of quantification of the centrally assessed PSA results. A PSA response must be confirmed by a second consecutive value at least 3 weeks later. The percentage of patients with a maximal PSA decline of at least 50%, 90%, and undetectable will each be compared between the 2 treatment groups using a stratified Cochran-Mantel-Haenszel mean score test.

#### 10.3.3.6. Quality of Life

FACT-P, EQ-5D-5L, and QLQ-PR25 quality-of-life data will be summarized descriptively by study visit.

### 10.4. Safety Analyses

All safety analyses will use the safety population.

Safety analyses will be summarized by treatment. The treatment-emergent period is defined as the period of time from the first dose date of study drug to approximately 30 days after the last dose of study drug or the date of initiation of a new antineoplastic treatment, whichever occurs first.

Adverse events occurring during the adverse event reporting period 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 prior to 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. 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 prior to the date of the first dose of study drug.

### 10.5. Other Analyses

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

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

### 10.6. Determination of Sample Size

The following assumptions were used in determining the sample size for the MFS endpoint:

- 2:1 enzalutamide to placebo treatment allocation;
- Target hazard ratio of 0.72 at the 5% significance level with 90% power. The targeted difference in Kaplan-Meier estimated median is 9 months (24 months vs 33 months). The median MFS of 24 months for the placebo arm is based on published data from a similar clinical trial.[2]

A minimum of 440 MFS events provides 90% power to detect a target hazard ratio of 0.72 based on a 2-sided log-rank test at an overall significance level of 0.05. A sample size of approximately 1305 patients will achieve 440 events within approximately 43 months. It is assumed that a number of patients will be lost to follow-up, will be found to have metastatic disease at enrollment, or will have events censored due to required analytical methods. To account for this anticipated loss in contribution of events to the primary and

secondary endpoint analyses, an additional 135 patients (approximately 10% of 1305) will be enrolled to achieve a final sample size of 1440 patients (960 enzalutamide and 480 placebo).

The study is also powered for overall survival. Specifically, 590 death events will be required to provide 85% power to detect a target hazard ratio of 0.77 with a target difference in Kaplan-Meier estimated median of 13.7 months (46 months for placebo vs 59.7 months for enzalutamide) at the 5% significance level. The power analysis for the remaining key secondary endpoints will be discussed in the statistical analysis plan.

## 11. STUDY COMMITTEES AND COMMUNICATIONS

An independent Data Monitoring Committee consisting of experts in prostate cancer, clinical trial safety monitoring, and statistics will periodically evaluate safety data for this study. Approximately every 6 months after the first 50 patients are enrolled and have reached their week 17 assessment, the Data Monitoring Committee will review all available safety data. A separate charter will outline the details for the composition and responsibilities of the Data Monitoring Committee.

## 12. LABORATORY REQUIREMENTS

A central laboratory will analyze the clinical laboratory safety samples (hematology, serum chemistry) as described in Section 8.6, as well as the PSA and testosterone samples for this study. 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 to the sponsor a fully executed and signed Form FDA 1572, current curriculum vitae and financial disclosure, signed protocol signature page, and signed acknowledgment of receipt of the current enzalutamide investigator brochure. Current curriculum vitae and financial disclosure must also be provided for all subinvestigator(s) listed on the Form FDA 1572. Additional documents may also be 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.

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. Ethics

### 13.1.1. Ethics Committee

Before initiating the study, the investigator will obtain written confirmation from the EC that the EC is properly constituted and compliant with all requirements and local regulations. A copy of the confirmation will be provided to the sponsor.

The investigator will provide the EC with all appropriate material, such as the protocol, current enzalutamide investigator brochure, site-specific informed consent form, and other written information provided to the patients. The trial will not be initiated until appropriate EC approval of the protocol, informed consent document, and all recruiting materials are obtained in writing by the investigator and copies are received by the sponsor.

EC approval will be obtained for any substantial protocol amendments and informed consent revisions before implementing the changes. The investigator will provide appropriate reports on the progress of the study to the EC and to the sponsor or designee in accordance with applicable local regulations.

### 13.1.2. Ethical Conduct of the Study

This study will be conducted under the guiding principles of the World Medical Association Declaration of Helsinki, and including current Good Clinical Practice (GCP) according to ICH guidelines. Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an EC; the study will be conducted by scientifically and medically qualified persons; the anticipated benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will provide written informed consent before any protocol-specific tests or evaluations are performed.

### 13.1.3. Patient Information and Informed Consent

A properly executed, written informed consent, in compliance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations (CFR) for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), and local regulations, will be obtained from each patient before entering the patient in the trial. The investigator or designee will prepare the informed consent form and provide the documents to the sponsor or designee for approval before submission to the EC. The sponsor and the EC must approve the documents before the investigator implements them.

The investigator will provide copies of the signed informed consent form to each patient (or to the patient's legal representative) and will maintain the signed original document within the patient's record file per local requirements. The investigator will also fully document the informed consent process in the patient's source records.

### 13.1.4. Maintaining Patient Confidentiality

All reports and patient samples will be identified only by a screening ID number, a patient ID number, and/or actual initials (if permitted) or mock initials and date of birth (month/year only if no date is permitted) in order to maintain patient confidentiality. Additional patient confidentiality issues are addressed in the clinical trial agreement and in the informed consent form signed by each study participant.

## 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.

Interpretations of the radiographic and clinical data related to tumor assessments will be performed centrally by independent blinded review. Data will be recorded using standard source documents and case report forms developed by the blinded independent radiology review vendor in accordance with the standard operating procedures of the vendor. Vendor personnel will review the imaging data for completeness and inconsistencies and will generate queries as necessary. All data review will be blinded to treatment assignment.

### 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.

### 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 lot 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 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, 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

The investigator must make original study data (paper or electronic) accessible to the study monitor, other authorized sponsor representatives, and regulatory agency inspectors (eg, FDA) upon request. A file for each patient must be maintained that includes the signed informed consent form and copies of all source documentation related to that patient. The investigator must ensure the reliability and availability of source documents from which the information on the case report form was derived.

Patient identity information recorded will be maintained for at least 15 years on the patient confidentiality log or longer if required by local regulations.

Investigators must maintain all study documentation for at least 2 years following the approval of the drug, or until 2 years after the investigational drug program is discontinued, or longer if required by local regulations. Study documentation includes all essential documents as defined in ICH E6 Guidelines for Good Clinical Practice. The sponsor or designee will notify the investigator when any records may be discarded, but investigators must comply with local regulations.

### 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.

## 14. USE OF STUDY INFORMATION AND PUBLICATION

The results of this study may be published or presented at scientific meetings. However, the data generated in this clinical trial are the exclusive property of Medivation and are confidential. Written approval from Medivation is required prior to disclosing any information related to this clinical trial. The investigator agrees to submit all manuscripts or abstracts to Medivation prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator. 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 clinical study agreement.

In accord with standard editorial and ethical practice, Medivation 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.

Any formal publication of the study in which input of Medivation personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Medivation 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) or stricter local criteria. Medivation does not compensate for authorship of a publication and 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 Medivation or related entities, including sponsors of competing products that might be perceived to be a source of bias.

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.

## 15. REFERENCES

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## 16. INVESTIGATOR SIGNATURE

**Medivation, Inc.**

**PROSPER: A Multinational, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer**

Signature of Agreement for Protocol MDV3100-14 (C3431005)
Amendment 4, v5.0 – 26 Jan 2018

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practice and the Declaration of Helsinki, and complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR Part 312.

| | |
|---|---|
| Print Study Site Name | Study Site Number |
| Print Investigator Name | |
| Investigator Signature | Date |

## Appendix 1. Brief Pain Inventory (Short Form)

[redacted] 1903

Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject's Initials : _____

Study Subject #: ☐☐☐☐

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

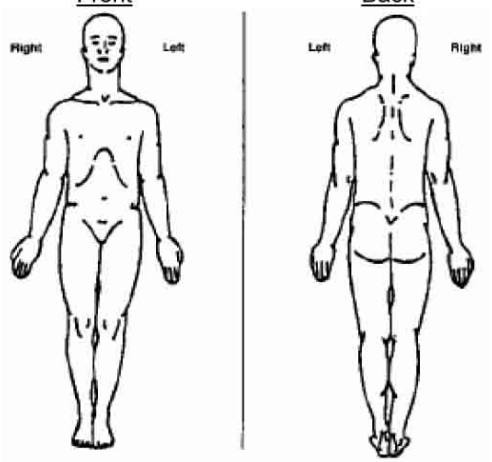
Revision: 07/01/05

### Brief Pain Inventory (Short Form)

**1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?**

☐ Yes ☐ No

**2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.**




**3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.**

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

**4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.**

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

**5. Please rate your pain by marking the box beside the number that best describes your pain on the average.**

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

**6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.**

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

[redacted] Page 1 of 2



[redacted]

1903

Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject's Initials : _____

Study Subject #: ☐☐☐☐

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

**7. What treatments or medications are you receiving for your pain?**

**8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.**

| 0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
|---|---|---|---|---|---|---|---|---|---|---|
| ☐ No Relief | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ Complete Relief |

**9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:**

**A. General Activity**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**B. Mood**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**C. Walking ability**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**D. Normal Work (includes both work outside the home and housework)**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**E. Relations with other people**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**F. Sleep**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**G. Enjoyment of life**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**Page 2 of 2**

## Appendix 2. Functional Assessment of Cancer Therapy - Prostate

### FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | PHYSICAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

| | SOCIAL/FAMILY WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

## FACT-P (Version 4)

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | EMOTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

| | FUNCTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

## FACT-P (Version 4)

**Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| P1 | I have aches and pains that bother me | 0 | 1 | 2 | 3 | 4 |
| P2 | I have certain parts of my body where I experience pain | 0 | 1 | 2 | 3 | 4 |
| P3 | My pain keeps me from doing things I want to do | 0 | 1 | 2 | 3 | 4 |
| P4 | I am satisfied with my present comfort level | 0 | 1 | 2 | 3 | 4 |
| P5 | I am able to feel like a man | 0 | 1 | 2 | 3 | 4 |
| P6 | I have trouble moving my bowels | 0 | 1 | 2 | 3 | 4 |
| P7 | I have difficulty urinating | 0 | 1 | 2 | 3 | 4 |
| BL2 | I urinate more frequently than usual | 0 | 1 | 2 | 3 | 4 |
| P8 | My problems with urinating limit my activities | 0 | 1 | 2 | 3 | 4 |
| BL5 | I am able to have and maintain an erection | 0 | 1 | 2 | 3 | 4 |

## Appendix 3. European Quality of Life-5 Dimensions-5 Levels Health Questionnaire

Adapted from http://www.euroqol.org/ (UK [English] v.2 © 2009). The original EQ-5D™ is a trademark of the EuroQol Group.

Under each heading, please tick the ONE box that best describes your health TODAY:

**Mobility**

I have no problems in walking about. ❑
I have slight problems in walking about. ❑
I have moderate problems in walking about. ❑
I have severe problems in walking about. ❑
I am unable to walk about. ❑

**Self Care**

I have no problems washing or dressing myself. ❑
I have slight problems washing or dressing myself. ❑
I have moderate problems washing or dressing myself. ❑
I have severe problems washing or dressing myself. ❑
I am unable to wash or dress myself. ❑

**Usual Activities** (eg, work, study, housework, family or leisure activities)

I have no problems doing my usual activities. ❑
I have slight problems doing my usual activities. ❑
I have moderate problems doing my usual activities. ❑
I have severe problems doing my usual activities. ❑
I am unable to do my usual activities. ❑

**Pain/Discomfort**

I have no pain or discomfort. ❑
I have slight pain or discomfort. ❑
I have moderate pain or discomfort. ❑
I have severe pain or discomfort. ❑
I have extreme pain or discomfort. ❑

**Anxiety/Depression**

I am not anxious or depressed. ❑
I am slightly anxious or depressed. ❑
I am moderately anxious or depressed. ❑
I am severely anxious or depressed. ❑
I am extremely anxious or depressed. ❑

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

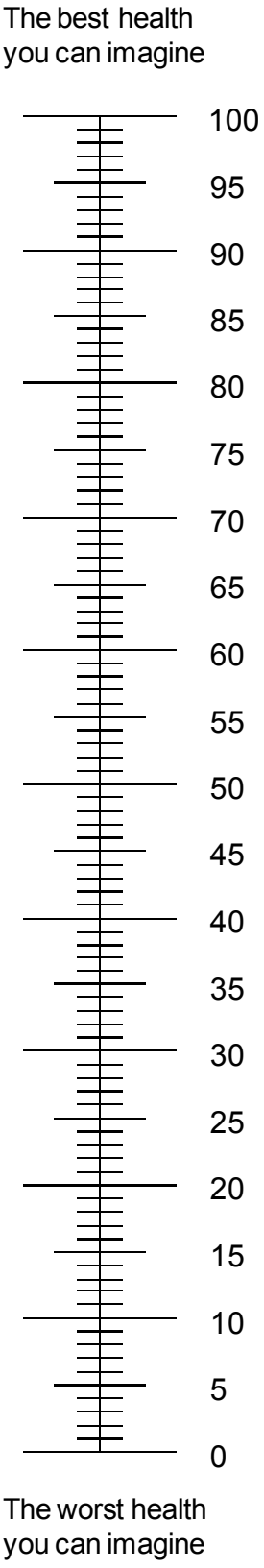
100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark and X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



## Appendix 4. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Disease Module: QLQ-PR25

Adapted from http://groups.eortc.be/qol/. EORTC QLQ-PR25 is a copyright of EORTC Study Group on Quality of Life (1999).

## EORTC QLQ-PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

| During the Past Week: | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 31. | Have you had to urinate frequently **during the day**? | 1 | 2 | 3 | 4 |
| 32. | Have you had to urinate frequently **at night**? | 1 | 2 | 3 | 4 |
| 33. | When you felt the urge to pass urine, did you have to hurry to get to the toilet? | 1 | 2 | 3 | 4 |
| 34. | Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate? | 1 | 2 | 3 | 4 |
| 35. | Have you had difficulty going out of the house because you needed to be close to a toilet? | 1 | 2 | 3 | 4 |
| 36. | Have you had any unintentional release (leakage) of urine? | 1 | 2 | 3 | 4 |
| 37. | Did you have pain when you urinated? | 1 | 2 | 3 | 4 |
| 38. | Answer this question only if you wear an incontinence aid. Has wearing an incontinence aid been a problem for you? | 1 | 2 | 3 | 4 |
| 39. | Have your daily activities been limited by your urinary problems? | 1 | 2 | 3 | 4 |
| 40. | Have your daily activities been limited by your bowel problems? | 1 | 2 | 3 | 4 |
| 41. | Have you had any unintentional release (leakage) of stools? | 1 | 2 | 3 | 4 |
| 42. | Have you had blood in your stools? | 1 | 2 | 3 | 4 |
| 43. | Did you have a bloated feeling in your abdomen? | 1 | 2 | 3 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| 44. | Did you have hot flushes? | 1 | 2 | 3 | 4 |
| 45. | Have you had sore or enlarged nipples or breasts? | 1 | 2 | 3 | 4 |
| 46. | Have you had swelling in your legs or ankles? | 1 | 2 | 3 | 4 |

Please go to the next page

| **During the Last 4 Weeks...** | | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|---|
| 47. | Has weight **loss** been a problem for you? | 1 | 2 | 3 | 4 |
| 48. | Has weight **gain** been a problem for you? | 1 | 2 | 3 | 4 |
| 49. | Have you felt less masculine as a result of your illness or treatment? | 1 | 2 | 3 | 4 |
| 50. | To what extent were you interested in sex? | 1 | 2 | 3 | 4 |
| 51. | To what extent were you sexually active (with or without intercourse)? | 1 | 2 | 3 | 4 |
| **PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS** | | | | | |
| 52. | To what extent was sex enjoyable for you? | 1 | 2 | 3 | 4 |
| 53. | Did you have difficulty getting or maintaining an erection? | 1 | 2 | 3 | 4 |
| 54. | Did you have ejaculation problems (eg, dry ejaculation)? | 1 | 2 | 3 | 4 |
| 55. | Have you felt uncomfortable about being sexually intimate? | 1 | 2 | 3 | 4 |

## Appendix 5. Study Schedule of Activities

| **Study Period or Visit** | **Screening** | **Treatment** | | | **Unscheduled** | **Safety FU** | **Long-Term FU** |
|---|---|---|---|---|---|---|---|
| **Study Week** | **−4 to −1** | **1** | **5** | **17 Then Every 16** | **Varies [1]** | **Varies [2]** | **Every 16** |
| **Study Day** | **-28 to -1** | **1** | **29** | **113** | **na** | **na** | **na** |
| **Window (Days) [3]** | **na** | **na** | **±5** | **±5** | **na** | **±7** | **±7** |
| **General Activities** | | | | | | | |
| Informed consent and screening number (IXRS) [4] | X | | | | | | |
| Medical history | X | | | | | | |
| Eligibility criteria | X | | | | | | |
| 12-Lead electrocardiogram (local read) | X | | | | | | |
| Radiographic assessments | X [5] | | | X [6] | X opt [7] | | X [6] |
| Randomization (IXRS) [8] | | X | | | | | |
| Complete physical examination [9] | X | | | | | X | |
| Brief physical examination [10] | | X | X | X | X | | |
| ECOG performance status | X | X | X | X | X | X | |
| BPI-SF, FACT-P, EQ-5D-5L, QLQ-PR25 questionnaires | | X | | X | | X | X [11] |

| **Study Period or Visit** | **Screening** | **Treatment** | | | **Unscheduled** | **Safety FU** | **Long-Term FU** |
|---|---|---|---|---|---|---|---|
| **Study Week** | **−4 to −1** | **1** | **5** | **17 Then Every 16** | **Varies [1]** | **Varies [2]** | **Every 16** |
| **Study Day** | **-28 to -1** | **1** | **29** | **113** | **na** | **na** | **na** |
| **Window (Days) [3]** | **na** | **na** | **±5** | **±5** | **na** | **±7** | **±7** |
| Adverse events review [12] | | X | X | X | X | X | |
| Concomitant medications review | X | X | X | X | X | X | |
| Study drug dispensing | | X | | X | | | |
| Study drug accountability | | | X | X | | X | |
| Long-term follow-up assessments [13] | | | | | | | X |
| **Central Laboratory Evaluations [14]** | | | | | | | |
| Hematology, serum chemistry | X | X | | X | X | X | |
| Testosterone | X | | | | | | |
| Prostate-specific antigen | X | X | | X | | X | |

| Study Period or Visit | Screening | Treatment | | | Unscheduled | Safety FU | Long-Term FU |
|---|---|---|---|---|---|---|---|
| Study Week | −4 to −1 | 1 | 5 | 17 Then Every 16 | Varies [1] | Varies [2] | Every 16 |
| Study Day | -28 to -1 | 1 | 29 | 113 | na | na | na |
| Window (Days) [3] | na | na | ±5 | ±5 | na | ±7 | ±7 |

1. Anytime necessary to assess or follow-up adverse events, perform scans, at the patient's request, or per investigator decision.
2. 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.
3. 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.
4. Must obtain informed consent before performing any study-specific procedures.
5. Must be within 42 days before randomization. Screening includes posteroanterior and lateral chest x-ray or chest CT scan, whole-body radionuclide bone scan, and abdominopelvic CT/MRI. 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) excludes bone metastasis. If the imaging results are equivocal or consistent with metastasis, the patient is not eligible for enrollment. Use the same imaging method throughout the study.
6. Perform approximately every 16 weeks, but obtain images sooner if progression is clinically suspected. Radiographic imaging should be performed until radiographic progression is identified and confirmed by independent central radiology review per protocol. A second imaging modality (plain film, CT, or MRI) confirmation of bone progression is required when bone lesions are found in a single region on the bone scan.
7. If disease progression is suspected, perform imaging studies as appropriate.
8. Complete, sign, and fax the randomization authorization form to the medical monitor at the number provided on the form at least 2 business days before the day 1 visit.
9. Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes assessment of vital signs and weight (height only at screening).
10. Symptom directed and includes investigating any new abnormalities and assessment of vital signs.
11. Questionnaires will be completed for patients who come to the clinic.
12. Collect nonserious adverse event information from the time of first dose of study drug through safety follow-up. If no safety follow-up, collect adverse event information through 30 days after the last dose of study drug. Phone patients for follow-up if they do not come to the clinic.
13. May obtain at clinic visits, by phone contact, chart review, etc. Includes survival status, new antineoplastic therapies for prostate cancer, opiate use, skeletal-related events, and interventions due to locoregional progression.
14. Refer to the laboratory instruction manual for sample processing.

| Study Period or Visit | Screening | Treatment | | | Unscheduled | Safety FU | Long-Term FU |
|---|---|---|---|---|---|---|---|
| Study Week | −4 to −1 | 1 | 5 | 17 Then Every 16 | Varies [1] | Varies [2] | Every 16 |
| Study Day | -28 to -1 | 1 | 29 | 113 | na | na | na |
| Window (Days) [3] | na | na | ±5 | ±5 | na | ±7 | ±7 |

BPI-SF, Brief Pain Inventory Short Form; CT, computed tomography; 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; IXRS, interactive voice/web recognition system; MRI, magnetic resonance imaging; na, not applicable; opt, optional; QLQ-PR25, Quality of Life Questionnaire-Prostate 25.

## Supplement 1: Open-Label Period

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

**Rationale:** As the study met the primary efficacy endpoint of metastatis-free survival and the established safety profile of enzalutamide was confirmed all patients will be unblinded. Eligible patients will receive enzalutamide at the discretion of the investigator. For patients that have not progressed radiographically, scans (CT/MRI and bone scan) will be performed per investigator discretion until patient has progressed radiographically. Continuation of treatment on the open-label period after radiographic progression will at the discretion of the investigator. Patients who do not participate in the open-label period or withdraw consent for further treatment will continue long-term follow-up assessments per protocol. Treatment with open-labeled Enzalutamide will be stopped upon disease progression when in the opinion of the Investigator, there is no added clinical benefit to continue treatment with Enzalutamide.

Long-term follow-up data (Includes survival status, new antineoplastic therapies for prostate cancer, skeletal-related events, and interventions due to locoregional progression) will be collected every 16 weeks.

Day 1 of the open-label period will occur after consent is signed and eligibility for all patients is verified. Patients who choose not to continue in the open-label period will discontinue treatment and return for safety follow-up within approximately 30 days after last dose.

Sites must have all open-label day 1 visits completed within 16 weeks after IRB/EC approval of this protocol amendment.

Patients who will receive any other treatment for prostate cancer after unblinding, will not be eligible for an open label enzalutamide extension.

**Schedule and Assessments:**

For procedures see Supplement Table 1: Study Schedule of Activities (Open-Label Period).

Patients previously receiving enzalutamide will sign informed consent on open-label day 1 (their next regular scheduled visit following approval and activation of this protocol at the study site) and have clinic visits whenever clinically indicated or needed. Patients previously receiving placebo will sign informed consent at screening and have clinic visits on open-label day 1, week 5, week 17, and every 16 weeks thereafter. All patients must have their open-label day 1 visit within 16 weeks after the approval and activation of this protocol at the study site and no later than 6 weeks after screening (for placebo patients only). The enrollment period will end after this time.

Patients will take enzalutamide as four 40-mg soft gelatin capsules (160 mg/day) by mouth once daily with or without food.

Study assessments will include survival status, new prostate cancer therapies, and safety evaluations including adverse events, concomitant medications, clinical laboratory tests, brief physical examinations, screening electrocardiograms (ECGs), and vital signs. For patients that have not progressed radiographically, scans (CT/MRI and bone scan) will be performed per investigator discretion until patient has progressed radiographically by local determination.

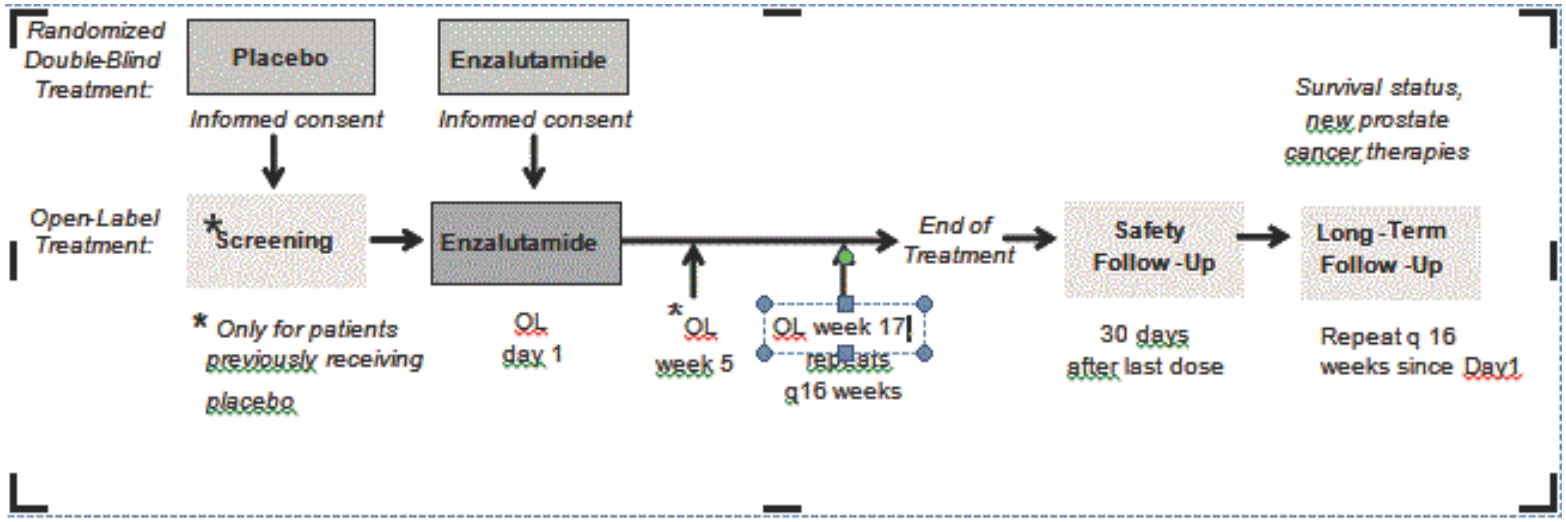
At a minimum, the following laboratory values from those listed in protocol Section 8.6 must be evaluated at screening (for placebo patients) and throughout the study locally:

- 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 (alanine aminotransferase), AST (aspartate aminotransferase), creatinine, blood urea nitrogen (BUN) or urea, $Ca^{++}$, total $CO_2$ (bicarbonate), glucose, $Na^{+}$, $K^{+}$, $Cl^{-}$, total bilirubin.

Patients are to have a safety follow-up approximately 30 days after the last dose of open-label enzalutamide. 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 the new treatment.

Long-term follow-up data will be collected every 16 weeks. The information collected will include survival status, new antineoplastic therapies for prostate cancer, skeletal-related events, and interventions due to locoregional progression.

**Schematic - Open Label Treatment Period:**



**Inclusion Criteria:**

The inclusion criteria apply to patients receiving enzalutamide or placebo during double-blind treatment. Eligible patients must meet all inclusion criteria.

1. Received randomized double-blind treatment in PROSPER;
2. Open-label day 1 visit is within 16 weeks after this amendment is approved and becomes effective at the study site;
3. Is willing to maintain androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) agonist/antagonist or has had a bilateral orchiectomy;
4. Is able to swallow enzalutamide capsules whole and to comply with study requirements throughout the study;
5. Throughout the study, a male 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 of contraception) starting at screening and continuing through 3 months after the final study drug administration 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);

   AND

   - 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: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner;
     - Tubal ligation in the female partner;
     - Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy), for > 6 months.
6. Male patient agrees to use a condom if having sex with a pregnant woman throughout the study;
7. Agrees to avoid sperm donation while taking enzalutamide.

**Exclusion Criteria**:

The exclusion criteria apply only to patients starting new treatment with enzalutamide after receiving placebo as randomized treatment. Each patient must NOT meet any of the following criteria:

1. Has taken commercially available enzalutamide (Xtandi).
2. Patients who progressed radiographically on double-blind portion of the trial and stopped treatment with investigational drug due to any reason. Note that patients who progressed radiographically on double-blind portion of the trial and continued treatment per protocol are allowed to participate in the open-label period.
3. Patients who started any other prostate cancer-related treatment after unblinding.
4. Has any clinically significant cardiovascular, dermatologic, endocrine, gastrointestinal, hematologic, hepatic, infectious, metabolic, neurologic, psychological, pulmonary, or renal disorder or any other condition, including excessive alcohol or drug abuse, or secondary malignancy, that may interfere with study participation in the opinion of the investigator or medical monitor;
5. Has current or previously treated brain metastasis or active leptomeningeal disease;
6. Has a history of seizure or a condition that may increase the risk of seizure;
7. Has any of the following: total bilirubin ≥1.5-times the upper limit of normal (ULN) (except patients with a diagnosis of Gilbert's disease), ALT ≥2.5-times ULN at screening, AST ≥2.5-times ULN at screening. For patients with documented liver metastases, ALT and AST exclusion is >5-times ULN; Absolute neutrophil count < 1000/μL, platelet count < 100,000/μL, or hemoglobin < 10 g/dL (6.2 mmol/L) at screening. NOTE: may not have received growth factors or blood transfusions within 7 days before obtaining the hematology values at screening. Albumin < 3.0 g/dL (30 g/L) at screening.
8. Has creatinine >2 mg/dL (177 μmol/L) at screening.

**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 (treatment will continue at the reduced dose). Patients should return all study drug bottles, including unused study drug to the site at each visit.

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. Please refer to IP Manual.

**Duration of Treatment and Criteria for Discontinuation:**

Open-label enzalutamide administration may continue as long as the investigator considers treatment to be beneficial or until any intolerable adverse event develops.

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 (160 mg/day) or a reduced dose (120 or 80 mg/day) in consultation with the medical monitor.

If enzalutamide is coadministered with a strong CYP2C8 inhibitor (ie, 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.

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 open-label period. Patients will permanently discontinue treatment with enzalutamide for the following reasons:

- Adverse event: If intolerable and cannot be ameliorated by adequate medical intervention; or that in the opinion of the investigator or medical monitor will lead to undue risk if enzalutamide continues;
- Seizure or any condition that significantly predisposes the patient to seizure such as brain metastasis or clinically evident stroke;
- Initiation of cytotoxic chemotherapy or investigational therapy for prostate cancer;
- Persistent laboratory abnormality as follows:
  - Creatinine >354 μmol/L (4.0 mg/dL);
  - Bilirubin, AST, or ALT >5-times the ULN;
  - AST or ALT > 3 times ULN and total bilirubin > 2 times ULN without findings of cholestasis;
  - Absolute neutrophil count ≤750/μL;
  - Platelet count < 50,000/μL.

Patients may also permanently discontinue enzalutamide treatment for the following reasons:

- Withdrawal of consent (patient decision anytime for any reason). Patients may withdraw consent for further treatment, but may still consent to participate in the long-term follow-up assessments of survival status and new prostate cancer therapies (via family, physician contacts, and public records). Study site personnel should document in the patient's source records the specific details of the procedures the patient allows (eg, long-term follow-up) or declines (eg, further treatment);

- Gross noncompliance with protocol procedures and/or study drug management;

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

Patients who discontinue treatment with enzalutamide for any reason 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 anticancer treatment is initiated before 30 days after the last dose of enzalutamide, then safety follow-up should occur immediately before starting the new treatment. Long-term follow-up will commence after completion of safety follow-up.

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.

**Prior and Concomitant Medications:**

Medications taken within 4 weeks before open-label day 1 and any medications prescribed for chronic or intermittent use, or dose adjustments of these medications, must be recorded on the case report forms and source documents.

Concomitant medications include all vitamins, herbal remedies, and over-the-counter and prescription medications. Concomitant medications will be assessed at screening and all clinic visits. 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 clinical record.

Ongoing androgen deprivation therapy with a GnRH agonist/antagonist to maintain castrate levels of testosterone is required throughout the study if the patient has not had a prior bilateral orchiectomy.

The use of concurrent cytotoxic chemotherapy or investigational anticancer agents is prohibited.

Initiation of bisphosphonates or denosumab for bone health is allowed. Standard of care supplementation with calcium and vitamin D is encouraged.

**Statistical Methods:**

Two additional interim analyses and the final analysis of overall survival are planned after approximately 285, 440, and 596 deaths occur, respectively. Analyses will be performed using a stratified log-rank test to compare the 2 treatment groups on ITT population. A multiplicity adjusted inferential procedure will be used to maintain the family-wise 2-sided type I error rate at 0.05. If an interim analysis of overall survival is statistically significant, it will be reported as the final analysis and no subsequent analyses will be performed.

The primary analysis of OS in the aforementioned interim and final analyses will be based on an ITT approach, which does not adjust for the potential confounding effects of crossover, and will be performed as planned per protocol. An additional confounding factor for the OS analysis may come from patients who choose to access commercial enzalutamide and other commercially available treatments for CRPC. The sponsors plan to explore the effect of crossover and post-study systemic anticancer therapy using Rank-Preserving Structural Failure Time Model (RPSFTM), and the inverse probability of treatment weighting (IPTW) method. Justifications, limitations and assumptions of RPFSTM and IPTW methods will be provided with further details in Statistical Analysis Plan.

No other efficacy endpoints will be formally tested. CCI [redacted]

- Time to First Use of New Antineoplastic Therapy: Time to first use of new antineoplastic therapy is defined as the time from randomization to the first use of new antineoplastic therapy for prostate cancer;
- Time to First Use of Cytotoxic Chemotherapy: Time to first use of cytotoxic chemotherapy is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer;
- Chemotherapy-Free Disease-Specific Survival: Chemotherapy-free disease-specific survival is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer as assessed by the investigator;
- Chemotherapy-Free Survival: Chemotherapy-free survival is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer or death due to any cause.

CCI [redacted]

Safety analyses will include all patients who receive 1 dose or partial dose of study drug (safety population).

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.

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.

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

| Study Period or Visit | OL Screen [1] | Treatment | | | Unscheduled | Safety FU | Long Term FU |
|---|---|---|---|---|---|---|---|
| Study Week | na | OL 1 [2] | OL 5 [3] | OL 17 Then Every 16 | Varies [4] | Varies [5] | Every 16 |
| Window (Days) [6] | na | na | ±5 | ±5 | na | ±7 | ±7 |
| **General Activities** | | | | | | | |
| Informed consent [7] | X | X [8] | | | | | |
| Eligibility criteria for OLE | X | | | | | | |
| Enrollment Authorization Form [9] | X | | | | | | |
| 12 Lead electrocardiogram [10] | X | | | | | | |
| Brief physical examination [11] | X | X | | X | X | X | |
| Radiographic assessments [12] | | | | X | X | | X |
| Serious and non-serious adverse event monitoring [13] | X | | X [3] | X | X | X | |
| Concomitant medications review | X | X | X [3] | X | X | X | |
| Dispense enzalutamide (via IWRS) | | X | | X | | | |
| Study drug accountability | | | X [3] | X | | X | |
| Local laboratory evaluation [14] | X | X | | X | X (optional) | X | |
| Long Tern Follow-up Assessments[15] | | X [8] | | | | | X |

1. Only for patients starting new treatment with enzalutamide (previously received placebo). Qualifying patients continuing treatment with enzalutamide may proceed to open label day 1 procedures. The investigator will assess and confirm patient eligibility for open label extension. All screening procedure results and relevant medical history must be available to determine eligibility. All inclusion criteria must be met and no exclusion criteria may apply. No eligibility waivers will be granted.
2. For patients previously receiving placebo, open label day 1, week 1, must be within 16 weeks after the approval and activation of this protocol at the study site and no later than 16 weeks after screening. For patients continuing treatment with enzalutamide, open label day 1 will be their next regular scheduled visit following approval and activation of this protocol at the study site.
3. Only for patients starting new treatment with enzalutamide (previously received placebo).
4. Anytime necessary to assess or follow up adverse events, at the patient's request, or per investigator decision.
5. 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.
6. 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.
7. Must obtain informed consent before performing any study specific procedures at screening for patients starting new treatment with enzalutamide and on day 1 for all patients continuing treatment with enzalutamide.
8. Only for patients continuing enzalutamide treatment.
9. When the investigator determines a patient is eligible, study site personnel will complete and email this form to the e-mail address provided on the form. The sponsor medical monitor will approve the enrollment in writing or contact the study site. No form is required for patients continuing enzalutamide treatment.
10. Read locally.
11. Symptom directed and includes investigating any new abnormalities and assessment of vital signs.
12. For patients that have not progressed radiographically, scans (CT/MRI and bone scan) will be performed per investigator discretion until patient has progressed radiographically.
13. Collect nonserious adverse event information from the time of signing of informed consent through safety follow up. Collect and report serious adverse event information from the time of signed informed consent through screen failure or safety follow up. If no safety follow up, collect adverse event information through 30 days after the last dose of study drug. Phone patients for follow up if they do not come to the clinic.
14. Hematology, serum chemistry. Report any clinically significant abnormalities as adverse events per CTCAE v4 criteria. For patients previously receiving placebo, if the open label day 1 visit occurs within 7 days of performing the screening labs, then the laboratory assessments do not need to be repeated on day 1.
15. May obtain at clinic visits, by phone contact, chart review, etc. Includes survival status, new antineoplastic therapies for prostate cancer, skeletal related events, and interventions due to locoregional progression.

CTCAE v4, Common Terminology Criteria for Adverse Events, version 4; FU, Follow-up; L T, long term; na, not applicable; OL, open label; PC, prostate cancer; q16.

# Document Approval Record

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