**Medivation, Inc.**

# CLINICAL RESEARCH PROTOCOL

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|---|---|
| **Study Title:** | A Phase 2, Open-Label, Single-Arm Study of $^{18}$F-Sodium Fluoride PET/CT Bone Imaging in Enzalutamide-Treated Chemotherapy-Naïve Patients With Bone-Metastatic Castration-Resistant Prostate Cancer |
| **Protocol Identifier:** | MDV3100-18 |
| **Phase:** | 2 |
| **Investigational Product:** | Enzalutamide (formerly MDV3100) |
| **Indication:** | Prostate Cancer |
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| **Reference Number:** | United States IND 74,563 |
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| **Original Protocol:** | v1.0 – 27 AUG 2014 |
| **Amendment 1:** | v2.0 – 25 FEB 2015 |
| **Amendment 2:** | v3.0 – 08 DEC 2016 |

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.

[redacted]

## SYNOPSIS

**Title of Study:** A Phase 2, Open-Label, Single-Arm Study of $^{18}$F-Sodium Fluoride PET/CT Bone Imaging in Enzalutamide-Treated Chemotherapy-Naïve Patients With Bone-Metastatic Castration-Resistant Prostate Cancer

**Protocol Identifier:** MDV3100-18

**Phase of Development:** 2

**Number of Patients:** Approximately 20

**Study Centers:** 3 in the United States (US)

**Study Objectives:**

Primary:

- Evaluate $^{18}$F-sodium fluoride positron-emission tomography / computed tomography ($^{18}$F-NaF PET/CT) imaging as a method for determining treatment response in metastatic bone lesions at the time of disease progression (prostate-specific antigen [PSA], bone or soft tissue, or other clinically relevant progression) or at 2 years without progression after treatment initiation in patients who are chemotherapy-naïve in the castration-resistant setting with progressive bone-metastatic castration-resistant prostate cancer (CRPC) treated with enzalutamide

Secondary:

- Evaluate heterogeneity of response in metastatic bone lesions at the time the primary objective is assessed

CCI [redacted]

**Methods:** This phase 2, open-label, single-arm study in patients who are chemotherapy-naïve in the castration-resistant setting with progressive bone-metastatic CRPC is designed to evaluate $^{18}$F-NaF PET/CT imaging as a method to quantify changes in total tumor burden in bone metastases in individual lesions as well as across all lesions, and the heterogeneity of response in those bone lesions after treatment with enzalutamide. The primary endpoint is the proportion of patients with at least 1 responding bone lesion at the time of PSA, radiographic (bone or soft tissue), or other clinically relevant progression or at 2 years without progression after treatment initiation.

The study will enroll approximately 20 patients at 3 study sites in the US. $^{18}$F-NaF PET/CT imaging will be performed during the study as follows:

- NaF-1: Following screening, before first dose
- NaF-2: At week 13
- NaF-3: At the time of PSA, radiographic (bone or soft tissue), or other clinically relevant progression, or at 2 years without progression after treatment initiation

Following screening including a $^{99m}$Tc-MDP bone scintigraphy, enrolled patients will have baseline $^{18}$F-NaF PET/CT imaging (NaF-1) and then begin open-label treatment with enzalutamide (160 mg) administered as four 40-mg capsules by mouth once daily.

PSA response will be determined at week 13 when a second $^{18}$F-NaF PET/CT imaging (NaF-2) is obtained. Patients with any increase in PSA at week 13 may discontinue treatment and proceed to safety follow-up unless the investigator considers continuation of study drug to be beneficial. For all continuing patients, PSA will be monitored every 8 weeks after week 13 and other study assessments will continue to be obtained. A third $^{18}$F-NaF PET/CT imaging (NaF-3) and a follow-up $^{99m}$Tc-MDP bone scintigraphy will be performed when PSA progression (an increase of at least 25% AND an absolute increase of at least 2.0 ng/mL above nadir), radiographic progression (bone or soft tissue), or other clinically relevant progression (eg, significant bone pain or a skeletal-related event) is observed, or at 2 years without progression after initiation of treatment. No $^{99m}$Tc-MDP bone scintigraphy will be required at the time the NaF-3 bone scan is obtained if bone disease progression was confirmed earlier on bone scintigraphy obtained at investigator discretion.

Bone disease progression will be defined as the appearance of at least 2 new lesions after screening assessed by $^{99m}$Tc-MDP bone scintigraphy. Progression at week 13 or earlier will require a confirmatory $^{99m}$Tc-MDP bone scintigraphy at least 6 weeks later showing at least 2 additional new lesions related to prostate cancer (compared with the previous scan). After week 13, no confirmation of progression will be required if at least 2 new lesions related to prostate cancer are observed. Assessment of soft tissue disease will be by CT or magnetic resonance imaging (MRI) obtained at investigator discretion. Radiographic progression for soft tissue disease will be defined by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).

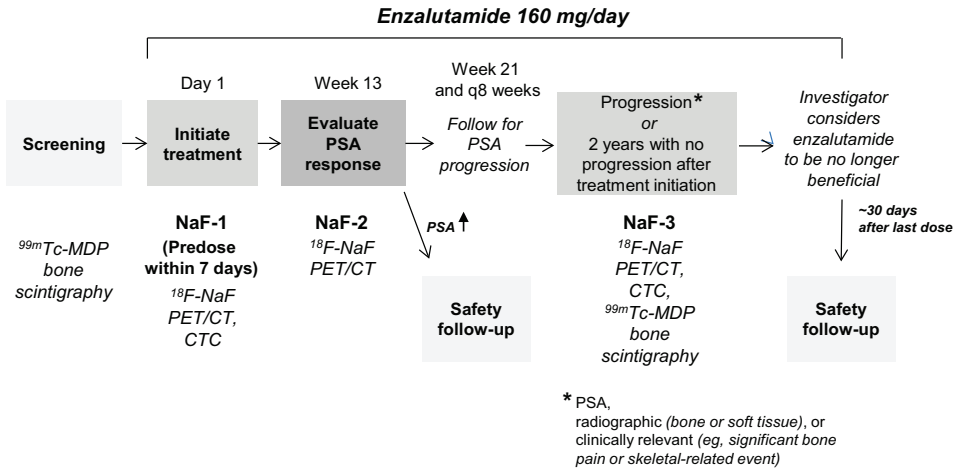
Treatment with enzalutamide may continue thereafter for as long as the investigator considers it beneficial. Continuation of enzalutamide treatment is strongly encouraged at least through completion of NaF-3.

Blood samples will be collected at baseline and at the time of the third $^{18}$F-NaF PET/CT imaging for the isolation CCI [redacted]. These cells will be stained for the androgen receptor and glucocorticoid receptor, and receptor protein expression will be quantified using quantitative immunocytochemistry. The subcellular localization of these receptors (cytoplasmic vs nuclear) will be determined. Additionally, DNA and RNA will be extracted from recovered circulating tumor cells and stored for potential future analyses if warranted.

All patients are required to maintain castrate levels of testosterone (≤ 1.73 nmol/L) during the study either by receiving a luteinizing hormone-releasing hormone (LHRH) analogue or by prior bilateral orchiectomy. Treatment with abiraterone acetate, ketoconazole, aminoglutethimide, radium Ra 223 dichloride or other bone-targeting radionuclides, cytotoxic chemotherapy in the CRPC setting, radiation therapy to bone, or other experimental therapies for the treatment of cancer is prohibited during the study before NaF-3. Initiation of bisphosphonates or denosumab for any reason is not allowed; however, treatment with these agents may continue if initiated at least 4 weeks before enrollment. Standard of care supplementation with calcium and vitamin D is encouraged.

Assessments of safety will include adverse events, clinical laboratory tests, physical examinations, and vital signs. Patients will have safety follow-up approximately 30 days after the last dose of study drug or before initiation of cytotoxic chemotherapy, a lutamide (bicalutamide, nilutamide, or flutamide), or a new investigational therapy, whichever occurs first.

**Study Schematic:**



**Key Eligibility Criteria:**

Patients must have bone-metastatic CRPC as assessed by at least 2 lesions on conventional whole-body $^{99m}$Tc-MDP radionuclide bone scintigraphy that did not show a superscan. Patients with visceral metastatic disease are excluded. They must have progressive disease on androgen deprivation therapy at screening, defined as a minimum of 2 sequentially rising PSA values (PSA1 < PSA2 < PSA3) assessed by the local laboratory with an interval of ≥ 1 week between each determination. The most recent PSA must be ≥ 2 µg/L (≥ 2 ng/mL). Patients must agree to continue androgen deprivation therapy with an LHRH analogue throughout the study or have had a prior bilateral orchiectomy. Testosterone at screening must be ≤ 1.73 nmol/L (≤ 50 ng/dL). Additionally, patients must have asymptomatic or minimally symptomatic prostate cancer (Brief Pain Inventory Short Form question 3 score < 4) without use of opiate analgesics for prostate cancer pain within 4 weeks before enrollment (day 1); an Eastern Cooperative Oncology Group (ECOG) performance score ≤ 1; and an estimated life expectancy of ≥ 12 months at screening. Prior enzalutamide, abiraterone acetate, aminoglutethimide, ketoconazole, radium Ra 223 dichloride or other bone-targeting radionuclides, cytotoxic chemotherapy in the CRPC setting for the treatment of prostate cancer, and participation in a clinical trial of an investigational agent that inhibits the androgen receptor or androgen synthesis (unless treatment was placebo) are prohibited. Patients with a history of seizure any time in the past for any reason or any condition that may predispose to seizure are excluded.

**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:** None

**Duration of Treatment:** Patients will receive enzalutamide treatment daily as defined in Methods. After NaF-3 is completed, another therapy may be added to enzalutamide as long as it is not another androgen receptor inhibitor, cytotoxic chemotherapy, or an investigational drug. Patients may continue to receive treatment with enzalutamide for as long as the investigator considers it beneficial.

**Statistical Methods:**

The study endpoints are as follows:

Primary:

- The proportion of patients with at least 1 responding bone lesion (defined as a lesion with a total standardized uptake value [$SUV_{total}$] less than that at baseline) on the third $^{18}$F-NaF PET/CT [NaF-3] scan performed for each patient. This assessment will be triggered by disease progression (as defined in Methods) or at 2 years without progression after treatment initiation.

Secondary:

- The heterogeneity of response across all bone lesions as determined by the global heterogeneity of NaF standardized uptake value ($SUV_{hetero}$) when the primary endpoint is determined for each patient

CCI [redacted]

CCI [redacted]

The primary efficacy endpoint analysis will include patients who undergo at least NaF-1 and NaF-3 $^{18}$F-NaF PET/CT imaging. Definitions of the NaF uptake measures are as follows:

- $SUV_{total}$ Total NaF uptake, which represents the tumor burden across all (global) bone lesions or in individual lesions
- $SUV_{hetero}$ Heterogeneity of NaF uptake, which represents heterogeneity of lesion activity
- $SUV_{mean}$ Mean NaF uptake, which represents the average activity of all lesions
- $SUV_{max}$ Maximum NaF uptake, which represents the activity of the most aggressive lesion
- N Total number of lesions, which represents a numerical sum of all lesions
- VF Volume fraction, which represents the fraction of skeletal involvement

The global $SUV_{hetero}$ score is a measure of the heterogeneity of tumor activity across all bone lesions and is defined as follows, where $g$ = global, $l$ = lesion, $N$ = number of bone lesions.

$$gSUV_{hetero} = \frac{\sum_{i=1}^{N}\left(lSUV_{mean}^{i} - gSUV_{mean}\right)^{2}}{N}$$

In other words, the global $SUV_{hetero}$ score is the sum of the squares of the differences between the $SUV_{mean}$ for each bone lesion and the global $SUV_{mean}$, divided by the number of lesions. Thus, a higher global $SUV_{hetero}$ score reflects more heterogeneity in bone lesion activity.

CCI [redacted]

Circulating tumor cells:

*Androgen receptor and glucocorticoid receptor subcellular localization and expression*. Circulating tumor cells will be collected at baseline and NaF-3. Standard descriptive statistics will be calculated (n, mean, standard deviation, median, and range) CCI [redacted] as well as for androgen receptor and glucocorticoid receptor subcellular expression and localization (cytoplasmic vs nuclear).

*Correlation of circulating tumor cell analyses with NaF uptake measures and clinical outcomes*. CCI [redacted]

The laboratory manual has instructions for the extraction and storage of RNA samples for other analyses that may be performed in the future if warranted.

Safety:

All safety analyses will be based on the safety population, defined as all patients who receive any amount of study drug.

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

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

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

**Sample Size Considerations:**

The total number of patients to be included in this study is approximately 20 and is based on practical clinical considerations.

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## LIST OF ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| $AUC_{0-\infty}$ | Area under the curve from time zero to infinity |
| CFR | Code of Federal Regulations |
| $C_{max}$ | Maximum plasma concentration |
| CRPC | Castration-resistant prostate cancer |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| $C_{trough}$ | Predose trough plasma concentration |
| CYP | Cytochrome P450 |
| Δ | Change |
| $\Delta SUV_{total}$ | Change in total NaF uptake |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| CCI [redacted] | |
| $^{18}$F-NaF | $^{18}$F-sodium fluoride |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HR | Hazard ratio |
| ICH | International Council for Harmonisation |
| ID | Identification |
| INR | International normalized ratio |
| IRB | Institutional review board |
| LHRH | Luteinizing hormone-releasing hormone |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| NaF-1 | $^{18}$F-NaF PET/CT following screening, before first dose |
| NaF-2 | $^{18}$F-NaF PET/CT at week 13 |
| NaF-3 | $^{18}$F-NaF PET/CT at the time of disease progression or at 2 years without progression after treatment initiation |
| PET | Positron-emission tomography |
| PK | Pharmacokinetic |
| PSA | Prostate-specific antigen |
| RECIST 1.1 | Response Evaluation Criteria in Solid Tumors, version 1.1 |
| SUSAR | Suspected unexpected serious adverse reaction |
| SUV | Standardized uptake value |
| $SUV_{mean}$ | Mean NaF uptake |
| $SUV_{total}$ | Total NaF uptake |

| Abbreviation | Definition |
|---|---|
| $SUV_{hetero}$ | Heterogeneity of NaF uptake |
| $^{99m}$Tc-MDP | Technetium Tc 99m medronate |
| ULN | Upper limit of normal |
| US | United States |

# 1 INTRODUCTION

## 1.1 Background

Recurrence of prostate cancer during luteinizing hormone-releasing hormone (LHRH) analogue therapy or after a bilateral orchiectomy, as detected by prostate-specific antigen (PSA) or radiographic progression, signals transition to the lethal phenotype of castration-resistant prostate cancer (CRPC). PSA progression alone may predict later radiographic progression, which frequently entails the development or worsening of existing bone metastases that can lead to spinal cord compression, pathologic fracture, and the need for new treatment measures spanning multiple modalities (surgical, radiologic, pharmacologic). Depending on the extent of disease and symptomatology, patients with such disease progression may then receive new hormonal (enzalutamide, abiraterone), immunologic (sipuleucel-T), radiologic (radium Ra 223 dichloride), or cytotoxic (docetaxel, then cabazitaxel) therapy. Of note, LHRH analogue therapy is almost always continued when prostate cancer becomes castration resistant.

$^{18}$F-sodium fluoride positron-emission tomography / computed tomography bone imaging ($^{18}$F-NaF PET/CT) predates conventional technetium Tc 99m medronate ($^{99m}$Tc-MDP) bone scintigraphy and is more sensitive and specific in identifying bone metastases.[1,2,3,4,5] Use of $^{18}$F-NaF PET/CT at select academic centers in the United States (US) offers the opportunity to test the hypothesis that continuing enzalutamide may be of therapeutic benefit for the treatment of bone metastases after PSA or radiographic progression, including conventionally defined bone or soft tissue disease progression.

This phase 2, open-label study of enzalutamide will determine the proportion of patients with at least 1 responding metastatic bone lesion and the heterogeneity of response across all bone lesions for patients who have $^{18}$F-NaF PET/CT bone imaging at the time of PSA, radiographic (bone or soft tissue), or other clinically relevant progression (eg, significant bone pain or a skeletal-related event), or at 2 years without progression after initiation of enzalutamide treatment.

## 1.2 Summary of Relevant Clinical Experience With Enzalutamide

The US Food and Drug Administration (FDA) approved Xtandi (enzalutamide) capsules in August 2012 based on a benefit in overall survival for men with metastatic CRPC who previously received docetaxel therapy.[6] Xtandi was later approved in Canada, the European Union, and other countries for use in this patient population.

Medivation PPD , Inc. are in a partnership to codevelop enzalutamide for the treatment of cancer.

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

CRPC2 (AFFIRM): A phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide (160 mg daily) in patients with progressive CRPC previously treated with docetaxel-based chemotherapy was conducted in 1199 men, 800 of whom received treatment with enzalutamide.[6] The primary endpoint was overall survival. The prespecified interim analysis at the time of 520 events demonstrated a statistically significant improvement in overall survival in patients treated with enzalutamide versus placebo (HR 0.63 [95% CI: 0.53, 0.75]; $p < 0.0001$). Current marketing application approvals for men with metastatic CRPC who have previously received docetaxel therapy are based on the results of this pivotal study.

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

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

9785-CL-0321: A phase 2, open-label, single-arm, multicenter, efficacy and safety study of enzalutamide monotherapy (160 mg daily) in 67 patients with hormone-naïve prostate cancer for whom androgen deprivation therapy was indicated. The primary objective was to determine the incidence of patients with a ≥ 80% PSA response at week 25. Secondary objectives included evaluation of safety and tolerability; CCI [redacted]

In the phase 3 study CRPC2 (AFFIRM; N = 1199), the most common adverse drug reactions (≥ 5%) in patients treated with enzalutamide (N = 800) were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Discontinuations due to adverse events were reported for 16% of enzalutamide-treated patients and 18% of placebo-treated patients. The most common

adverse reaction leading to treatment discontinuation was seizure, which occurred in 7 (0.9%) of the enzalutamide-treated patients and none (0%) of the placebo-treated patients.

In the phase 3 study MDV3100-03 (PREVAIL; N = 1715), enzalutamide was generally well tolerated with an overall safety profile consistent with that observed in study CRPC2, with a lower seizure rate observed in MDV3100-03 (1 patient [0.1%] each in the enzalutamide and placebo treatment groups). The new adverse drug reactions observed in study MDV3100-03, gynecomastia and restless legs syndrome, were uniformly nonserious events occurring at low frequency (3.3% and 2.1%, respectively, in enzalutamide-treated patients vs 1.3% and 0.4%, respectively, in placebo-treated patients).

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

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

### 1.2.1 Pharmacokinetics and Drug Metabolism

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

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

decreases in exposure, enzalutamide is considered a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19 (Section 7.3.1.1). Orally administered substrates of CYP3A4, CYP2C9, and CYP2C19 with a narrow therapeutic index should be avoided if possible, as enzalutamide may decrease plasma exposure of these drugs. If enzalutamide is coadministered with warfarin (CYP2C9 substrate), additional international normalized ratio (INR) monitoring should be conducted. Enzalutamide did not cause clinically meaningful changes in exposure to pioglitazone (CYP2C8 substrate).

In a drug-drug interaction study in healthy male volunteers (9785-CL-0006), a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor). CCI [redacted] The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated in vivo (Section 7.3.1.2.1).

In the drug-drug interaction study in healthy male volunteers (9785-CL-0006), a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of itraconazole (strong CYP3A4 inhibitor). CCI [redacted] The effects of CYP3A4 inducers on the PK of enzalutamide have not been evaluated in vivo (Section 7.3.1.2.2).

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

### 1.3 Summary of Relevant Nonclinical Experience With Enzalutamide

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

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

Long-term animal studies have not been 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 toxicity studies, which were consistent with the pharmacologic activity of enzalutamide, male fertility may be impaired by treatment with enzalutamide. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-week and 13-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3-times the human exposure based on AUC).

Additional toxicity 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

Approximately 5000 subjects and patients have been enrolled worldwide in completed and ongoing clinical trials evaluating enzalutamide. Approximately 3200 have received at least 1 dose of enzalutamide. Available data for enzalutamide in men with metastatic prostate cancer that has progressed despite therapy with an LHRH analogue or bilateral orchiectomy support a positive benefit-risk profile for the use of enzalutamide as an investigational agent in this study, which will enroll patients similar to those who participated in MDV3100-03, with the caveat that patients must have bone metastatic disease to enter this study. The clinical experience with enzalutamide is discussed briefly in Section 1.2.

## 2 STUDY OBJECTIVES

### 2.1 Primary Objective

- Evaluate $^{18}$F-NaF PET/CT imaging as a method for determining treatment response in metastatic bone lesions at the time of disease progression (PSA, bone or soft tissue, or other clinically relevant progression) or at 2 years without progression after treatment initiation in patients who are chemotherapy-naïve in the castration-resistant setting with progressive bone-metastatic CRPC treated with enzalutamide

### 2.2 Secondary Objective

- Evaluate heterogeneity of response in metastatic bone lesions at the time the primary objective is assessed

CCI [redacted]

# 3 INVESTIGATIONAL PLAN

## 3.1 Overall Study Design and Plan: Description

This phase 2, open-label, single-arm study in patients who are chemotherapy-naïve in the castration-resistant setting with progressive bone-metastatic CRPC is designed to evaluate $^{18}$F-NaF PET/CT imaging as a method to quantify changes in total tumor burden in bone metastases in individual lesions as well as across all lesions, and the heterogeneity of response in those bone lesions, after treatment with enzalutamide. The primary endpoint is the proportion of patients with at least 1 responding bone lesion at the time of PSA, radiographic (bone or soft tissue), or other clinically relevant progression or at 2 years without progression after treatment initiation.

The study will enroll approximately 20 patients at 3 study sites in the US. $^{18}$F-NaF PET/CT imaging will be performed during the study as follows:

- NaF-1: Following screening, before first dose
- NaF-2: At week 13
- NaF-3: At the time of PSA, radiographic (bone or soft tissue), or other clinically relevant progression, or at 2 years without progression after treatment initiation

Following screening including a $^{99m}$Tc-MDP bone scintigraphy, enrolled patients will have baseline $^{18}$F-NaF PET/CT imaging (NaF-1) and then begin open-label treatment with enzalutamide (160 mg) administered as four 40-mg capsules by mouth once daily. PSA response will be determined at week 13 when a second $^{18}$F-NaF PET/CT imaging (NaF-2) is obtained. Patients with any increase in PSA at week 13 may discontinue treatment and proceed to safety follow-up unless the investigator considers continuation of study drug to be beneficial. For all continuing patients, PSA will be monitored every 8 weeks after week 13 and other study assessments will continue to be obtained. A third $^{18}$F-NaF PET/CT imaging

(NaF-3) and a follow-up $^{99m}$Tc-MDP bone scintigraphy will be performed when PSA progression (an increase of at least 25% AND an absolute increase of at least 2.0 ng/mL above nadir), radiographic progression (bone or soft tissue), or other clinically relevant progression (eg, significant bone pain or a skeletal-related event) is observed, or at 2 years without progression after initiation of treatment. No $^{99m}$Tc-MDP bone scintigraphy will be required at the time the NaF-3 bone scan is obtained if bone disease progression was confirmed earlier on bone scintigraphy obtained at investigator discretion.

Bone disease progression will be defined as the appearance of at least 2 new lesions after screening assessed by $^{99m}$Tc-MDP bone scintigraphy. Progression at week 13 or earlier will require a confirmatory $^{99m}$Tc-MDP bone scintigraphy at least 6 weeks later showing at least 2 additional new lesions related to prostate cancer (compared with the previous scan). After week 13, no confirmation of progression will be required if at least 2 new lesions related to prostate cancer are observed. Assessment of soft tissue disease will be by CT or magnetic resonance imaging (MRI) obtained at investigator discretion. Radiographic progression for soft tissue disease will be defined by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).[7]

Treatment with enzalutamide may continue thereafter for as long as the investigator considers it beneficial. Continuation of enzalutamide treatment is strongly encouraged at least through completion of NaF-3.

Blood samples will be collected at baseline and at the time of the third $^{18}$F-NaF PET/CT imaging for the isolation CCI [redacted]. These cells will be stained for the androgen receptor and glucocorticoid receptor, and receptor protein expression will be quantified using quantitative immunocytochemistry. The subcellular localization of these receptors (cytoplasmic vs nuclear) will be determined. Additionally, DNA and RNA will be extracted from recovered circulating tumor cells and stored for potential future analyses if warranted.

All patients are required to maintain castrate levels of testosterone (≤ 1.73 nmol/L) during the study either by receiving an LHRH analogue or by prior bilateral orchiectomy. Treatment with abiraterone acetate, ketoconazole, aminoglutethimide, radium Ra 223 dichloride or other bone-targeting radionuclides, cytotoxic chemotherapy in the CRPC setting, radiation therapy to bone, or other experimental therapies for the treatment of cancer is prohibited during the study before NaF-3. Initiation of bisphosphonates or denosumab for any reason is not allowed; however, treatment with these agents may continue if initiated at least 4 weeks before enrollment.

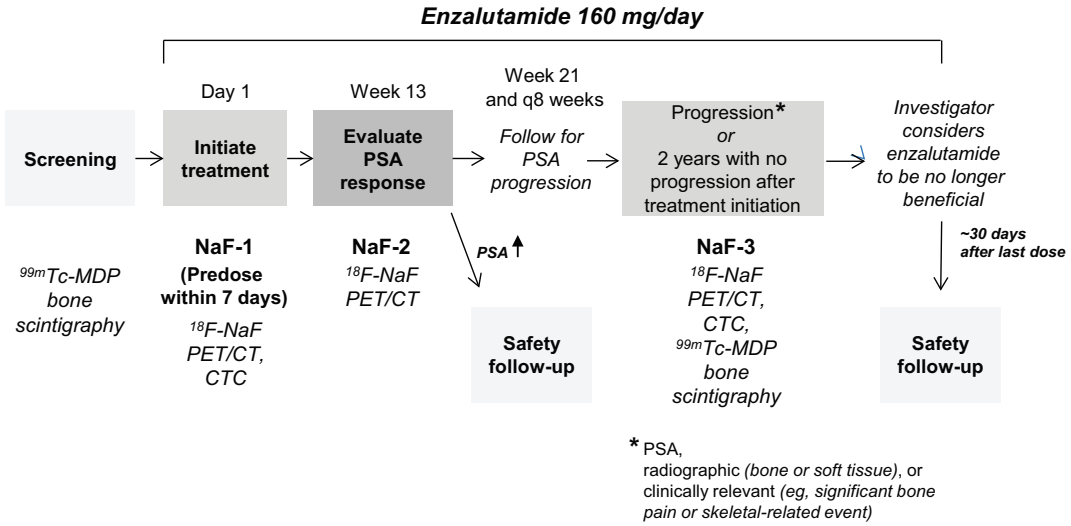
Standard of care supplementation with calcium and vitamin D is encouraged.

Assessments of safety will include adverse events, clinical laboratory tests, physical examinations, and vital signs. Patients will have safety follow-up approximately 30 days after the last dose of study drug or before initiation of cytotoxic chemotherapy, a lutamide (bicalutamide, nilutamide, or flutamide), or a new investigational therapy, whichever occurs first.

The study schematic is provided in Figure 1.

## 3.2 Study Schematic

**Figure 1: Study Schematic**




## 3.3 Blinding

Treatment with enzalutamide will be open label.

## 3.4 Duration of Study

The total duration of this study will be approximately 36 months to accommodate NaF-3 in patients without protocol-defined disease progression.

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

Enzalutamide is hypothesized to cause an ongoing treatment response in bone metastases as detected by $^{18}$F-NaF PET/CT imaging at the time of conventionally defined disease progression in progressive, bone-metastatic CRPC. Key features of the study design include $^{18}$F-NaF PET/CT imaging at baseline and week 13 (when patients without a PSA response may exit the study), and at the time of disease progression when new treatments are often introduced. NaF measurements at these 3 time points are based on the standardized uptake value (SUV), the ratio of tissue radioactivity concentration to the total injected activity per patient mass, lean body mass, or body surface area.[8] CCI [redacted]

This open-label, single-arm (no control group) study is designed to determine the proportion of patients with at least 1 bone lesion responding to enzalutamide treatment in patients who

have $^{18}$F-NaF PET/CT imaging when disease progression occurs (PSA, radiographic [bone or soft tissue], or other clinically relevant progression), or who are progression-free 2 years after initiation of treatment. The heterogeneity of response across all bone lesions will also be determined at this time.

$^{99m}$Tc-MDP bone scintigraphy will be used to qualify patients for the study and will be repeated at NaF-3 (except in cases of bone disease progression confirmed earlier) to study the relationship between conventionally defined bone disease progression and measures of bone tumor activity on $^{18}$F-NaF PET/CT imaging, including the change (Δ) in total SUV ($\Delta SUV_{total}$) and the heterogeneity of NaF uptake ($SUV_{hetero}$). CCI [redacted] Additionally, DNA and RNA will be collected and stored for potential future analyses (eg, analysis of androgen receptor mutations and splice variants) if warranted.

The study population will be composed of men with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or signet cell or small cell features, as responsiveness to endocrine therapy has been best demonstrated in adenocarcinoma of the prostate without these features. Qualifying patients will have bone metastatic disease as assessed by at least 2 lesions on $^{99m}$Tc-MDP bone scintigraphy that did not show a superscan, to enable the potential demonstration of discordance in treatment response across a given patient's bone lesions over time and to enable determination of conventionally defined bone disease progression. Thus, patients will serve as their own controls.

Patients will need to demonstrate progressive disease on androgen deprivation therapy at screening defined as a minimum of 2 sequentially rising PSA values (PSA1 < PSA2 < PSA3) to ensure the inclusion of patients whose disease is driven by signaling through the androgen axis pathway. Patients will also need to maintain androgen deprivation therapy with an LHRH analogue throughout the study or have had a prior bilateral orchiectomy. Finally, patients ever previously treated with enzalutamide, abiraterone acetate, aminoglutethimide, ketoconazole, radium Ra 223 dichloride or other bone-targeting radionuclide therapy, cytotoxic chemotherapy in the CRPC setting, or investigational agents that inhibit the androgen receptor or androgen synthesis will be prohibited from participating due to the unknown long-term effects of these treatments on $^{18}$F-NaF PET/CT imaging.

## 4 SELECTION OF STUDY POPULATION

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

## 4.1 Inclusion Criteria

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

1. Age 18 years or older and willing and able to provide informed consent.
2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, or signet cell or small cell features.
3. Ability to comply with all study procedures and willingness to remain supine for 30 minutes during imaging.
4. Presence of bone metastatic disease as assessed by at least 2 lesions on whole-body radionuclide $^{99m}$Tc-MDP bone scintigraphy.
5. Throughout the study, ongoing androgen deprivation therapy with an LHRH analogue or prior bilateral orchiectomy (medical or surgical castration).
6. Testosterone ≤ 1.73 nmol/L (≤ 50 ng/dL) at screening.
7. Progressive disease on androgen deprivation therapy at screening defined as a minimum of 2 sequentially rising PSA values (PSA1 < PSA2 < PSA3) assessed by the local laboratory with an interval of ≥ 1 week between each determination where PSA3 (the screening PSA) is obtained within 4 weeks before planned enrollment.
8. The screening PSA (PSA3) must be ≥ 2 µg/L (≥ 2 ng/mL). In the event of prior androgen receptor inhibitor use, the screening PSA must be obtained at least 4 weeks after the last dose of the androgen receptor inhibitor.
9. Asymptomatic or minimally symptomatic prostate cancer (Brief Pain Inventory Short Form question 3 score < 4) at screening.
10. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.
11. Estimated life expectancy of ≥ 12 months at screening.
12. Ability to swallow study capsules after a picture to scale of the capsules is shown to the patient and to comply with study requirements throughout the study.
13. Throughout the study, patient and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) from screening through 3 months after last dose of study drug. Two acceptable methods of birth control thus include the following:
    - A condom (barrier method of contraception)

      AND
    - One of the following is required:
      - Established and ongoing use of oral, injected, or implanted hormonal method of contraception by the female partner
      - Placement of an intrauterine device or intrauterine system by the female partner
      - Additional barrier method: Contraceptive sponge or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner
      - Tubal ligation in the female partner performed at least 6 months before screening
      - Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy), performed at least 6 months before screening

14. Throughout the study, the patient must use a condom if having sex with a pregnant woman.
15. Must agree not to donate sperm from first dose of study drug through 3 months after the last dose of study drug.

### 4.2 Exclusion Criteria

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

1. Prior enzalutamide, abiraterone acetate, aminoglutethimide, ketoconazole, radium Ra 223 dichloride or other bone-targeting radionuclides, or cytotoxic chemotherapy in the CRPC setting 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, 5-alpha reductase inhibitors) or biologic therapy for prostate cancer (other than LHRH analogue therapy) within 4 weeks before day 1.
3. Initiation of new treatment with denosumab, bisphosphonates, or systemic corticosteroids for treatment of prostate cancer within 4 weeks before day 1.
4. Use of an investigational agent within 4 weeks before the screening visit.
5. Radiation therapy to bone within 4 weeks before day 1.
6. Use of opiate analgesics for prostate cancer pain within 4 weeks before day 1.
7. History of another invasive cancer within 3 years before screening, with the exception of fully treated cancers with a remote probability of recurrence. The medical monitor and investigator must agree that the possibility of recurrence is remote for exceptions.
8. Screening $^{99m}$Tc-MDP bone scintigraphy showing a superscan.
9. Visceral (eg, lung, liver) metastatic disease (biopsy not necessary). Adenopathy is allowed.
10. Absolute neutrophil count < 1500/μL, platelet count < 100,000/μL, or hemoglobin < 6.2 mmol/L (< 10 g/dL) at screening. Patients may not have received growth factors or blood transfusions within 7 days, inclusive, before obtaining the screening hematology values.
11. Total bilirubin ≥ 1.5 times the upper limit of normal (ULN) (except patients with a diagnosis of Gilbert's disease), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times ULN at screening.
12. Creatinine > 177 μmol/L (> 2 mg/dL) at screening.
13. Albumin < 30 g/L (< 3.0 g/dL) at screening.
14. Current or previously treated brain metastasis or active leptomeningeal disease.
15. History of seizure any time in the past for any reason or any condition that may predispose to seizures.
16. History of loss of consciousness or transient ischemic attack within 12 months before screening.

17. Clinically significant cardiovascular disease, including the following:
    - Myocardial infarction within 6 months before screening
    - Unstable angina within 3 months before screening
    - New York Heart Association class III or IV congestive heart failure, or a history of New York Heart Association class III or IV congestive heart failure, unless a screening echocardiogram or multigated acquisition scan performed within 3 months before screening 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 mm Hg at screening
    - Bradycardia as indicated by a heart rate < 45 beats per minute on the screening electrocardiogram (ECG) and physical examination
    - Uncontrolled hypertension as indicated by a systolic blood pressure > 170 mm Hg or a diastolic blood pressure > 105 mm Hg at screening
18. Gastrointestinal disorder affecting absorption.
19. Major surgery within 4 weeks before screening.
20. Any concurrent disease, infection, or comorbid condition that interferes with the ability of the patient to participate in the trial; places the patient at undue risk; or complicates the interpretation of the data, in the opinion of the investigator or medical monitor.

# 5 ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is also provided in the schedule of activities (Appendix 2).

## 5.1 Screening Period

The screening period will be from day -28 through day -1. Screening procedures are listed in Table 1. 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 Study Identification Numbers

After obtaining informed consent, study site personnel will assign a study 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 document the screen failure in the patient's source documents. The documentation should include demographics and medical history, the reason for screen failure, the eligibility criteria reviewed, and procedures performed.

### 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, and must document the informed consent process in the patient's source documents. Informed consent may be obtained before the 28-day screening period.

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, study site personnel will complete an Enrollment Authorization Form and fax or email it to the medical monitor or designee to approve the enrollment in writing.

**Table 1: Screening Procedures**

| Activity / Assessment / Timing | Comment |
|---|---|
| **General** | All screening procedures must be performed within the 28-day screening period (see below for informed consent). |
| Informed consent | Must obtain informed consent before performing any study-specific procedures. May obtain before the 28-day screening period.<br>Ensure consent is on the current version of the form approved by the IRB. |
| Study ID | Assign study ID number to patient. |
| Medical history | Review any time after obtaining informed consent. |
| Eligibility criteria including BPI (Short Form) and ECOG performance status | All inclusion criteria must be met and none of the exclusion criteria may apply per Section 4.<br>Refer to Appendix 1 for BPI and Table 13 for ECOG. |
| 12-Lead ECG | Obtain per local practice and read locally to confirm eligibility. |
| Technetium Tc 99m medronate bone scintigraphy<br>→ ***Perform within 28 days before day 1*** | Whole-body radionuclide bone scintigraphy to establish the presence of bone metastatic disease; read locally.<br>Send copy of image to the central imaging vendor for archiving. |
| CT or MRI of chest, abdomen, and pelvis<br>→ ***Perform within 28 days before day 1*** | To establish the absence of visceral metastatic disease (adenopathy is allowed). |
| Complete physical examination | Measure vital signs (temperature, blood pressure, and heart rate), weight, and height.<br>Assess systems per standard of care at the study site. |

| Activity / Assessment / Timing | Comment |
|---|---|
| Adverse event review | Record adverse events (nonserious and serious) occurring during screening on the medical history case report form and in the patient's source documents for any patient who subsequently meets eligibility criteria and proceeds to enrollment. If the adverse event is serious, also record it on the adverse event case report form.<br>Collect serious adverse event information from the time of signed informed consent and report it per Section 8.3.5. |
| Concomitant medications review | Record all ongoing medications and those discontinued within 28 days before the visit. |
| Enrollment Authorization Form | Complete, sign, and fax or email the form to the medical monitor or designee at least 2 business days before the anticipated day 1 visit, if possible.<br>The patient may proceed to the day 1 visit when the medical monitor or designee approves by signed form or email correspondence. |
| **Local Laboratory Evaluations** | |
| Serum chemistry, hematology | Refer to analytes listed in Table 12. |
| Testosterone | |
| PSA | |

## 5.2 Treatment Period

Day 1 is the day of the first dose of study drug. Patients will return to the study site at weeks 5, 13, 21, and every 8 weeks thereafter, unless study drug is permanently discontinued for reasons outlined in Section 5.3.

### 5.2.1 Visit Windows

At each specified study visit, procedures will be performed according to the schedule of activities (Appendix 2).

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 ±7 days (ie, 7 days before or after the given day) except for weeks 5 and 13 (±3 days). There is no visit window for week 1, day 1.

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

### 5.2.2 Week 1, Day 1

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

**Table 2: Week 1, Day 1 Procedures**

| Activity / Assessment | Comment |
|---|---|
| **General Activities** | |
| Complete physical examination | May skip if performed within prior 3 days.<br>Measure vital signs (temperature, blood pressure, and heart rate), and weight.<br>ECOG performance status (Table 13).<br>Assess systems per standard of care at the study site. |
| Adverse events review | Record adverse events that occurred during screening on the medical history case report form and in the patient's source documents. Do not record such events on the adverse event case report form. |
| Concomitant medications review | Record any new medications or changes in ongoing medications. |
| Enzalutamide dispensing | Provide the patient with a 12-week supply. Provide instructions for dosing, storage, and return of all bottles (used and unused) of study drug at future visits. |
| **Local Laboratory Evaluations** | |
| Serum chemistry, hematology | May skip if performed within prior 3 days.<br>Refer to analytes listed in Table 12. |
| PSA | |
| **Central Laboratory/Imaging Evaluations** | Refer to laboratory and imaging instruction manuals for sample processing and imaging acquisition requirements. |
| Circulating tumor cells | Collect blood sample predose and process per laboratory manual instructions. |
| $^{18}$F-NaF PET/CT imaging (NaF-1) | Perform predose.<br>Must perform within 7 days before first dose of enzalutamide.<br>Perform a second baseline scan on up to 5 patients at each study site to assess reproducibility. |

### 5.2.3 Week 5

The visit window is ±3 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), weight, and ECOG performance status (Table 13).<br>Perform symptom-directed examination and investigate any new abnormalities. |
| Adverse events review | Record any new or ongoing adverse events. |
| Concomitant medications review | Record any new medications or changes in ongoing medications. |
| Study drug accountability | Record study drug returned and remind patient to return all bottles (used and unused) at each future visit. |
| **Local Laboratory Evaluations** | |
| Serum chemistry, hematology | Refer to analytes listed in Table 12. |

### 5.2.4 Week 13

The visit window is ±3 days. Drug supply must be taken into account if a window is used to schedule the next visit.

Week 13 procedures are listed in Table 4.

**Table 4: Week 13 Procedures**

| Activity / Assessment | Comment |
|---|---|
| **General Activities** | |
| Brief physical examination | Measure vital signs (temperature, blood pressure, and heart rate), weight, and ECOG performance status (Table 13).<br>Perform symptom-directed examination and investigate any new abnormalities. |
| Adverse events review | Record any new or ongoing adverse events. |
| Concomitant medications review | Record any new medications or changes in ongoing medications. |
| Enzalutamide dispensing (if applicable) | **As appropriate according to PSA value.** Per PSA assessment below, patients with PSA values increased from baseline may discontinue study drug and have safety follow-up unless the investigator considers continuation of study drug to be beneficial.<br>Provide the patient with an 8-week supply. Provide instructions for dosing, storage, and return of all bottles (used and unused) of study drug at future visits. |
| Study drug accountability | Record study drug returned and remind patient to return all bottles (used and unused) at each future visit. |
| **Local Laboratory Evaluations** | |
| Serum chemistry, hematology | Refer to analytes listed in Table 12. |
| PSA | Patients with PSA values increased from baseline may discontinue study drug and have safety follow-up unless the investigator considers continuation of study drug to be beneficial. |
| **Imaging Evaluations** | Refer to imaging instruction manual for imaging acquisition requirements. |
| $^{18}$F-NaF PET/CT imaging (NaF-2) | |

### 5.2.5 Week 21 and Repeating Every 8 Weeks

Visits repeat every 8 weeks (± 7 days) until criteria are met for permanent treatment discontinuation (Section 5.3). Drug supply must be taken into account if a window is used to schedule the next visit. Assessments are performed at every visit or every other visit as noted.

Week 21 procedures are listed in Table 5.

**Table 5: Week 21 and Repeating Every 8 Weeks Procedures**

| Activity / Assessment / Timing | Comment |
|---|---|
| **General Activities** | |
| Brief physical examination<br>→ ***Perform every 16 weeks (± 7 days)*** | Measure vital signs (temperature, blood pressure, and heart rate), weight, and ECOG performance status (Table 13).<br>Perform symptom-directed examination and investigate any new abnormalities. |
| Adverse events review | Record any new or ongoing adverse events. |
| Concomitant medications review | Record any new medications or changes in ongoing medications. |
| Enzalutamide dispensing (if applicable) | Provide the patient with an 8-week supply. Provide instructions for dosing, storage, and return of all bottles (used and unused) of study drug at future visits. |
| Study drug accountability | Record study drug returned and remind patient to return all bottles (used and unused) at each future visit. |
| **Local Laboratory Evaluations** | |
| Serum chemistry, hematology<br>→ ***Perform every 16 weeks (± 7 days)*** | Refer to analytes listed in Table 12. |
| PSA | |

### 5.2.6 Time of Third $^{18}$F-NaF PET/CT Imaging (NaF-3)

Patients with disease progression (Section 9.1.1.2) and those without progression at 2 years after treatment initiation will have a third $^{18}$F-NaF PET/CT imaging and other assessments.

No $^{99m}$Tc-MDP bone scintigraphy is required if bone disease progression was confirmed previously on bone scintigraphy obtained at investigator discretion. If no bone disease progression was seen by $^{99m}$Tc-MDP bone scintigraphy before NaF-3, $^{99m}$Tc-MDP bone scintigraphy will be required at the time of NaF-3.

The procedures are listed in Table 6.

**Table 6: Time of Third $^{18}$F-NaF PET/CT Imaging (NaF-3)**

| Activity / Assessment | Comment |
|---|---|
| **Central Laboratory/Imaging Evaluations** | Refer to laboratory and imaging instruction manuals for sample processing and imaging acquisition requirements. |
| Circulating tumor cells | Collect and process blood sample per laboratory manual instructions. |
| $^{18}$F-NaF PET/CT imaging (NaF-3) | Perform at the time of disease progression defined in Section 9.1.1.2 and briefly, as follows:<br>• PSA progression (increase of at least 25% and an absolute increase of at least 2.0 ng/mL above nadir),<br>• Radiographic progression (bone or soft tissue), or<br>• Other clinically relevant progression.<br>*Or* perform at 2 years after initiation of treatment for patients without progression. |
| $^{99m}$Tc-MDP bone scintigraphy | Whole-body radionuclide bone scintigraphy.<br>Send copy of image to the central imaging vendor for archiving.<br>Not required if bone disease progression was confirmed earlier on bone scintigraphy ordered by the investigator. If no bone disease progression was seen by $^{99m}$Tc-MDP bone scintigraphy before NaF-3, $^{99m}$Tc-MDP bone scintigraphy will be required at the time of NaF-3. |
| CT or MRI of chest, abdomen, and pelvis | Perform for suspicion of soft tissue disease progression (at investigator discretion). |
| **Local Laboratory Evaluations** | |
| PSA | |

### 5.2.7 Unscheduled Visits

Unscheduled visits may be performed any time to assess or follow up adverse events, to perform bone scintigraphy, at the patient's request, or at the investigator's request. The date and reason for the unscheduled visit must be recorded in the source documents.

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

Unscheduled visit procedures are listed in Table 7.

**Table 7: Unscheduled Visit Procedures**

| Activity / Assessment | Comment |
|---|---|
| **General Activities** | Perform as needed |
| Brief physical examination | Measure vital signs (temperature, blood pressure, and heart rate), weight, and ECOG performance status (Table 13).<br>Perform symptom-directed examination and investigate any new abnormalities. |
| Adverse events review | Record any new or ongoing adverse events. |
| Concomitant medications review | Record any new medications or changes in ongoing medications. |
| **Local Laboratory Evaluations** | |
| Serum chemistry, hematology | Refer to analytes listed in Table 12. |

## 5.3 Permanent Treatment Discontinuation

*Permanent* treatment discontinuation is defined as cessation of study drug treatment administration. Safety follow-up will be performed per Section 5.4.

*Temporary* treatment interruption is not considered permanent discontinuation. Regularly scheduled study visits will continue for patients based on their enrollment date when their treatment is interrupted any time and restarted.

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

- Adverse event or intercurrent illness: Any intolerable adverse event that cannot be ameliorated by the use of adequate medical intervention or that in the opinion of the investigator or medical monitor would lead to undue risk if study treatment were continued. Refer to Section 8.3.1.
- Gross noncompliance with protocol: The medical monitor or investigator may request permanent treatment discontinuation in the event of a major protocol deviation, lack of cooperation, or noncompliance.
- Administration of prohibited concomitant therapy: Refer to Section 7.2. NOTE: Patients who discontinue due to administration of a prohibited concomitant therapy will remain in the study and complete safety follow-up assessments per Section 5.4.
- Laboratory abnormality defined as follows, unless the cause is identified and satisfactorily addressed, and the abnormality subsequently improves:
  - Creatinine > 354 µmol/L (> 4.0 mg/dL)
  - AST, ALT, or total bilirubin > 5-times the ULN
  - Absolute neutrophil count ≤ 750/µL
  - Platelet count < 50,000/µL
- Seizure: Regardless of resolution of any identified etiology.
- Death

- Loss to follow-up: Refer to Section 5.5.
- Sponsor discontinuation of study: The sponsor reserves the right to terminate the study any time for any reason 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 drug treatment any time for any reason. Following permanent treatment discontinuation, patients should have protocol-required safety follow-up assessments approximately 30 days after the last dose of study drug or before initiation of cytotoxic chemotherapy, a lutamide (bicalutamide, nilutamide, or flutamide), or a new investigational therapy (whichever occurs first), unless the patient specifically declines further follow-up. Study site personnel must document the patient's decision in the source documents. The most specific reason possible for treatment discontinuation should be recorded on the case report form. "Withdrawal of consent" should be entered only as a last resort.

## 5.4 Safety Follow-Up

All patients will have safety follow-up after permanent discontinuation of study drug (enzalutamide). Safety follow-up should occur approximately 30 days after the last dose of study drug or before initiation of cytotoxic chemotherapy, a lutamide (bicalutamide, nilutamide, or flutamide), or a new investigational therapy, whichever occurs first. In the event that one of these treatments is initiated before safety follow-up occurs (eg, a physician not associated with protocol MDV3100-18 initiates the treatment, and study site personnel are not aware of the treatment until afterward), safety follow-up should be scheduled as soon as possible.

If treatment is discontinued due to an adverse event or serious adverse event, the event(s) must be followed up as described in Section 8.3.6. 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 or before initiation of cytotoxic chemotherapy, a lutamide (bicalutamide, nilutamide, or flutamide), or a new investigational therapy, whichever occurs first. There is no long-term follow-up phase.

Safety follow-up procedures are listed in Table 8.

**Table 8: Safety Follow-Up Procedures**

| Activity / Assessment | Comment |
|---|---|
| **General Activities** | |
| Complete physical examination | Measure vital signs (temperature, blood pressure, heart rate) and weight.<br>ECOG performance status (Table 13).<br>Assess systems per standard of care at the study site. |
| Adverse events review | Record any new or ongoing adverse events. |
| Concomitant medications review | Record any new medications or changes in ongoing medications. |
| Study drug accountability | Collect all remaining study drug and record study drug returned. |
| **Local Laboratory Evaluations** | |
| Serum chemistry, hematology | Refer to analytes listed in Table 12. |
| PSA | |

## 5.5 Loss to Follow-Up

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

Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives). Such efforts should be documented in the patient's source documents.

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

# 6 INVESTIGATIONAL PRODUCT INFORMATION

## 6.1 General Information

The study drug is enzalutamide. Enzalutamide (Xtandi) is approved in the US and other regions to treat men with metastatic CRPC who have previously received docetaxel.

The sponsor will provide enzalutamide capsules. Patients who did not have a bilateral orchiectomy will receive LHRH analogue therapy per standard of care.

## 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.[9] The chemical properties and list of excipients are presented in the investigator brochure.

### 6.2.1 Packaging of Enzalutamide

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

### 6.2.2 Storage of Enzalutamide

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

### 6.2.3 Directions for Administration of Enzalutamide

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

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

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

### 6.2.4 Directions for Dose Modification of Enzalutamide

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

If enzalutamide is coadministered with a strong CYP2C8 inhibitor, 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 before initiation of the strong CYP2C8 inhibitor.

## 6.3 Treatment Compliance

Accountability for the study drug capsules (enzalutamide) will be performed to document compliance with the dosing regimens. Patients will be asked to bring all used and unused study drug bottles to study visits. Study site personnel must make reasonable efforts to obtain used and unused study drug bottles from patients who do not routinely return them at study site 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 screening and any medications prescribed for chronic or intermittent use during the study, or dose adjustments of these medications, must be recorded on the case report form and in the patient's source documents. The dosage and regimen of any chronic permitted concomitant medications should be stable during the screening period (≥ 28 days before enrollment) and held constant throughout the study.

Certain prior medications and therapies for prostate cancer are prohibited. These include enzalutamide, abiraterone acetate, aminoglutethimide, ketoconazole, radium Ra 223 dichloride or other bone-targeting radionuclides, or cytotoxic chemotherapy in the CRPC setting. Patients who participated in a clinical study of an investigational agent that inhibits the androgen receptor or androgen synthesis are also excluded, unless treatment was placebo.

Investigational agents are prohibited within 4 weeks before the screening visit.

The following agents are prohibited within 4 weeks (28 days) before day 1: hormonal therapy (eg, androgen receptor inhibitors, 5-alpha reductase inhibitors), biologic therapy for prostate cancer (other than LHRH analogue therapy), and opiate analgesics for prostate cancer pain. However, these agents may be washed out (ie, discontinued for 4 weeks) to qualify for the study if all other eligibility criteria are met. Bone radiation therapy to treat prostate cancer is also prohibited within 4 weeks before day 1.

New treatment with denosumab, bisphosphonates, or systemic corticosteroids for prostate cancer is prohibited within 4 weeks (28 days) before day 1.

## 7.2 Concomitant Therapy

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

Initiation of bisphosphonates or denosumab for any reason is prohibited following enrollment; however, treatment with these agents may continue if initiated at least 4 weeks before enrollment. Standard of care supplementation with calcium and vitamin D is encouraged.

The following are prohibited during this study before NaF-3:

- Initiation of cytotoxic chemotherapy

- Radium Ra 223 dichloride or other bone-targeting radionuclide therapy
- Other hormonal therapy, including but not limited to commercially available enzalutamide (Xtandi), abiraterone acetate, androgen receptor inhibitors, 5-alpha reductase inhibitors, or (if for prostate cancer) aminoglutethimide, ketoconazole, or systemic corticosteroids for prostate cancer
- Biologic therapy (other than LHRH analogue therapy)
- Radiation therapy to bone
- Participation in another interventional clinical study of an investigational agent

Another therapy may be used in combination with enzalutamide after NaF-3 with the approval of the investigator and sponsor, except for cytotoxic chemotherapy, antiandrogen therapy (eg, bicalutamide, nilutamide, or flutamide), or another investigational agent. Study drug treatment must be permanently discontinued and patients will have safety follow-up before initiation of one of these prohibited treatments.

The following treatments are allowed:

- Blood transfusions and growth factor support per standard of care and institutional guidelines
- Corticosteroids for indications other than prostate cancer
- Pain therapy per standard of care and institutional guidelines

Deviation from these guidelines should occur only if it is absolutely necessary for the well-being of the patient and does not jeopardize the analysis of the study endpoints, and must follow discussion and agreement between the investigator and the medical monitor, who will determine the patient's suitability for continued treatment with study drug.

## 7.3 Potential Interactions Between the Test Products and Concomitant Medications

### 7.3.1 Enzalutamide

#### 7.3.1.1 Effects of Enzalutamide on Exposure to Other Drugs

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

#### 7.3.1.2 Drugs That May Affect Exposure to Enzalutamide

##### 7.3.1.2.1 Drugs That Inhibit or Induce CYP2C8

Coadministration of a strong CYP2C8 inhibitor (eg, gemfibrozil) increased the composite $AUC_{0-\infty}$ of enzalutamide plus its active metabolite in healthy volunteers by 2.2-fold (Section 1.2.1); therefore, coadministration of enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If coadministration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, the enzalutamide dose should be reduced to 80 mg once daily. If coadministration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used before initiation of the strong CYP2C8 inhibitor.

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

##### 7.3.1.2.2 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.

### 7.4 Precautions Regarding Concomitant Medications

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

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

## 8 SAFETY CONSIDERATIONS

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 8.1). Adverse events are discussed in detail in the context of patient management, study drug dose modification, and safety reporting requirements, including follow-up procedures (Sections 8.2 and 8.3). Clinical laboratory safety tests are presented

(Section 8.4). The study procedures for physical examinations and vital signs are also provided (Section 8.5).

## 8.1 Safety Monitoring

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

## 8.2 Special Safety Considerations

### 8.2.1 Study Drug Dose Modification Due to Adverse Event

The instructions for modifying the dose of study drug due to an adverse event are provided in Section 6.2.4 for enzalutamide.

### 8.2.2 Overdose Management

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

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

All overdose events are to be reported as events of special interest within 24 hours of awareness by the study site according to Section 8.3.5, whether or not the event meets adverse event criteria.

### 8.2.3 Contraception

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

A patient and his female partner of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method) from screening through 3 months after the last dose of study drug. The 2 acceptable methods of birth control are as follows:

1. A condom (barrier method is required)
   AND
2. One of the following is required:

- Established and ongoing use of oral, injected, or implanted hormonal method by the female partner
- Placement of an intrauterine device or intrauterine system by the female partner
- Additional barrier method including contraceptive sponge or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner
- Tubal ligation in the female partner performed at least 6 months before screening
- Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy) performed at least 6 months before screening

## 8.3 Adverse Event Definitions and Reporting

### 8.3.1 Adverse Event Definitions

Definitions are provided in this section for adverse events, events of special interest, serious adverse events, treatment-emergent adverse events, suspected unexpected serious adverse reactions (SUSARs), and unexpected adverse events.

Adverse events: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Examples of adverse events include the following:

- A change, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition
- Development of an intercurrent illness during the study
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product
- Injury or accidents: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately)
- Investigational abnormalities (eg, laboratory parameters, vital signs, ECG data) should be defined as adverse events only if the abnormality meets one of the following criteria:
  - Induces clinical signs or symptoms
  - Needs active intervention
  - Needs interruption or discontinuation of study medication
  - Abnormality or investigational value is clinically significant in the opinion of the investigator

An adverse event **does not** include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure as known at the time of informed consent)

Events of special interest: Adverse events of special interest are any events identified for intensive monitoring during the study. For MDV3100-18, events of special interest include overdose (Section 8.2.2) and pregnancy in the partner (Section 8.3.7).

Serious adverse events: Any adverse event that meets any of the criteria in Table 9 as determined by the investigator or sponsor.

**Table 9: Criteria for Serious Adverse Events**

| Criterion | Comment |
|---|---|
| Results in death | Death is an outcome, not an adverse event. The primary adverse event resulting in the death should be identified. |
| Is life threatening (immediate risk of death from the adverse event as it occurred) | Does not include an event that hypothetically might have caused death if it were more severe. |
| Results in or prolongs an existing inpatient hospitalization | For hospitalizations for surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure will be identified as the serious adverse event (not the procedure). |
| Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions | Permanent or substantial disruption of a person's ability to conduct normal life functions. |
| Results in a congenital anomaly/birth defect | |
| Important medical events which jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above | Examples include drug-induced bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse. |

Source: US Code of Federal Regulations: 21 CFR 312.32 [75 FR 59961]

Treatment-emergent adverse events: Adverse events observed following administration of the study drug.

Suspected unexpected serious adverse reactions (SUSARs): Adverse events assessed as serious, related, and unexpected.

Unexpected adverse events: Adverse events for which the nature or severity is not consistent with the reference safety information.

### 8.3.2 Adverse Event Reporting

To elicit adverse event reports from patients, the study site personnel should question the patient in a general way without suggesting specific symptoms.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or stabilizes. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted as described in Section 8.3.6.

All adverse events, whether or not related to the study drug, must be fully and completely documented on the adverse event case report form and in the patient's clinical record. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the treatment discontinuation case report form as well as documented in the patient's clinical record. Adverse event terms should include a diagnosis or underlying cause, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

#### 8.3.2.1 Adverse Event Reporting Periods

Collection and reporting of adverse event information will begin at the time the patient signs informed consent for serious adverse events and from the first dose of study drug for nonserious adverse events, and will continue through 30 days after the last dose of study drug treatment or before initiation of cytotoxic chemotherapy, a lutamide (bicalutamide, nilutamide, or flutamide), or a new investigational therapy, whichever occurs first. Additional reporting instructions for serious adverse events and events of special interest are provided in Section 8.3.5.

All adverse events from the time of the first dose of any study drug treatment must be documented on the adverse event case report form and in the patient's clinical record. Any event occurring during screening must be documented 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 treatment.

### 8.3.3 Assessment of Causal Relationship

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

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

**Table 10: Criteria for Determining Causal Relationship to Study Drug**

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

### 8.3.4 Assessment of Severity (Intensity)

Severity describes the intensity of a specific adverse event (mild, moderate, or severe). The particular event may be of relatively minor medical significance (such as severe headache). Severity is not the same as "serious," which is based on patient/event outcome or action criteria.

Investigators will grade the severity of adverse events according to the National Cancer Institute Cancer Therapy and Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), version 4. For terms not specified within the CTCAE, the criteria in Table 11 should be used to determine grade.

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

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

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

Source: Common Terminology Criteria for Adverse Events v4.0

### 8.3.5 Serious Adverse Event and Event of Special Interest Reporting

Study site personnel will collect and record serious adverse events on the adverse event case report form from the time the patient signs the informed consent form through screen failure or 30 days after the last dose of study drug treatment or before initiation of cytotoxic chemotherapy, a lutamide (bicalutamide, nilutamide, or flutamide), or a new investigational therapy, whichever occurs first. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug.

Using a serious adverse event report form, all serious adverse events and events of special interest must be reported **within 24 hours** of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study drug, to this contact:

| | |
|---|---|
| Name: | PPD |
| Fax: | PPD (US) |
| Backup Fax: | PPD (United Kingdom) |
| Email: | PPD |
| Phone: | PPD |

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

- Study number (MDV3100-18)
- Site name and number
- Investigator name
- Patient (study ID) number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the serious adverse event or event of special interest (event term, seriousness of the event)
- Causal relationship to the study drug

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

#### 8.3.5.1 Clarification in Reporting of Seizures

Seizure (convulsive or nonconvulsive) is always reported as a serious adverse event.

#### 8.3.5.2 Clarification in Reporting of Deaths

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

#### 8.3.5.3 Clarification in Reporting of Disease Progression as an Adverse Event

Disease progression is not unexpected in this study population and the term "disease progression" should not be reported as an adverse event unless a more specific clinical term is not defined or available. When clinical disease progression is identified, the clinical event that identifies the disease progression, if known, should be reported as the adverse event.

### 8.3.6 Follow-Up of Serious and Nonserious Adverse Events

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

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

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

### 8.3.7 Pregnancy Reporting Procedure

If a study participant impregnates his partner following the first dose of study drug through 3 months after permanent discontinuation of study drug treatment, the study participant should report the pregnancy to the investigator. The investigator will report the pregnancy to the sponsor in the same timeframe as a serious adverse event (Section 8.3.5). The sponsor will provide forms to the investigator for use in reporting. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information.

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

## 8.4 Clinical Laboratory Safety Tests

Routine clinical laboratory safety tests (hematology, serum chemistry) will be performed according to the schedule of activities (Appendix 2), as will PSA and testosterone tests. Samples will be stored until the specified analyses are completed and then they will be destroyed in accordance with standard laboratory practice and applicable local regulations.

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

All clinical laboratory safety tests will be performed by the local laboratory specified in Form FDA 1572 Section 4. The local laboratory reference ranges will be used. Eligibility at screening will be based on local laboratory assessments.

A different clinical laboratory may be used for unscheduled visits or for urgent care. Such laboratory data will not be entered into the study database and these local laboratories will not be included on the FDA 1572 form.

**Table 12: 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 aminotransferase)<br>Blood urea nitrogen and creatinine<br>$Ca^{++}$<br>Creatine phosphokinase<br>Glucose<br>Lactate dehydrogenase<br>Magnesium, phosphate<br>$Na^{+}$, $K^{+}$, total $CO_2$ (bicarbonate), $Cl^{-}$<br>Total bilirubin<br>Total protein |

## 8.5 Physical Examinations, Vital Signs, and Electrocardiograms

The investigator will perform complete or brief physical examinations according to the schedule of activities (Appendix 2).

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

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

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

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

# 9 ASSESSMENT OF EFFICACY AND SAFETY ENDPOINTS

## 9.1 Assessment of Efficacy

### 9.1.1 Assessments for the Primary and Secondary Efficacy Endpoints

The assessment for the primary and secondary efficacy endpoints will include $^{18}$F-NaF PET/CT imaging and assessment of disease progression.

#### 9.1.1.1 $^{18}$F-NaF PET/CT Imaging

$^{18}$F-NaF PET/CT imaging will be performed during the study as follows:

- NaF-1: Following screening, within 7 days before first dose
- NaF-2: At week 13
- NaF-3: At the time of PSA, radiographic (bone or soft tissue), or other clinically relevant progression, or at 2 years without progression after treatment initiation

Up to 5 patients at each study site will have a second baseline scan to assess reproducibility of the scans at each study site.

$^{18}$F-NaF PET/CT imaging will be performed according to the procedures detailed in the imaging instruction manual and interpreted at the central imaging vendor.

#### 9.1.1.2 Assessment of Disease Progression

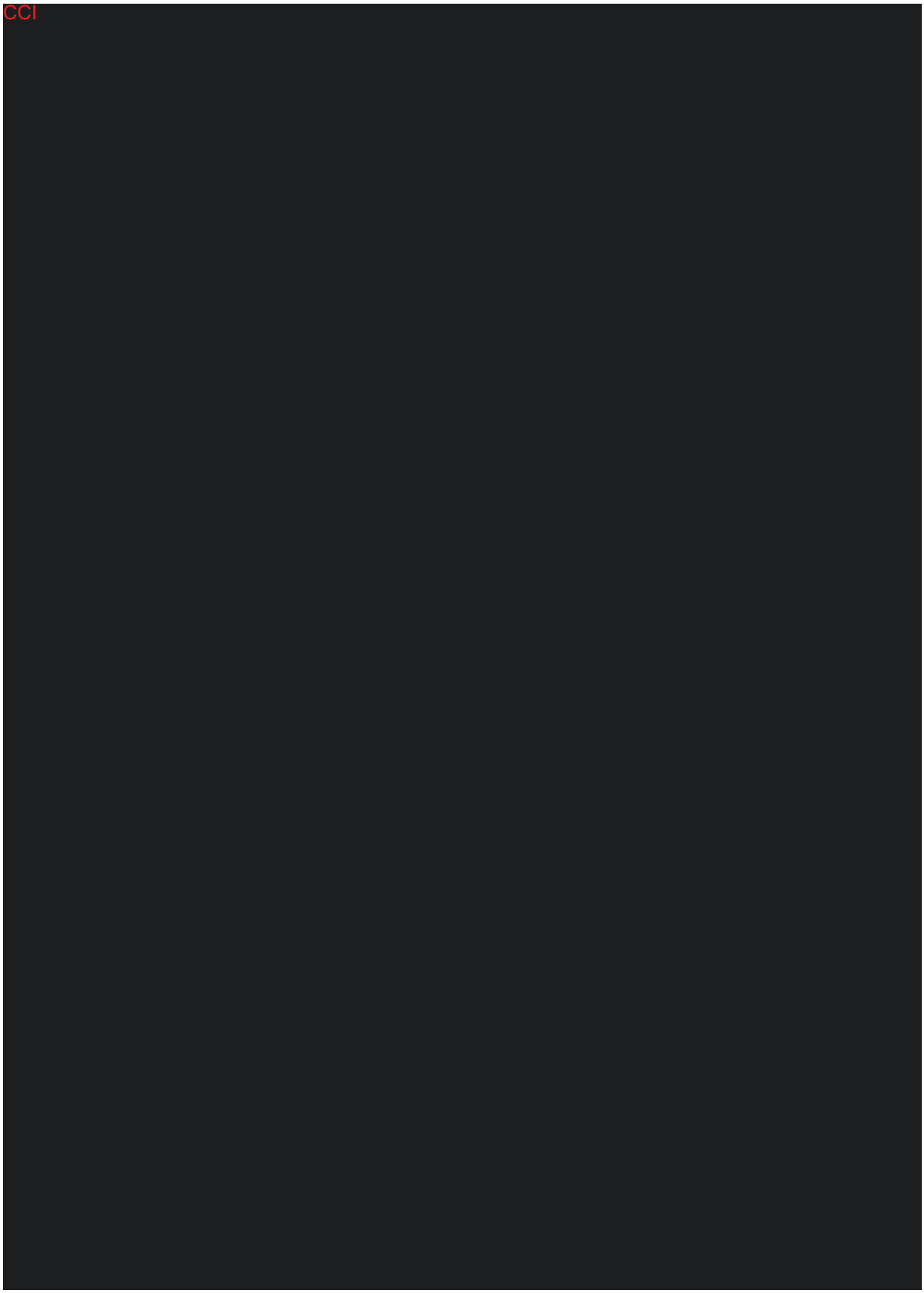
The assessment of disease progression will include PSA, radiographic (bone and soft tissue), and other clinically relevant events as follows:

PSA progression triggering NaF-3 will be defined as an increase of at least 25% AND an absolute increase of at least 2.0 ng/mL above nadir.

Bone disease progression will be defined as the appearance of at least 2 new lesions after screening assessed by $^{99m}$Tc-MDP bone scintigraphy. Progression at week 13 or earlier will require a confirmatory $^{99m}$Tc-MDP bone scintigraphy at least 6 weeks later showing at least 2 additional new lesions related to prostate cancer (compared with the previous scan). After week 13, no confirmation of progression will be required if at least 2 new lesions related to prostate cancer are observed.

Soft tissue disease will be assessed by CT or MRI obtained at investigator discretion. Radiographic progression for soft tissue disease will be defined by RECIST 1.1.[7]

Other clinically relevant events of progression will be determined by the investigator and may include, but are not limited to, significant bone pain or skeletal-related events.


CCI

### 9.2 ECOG Performance Status Assessments

ECOG performance status assessments are required to assess patient functional status for study eligibility purposes and will be performed throughout the study according to the schedule of activities (Appendix 2). Details of the assessment are shown in Table 13.

**Table 13: ECOG Performance Status Assessments**

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

Source: Oken et al (1982)[10]

## 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 enrolled in the study and will be used for all efficacy analyses unless otherwise specified.

The safety population is defined as all patients who receive any amount of study drug. The safety population will be used for all safety analyses.

### 10.3 Efficacy Analyses

The primary efficacy endpoint analysis will include patients who undergo NaF-1 and NaF-3 $^{18}$F-NaF PET/CT imaging. CCI [redacted]

**Table 14: Definition of Terms for NaF Uptake Measures**

| Term | Definition |
|---|---|
| $SUV_{total}$ | Total NaF uptake, which represents the tumor burden across all (global) bone lesions or in individual lesions reflecting bone-metastatic prostate cancer |
| $SUV_{hetero}$ | Heterogeneity of NaF uptake, which represents heterogeneity of lesion activity |
| $SUV_{mean}$ | Mean NaF uptake, which represents the average activity of all lesions |
| $SUV_{max}$ | Maximum NaF uptake, which represents the activity of the most aggressive lesion |
| N | Total number of lesions, which represents a numerical sum of all lesions |
| VF | Volume fraction, which represents the fraction of skeletal involvement |

### 10.3.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the proportion of patients with at least 1 responding bone lesion (defined as a lesion with an $SUV_{total}$ less than at baseline) on the third $^{18}$F-NaF PET/CT scan (NaF-3) performed for each patient. This assessment will be triggered by any of the following events:

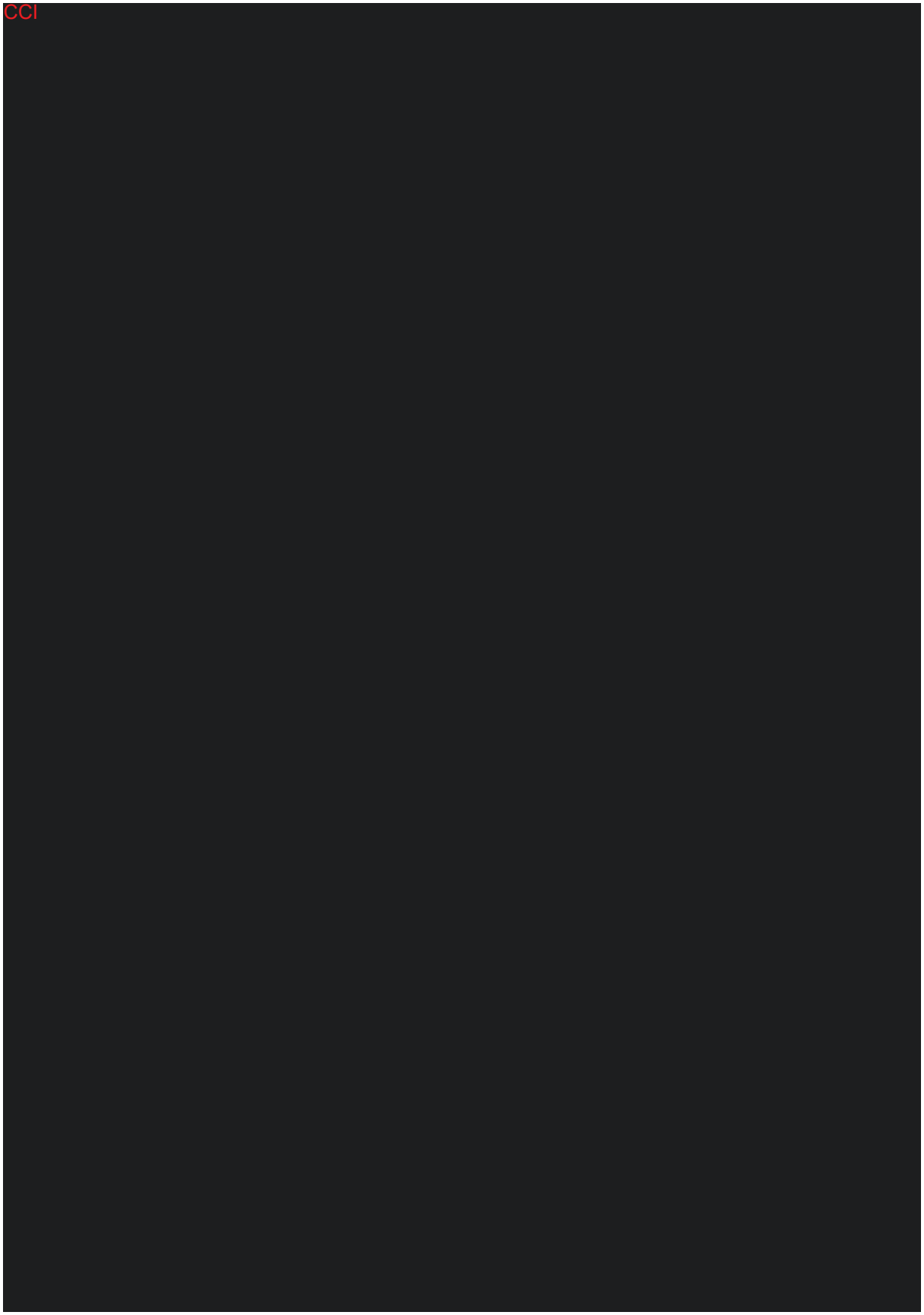
- PSA progression (an increase of at least 25% AND an absolute increase of at least 2.0 ng/mL above nadir)
- Bone disease progression (the appearance of at least 2 new lesions after screening assessed by $^{99m}$Tc-MDP bone scintigraphy)
- Soft tissue disease progression defined by RECIST 1.1[7]
- Clinically relevant progression (eg, significant bone pain or a skeletal-related event)
- At 2 years without progression after treatment initiation

### 10.3.2 Secondary Efficacy Endpoint Analysis

The secondary efficacy endpoint is the heterogeneity of response across all bone lesions as determined by the global $SUV_{hetero}$ at the time the primary endpoint is determined for each patient. The global $SUV_{hetero}$ score is a measure of the heterogeneity of tumor activity across all bone lesions and is defined as follows, where $g$ = global, $l$ = lesion, $N$ = number of bone lesions.

$$gSUV_{hetero} = \frac{\sum_{i=1}^{N}\left(lSUV_{mean}^{i} - gSUV_{mean}\right)^2}{N}$$

In other words, the global $SUV_{hetero}$ score is the sum of the squares of the differences between the $SUV_{mean}$ for each bone lesion and the global $SUV_{mean}$, divided by the number of lesions. Thus, a higher global $SUV_{hetero}$ score reflects more heterogeneity in bone lesion activity.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[redacted]

### 10.4 Safety Analyses

All safety analyses will be performed using the safety population.

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

The treatment-emergent period is defined as the duration of time from the date and time of the first dose of study drug treatment (enzalutamide) through 30 days after the last dose of study drug treatment (permanent treatment discontinuation) or the day before initiation of cytotoxic chemotherapy, a lutamide (bicalutamide, nilutamide, or flutamide), or a new investigational therapy, whichever occurs first.

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

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

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

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

### 10.5 Other Analyses

Exposure: The dose and cumulative dose of enzalutamide (mg) 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 entire study divided by the expected number of capsules, multiplied by 100%.

### 10.6 Determination of Sample Size

The total number of patients to be included in this study is approximately 20 and is based on practical clinical considerations.

## 11 STUDY COMMITTEES AND COMMUNICATIONS

No formal study committees are planned for this study.

## 12 LABORATORY REQUIREMENTS

Clinical laboratory safety samples (hematology, serum chemistry) will be analyzed locally as described in Section 8.4, as will the samples for testosterone (screening only) and PSA for this study. These samples should be collected according to local laboratory requirements.

# 13 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

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

- Fully executed and signed Form FDA 1572
- Fully executed clinical trial agreement
- Current curriculum vitae (also applies to all subinvestigators listed on the Form FDA 1572)
- Financial disclosure (also applies to all subinvestigators listed on the Form FDA 1572)
- Signed protocol signature page
- Signed acknowledgment of receipt of the current Enzalutamide Investigator Brochure
- Institutional review board (IRB) approval letter
- IRB-approved informed consent form
- Additional documents as necessary per local requirements

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

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

## 13.1 Ethics

### 13.1.1 Institutional Review Board

Before initiating the study, the investigator will obtain confirmation from the IRB that the IRB is properly constituted and compliant with all requirements and local regulations.

The investigator will provide the IRB 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 study will not be initiated until the investigator obtains appropriate IRB approval in writing for the protocol and informed consent document, and copies are received by the sponsor.

IRB 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 IRB, per local requirements, 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, including current Good Clinical Practice (GCP) according to International Council for Harmonisation (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 IRB; 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 IRB. The sponsor and the IRB must approve the documents before the investigator implements them.

The investigator will provide copies of the signed informed consent form to each patient and will maintain the signed original document within the patient's clinical record per local requirements. The investigator will also fully document the informed consent process in the patient's source documents.

### 13.1.4 Maintaining Patient Confidentiality

All reports and patient samples will be identified only by a study ID number and 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.

### 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 bottle identification numbers) of all study drug supplies received. All records must be made available to the sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

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

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

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

- The investigator agrees not to supply study drug to any persons except the patients in this study.
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions as required by the study drug label, accessible only to those authorized by the investigator to dispense these study drugs.
- The investigator/pharmacist will maintain a study drug inventory. The inventory will include details of material received and a clear record of when they were dispensed and to which patient.
- The investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the drug accountability record at the conclusion or termination of this study. It must be possible to reconcile delivery records with those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.
- Used or unused study drug may be destroyed at the study site according to standard institutional procedures if the sponsor agrees with the procedure, and after drug accountability has been conducted by the sponsor or representative, unless otherwise approved. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the sponsor or designee upon request for review and approval before the first onsite destruction. Unused study drug not

destroyed at the site must be returned to the sponsor-designated facility at the end of the study or upon expiration.

## 13.4 Compensation, Insurance, and Indemnity

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

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

## 13.5 Retention of Records

The investigator must make original study data (paper or electronic) accessible to the study monitor, other authorized sponsor representatives, and regulatory agency inspectors (eg, US 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 any time for any reason. 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 IRB 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 will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of Medivation[PPD] regardless of the outcome of the trial. The data generated in this clinical trial are the exclusive property of the sponsors and are confidential. Written approval from the sponsors is required prior to disclosing any information related to this clinical trial, and no publications initiated by investigators may be published until all protocol-defined primary and secondary endpoints are published in a manuscript. Every attempt will be made to minimize the interval between the completion of data analysis and publication of the study results. Recommendations for the timing of presentation of trial endpoint data and the publication venues (congresses/journals) will be given by the sponsor's Publications Steering Committee.

Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsors prior to submission. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement.

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

Any formal publication of the study in which input of sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate sponsor personnel. Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts or stricter local criteria.[11] The sponsors do 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 the sponsors or related entities, including sponsors of competing products that might be perceived to be a source of bias. Authorship is decided on an individual basis and the sponsor's Publications Steering Committee and sponsor representatives will mutually determine authors and their sequence on individual publications based on the relative contribution of each author to the study and/or publication.

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

Professional medical writing support is permissible, and any writing support will be acknowledged in each applicable publication, explaining the role the professional writer had in the drafting of the publication. Medical writing and publications support funded by the sponsors on behalf of investigator authors will be considered as a transfer of value under the reporting requirements of the Patient Protection Affordable Care Act: Physician Payment Sunshine Provision.[12] Transfer of value will be allocated to authors following sponsor guidelines.

## 15 REFERENCES

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## 16 INVESTIGATOR SIGNATURE

**MEDIVATION, INC.**

A Phase 2, Open-Label, Single-Arm Study of $^{18}$F-Sodium Fluoride PET/CT Bone Imaging in Enzalutamide-Treated Chemotherapy-Naïve Patients With Bone-Metastatic Castration-Resistant Prostate Cancer

Signature of Agreement for Protocol MDV3100-18, Amendment 2, v3.0, 08 DEC 2016

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] [redacted]
1903

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

Subject's Initials : _____

Study Subject #: ☐☐☐☐

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

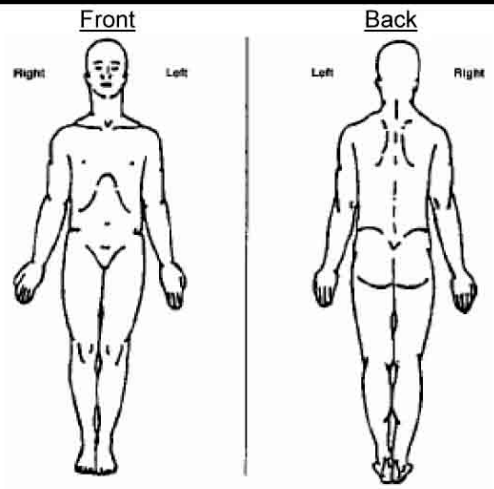
Revision: 07/01/05

### 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]

[redacted] [redacted] 1903

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

Subject's Initials : _____

Study Subject #: ☐☐☐☐

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05 [redacted]

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

**B. Mood**

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

**C. Walking ability**

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

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

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

**E. Relations with other people**

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

**F. Sleep**

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

**G. Enjoyment of life**

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





[redacted]

## Appendix 2: Study Schedule of Activities

| Study Period | Screening | Treatment | | | | | Unsched [1] | Safety FUP [2] |
|---|---|---|---|---|---|---|---|---|
| Study Week | −4 to −1 | 1 | 5 | 13 | 21 then q8w | Varies | Varies | Varies |
| Study Days | -28 to -1 | 1 | 29 | 85 | 141 then q56d | na | na | na |
| Window (Days) [3] | na | na | ±3 | ±3 | ±7 | na | na | na |
| **General Activities** | | | | | | | | |
| Informed consent, study ID number [4] | X | | | | | | | |
| Medical history | X | | | | | | | |
| Eligibility criteria incl. BPI, ECOG | X | | | | | | | |
| 12-lead electrocardiogram (local read) | X | | | | | | | |
| $^{99m}$Tc-MDP bone scintigraphy | X [5] | | | | | X [6] | | |
| CT or MRI of chest/abdomen/pelvis | X [5] | | | | | X [6] | | |
| Complete physical examination [7] | X | X [8] | | | | | | X |
| Brief physical examination [9] | | | X | X | X [10] | | X | |
| Adverse events review [11] | X | X | X | X | X | | X | X |
| Concomitant medications review | X | X | X | X | X | | X | X |
| Enzalutamide dispensing | | X | | X | X | | | |
| Study drug accountability | | | X | X | X | | | X |
| Enrollment authorization form [12] | X | | | | | | | |
| **Local Lab Evaluations** | | | | | | | | |
| Hematology, serum chemistry | X | X [8] | X | X | X [10] | | X | X |
| Testosterone | X | | | | | | | |
| Prostate-specific antigen | X | X | | X [13] | X | X | | X |
| **Central Lab/Imaging Evaluations [14]** | | | | | | | | |
| Circulating tumor cells | | X [15] | | | | X [16] | | |
| $^{18}$F-NaF PET/CT imaging | | X (F-1) [17] | | X (F-2) | | X (F-3) [18] | | |

[1] Any time necessary to assess or follow up adverse events, at the patient's request, or per investigator decision.

[2] Approximately 30 days after the last dose of study drug (permanent discontinuation) or before initiation of cytotoxic chemotherapy, a lutamide (bicalutamide, nilutamide, or flutamide), or a new investigational therapy, whichever occurs first.

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

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

[5] Must be within 28 days before day 1. Send copy of bone scintigraphy image to the central imaging vendor for archiving.

[6] At investigator discretion (eg, significant bone pain or a skeletal-related event for $^{99m}$Tc-MDP bone scintigraphy; or suspicion of soft tissue disease progression for CT or MRI) or (for $^{99m}$Tc-MDP bone scintigraphy only) to coincide with NaF-3 unless bone disease progression was confirmed earlier. Progression at week 13 or earlier will require a confirmatory $^{99m}$Tc-MDP bone scintigraphy at least 6 weeks later showing at least 2 additional new lesions related to prostate cancer (compared with the previous scan). After week 13, no confirmation of progression will be required if at least 2 new lesions related to prostate cancer are observed. If no bone disease progression was seen by $^{99m}$Tc-MDP bone scintigraphy before NaF-3, then $^{99m}$Tc-MDP bone scintigraphy will be required at the time of NaF-3. Send copies of bone scintigraphy images to the central imaging vendor for archiving.

[7] Includes vital signs (temperature, blood pressure, heart rate), ECOG performance status, weight. Height at screening only.

[8] May skip if performed within prior 3 days.

[9] Symptom-directed and includes vital signs, ECOG performance status, and weight.

[10] Repeats every 16 weeks ±7 days after week 21.

[11] Collect serious adverse event information from the time of signed informed consent and nonserious adverse event information from the time of first dose of study drug through 30 days after the last dose or initiation of cytotoxic chemotherapy, a lutamide (bicalutamide, nilutamide, or flutamide), or a new investigational therapy, whichever occurs first. Phone patients for follow-up if they do not come to the clinic.

[12] Complete, sign, and fax or email the form with requested items to the medical monitor or designee at least 2 business days before the anticipated day 1 visit, if possible. Patient may proceed to day 1 visit when medical monitor or designee approves by signed form or email correspondence.

[13] Patients with PSA values increased from baseline may discontinue study drug and have safety follow-up unless the investigator considers continuation of study drug to be beneficial.

[14] Refer to laboratory and imaging instruction manuals for sample processing and imaging acquisition requirements. Interpretation of $^{18}$F-NaF PET/CT imaging performed at the central imaging vendor.

[15] Collect predose.

[16] At time of NaF-3.

[17] Perform predose. Must occur within 7 days before first dose of enzalutamide. Perform a second baseline scan on up to 5 patients at each study site to assess reproducibility.

[18] At time of PSA, radiographic (bone or soft tissue), or other clinically relevant progression, or at 2 years without progression after treatment initiation.

$^{18}$F-NaF PET, $^{18}$F-sodium fluoride positron emission tomography; CT, computed tomography; BPI, Brief Pain Inventory; ECOG, Eastern Cooperative Oncology Group; $^{99m}$Tc-MDP, technetium Tc 99m medronate; (F-1), (F-2), (F-3) designators for sequential $^{18}$F-NaF PET/CT imaging; FUP, follow-up; lab, laboratory; ID, identification; MRI, magnetic resonance imaging; na, not applicable; q8w, every 8 weeks; unsched, unscheduled.