MEDIVATION, INC.
CLINICAL RESEARCH PROTOCOL

Study Title:	PROSPER: A Multinational, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer
Protocol Identifier:	MDV3100-14 (C3431005)
Phase:	3
Investigational Product:	Enzalutamide (formerly MDV3100)
Indication:	Prostate Cancer
Sponsor:	Medivation, Inc., a wholly owned subsidiary of Pfizer Inc 525 Market Street, 36th Floor San Francisco, CA 94105 Telephone: +1 (415) 543-3470 Fax: +1 (415) 543-3411 Medivation and Astellas Pharma Global Development, Inc. are in a partnership to codevelop enzalutamide for the treatment of cancer
Reference Numbers:	United States IND 74,563 EudraCT 2012-005665-12
Sponsor Medical Monitor:	PPD, MD, PhD Telephone: PPD Email: PPD
Original Protocol:	v1.0 – 29 Mar 2013
Amendment 1:	v2.0 – 16 May 2013
Amendment 2:	v3.0 – 31 May 2017
Amendment 3:	v4.0 – 11 Aug 2017

This study will be conducted according to the principles of Good Clinical Practice as described in International Council for Harmonisation guidelines, including the archiving of essential documents.

SYNOPSIS

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

Protocol Identifier: MDV3100-14 (C3431005)

Phase of Development: 3

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

Study Centers: Approximately 250 (global)

Study Objectives:

Primary:

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

Secondary:

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

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

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

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

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

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

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

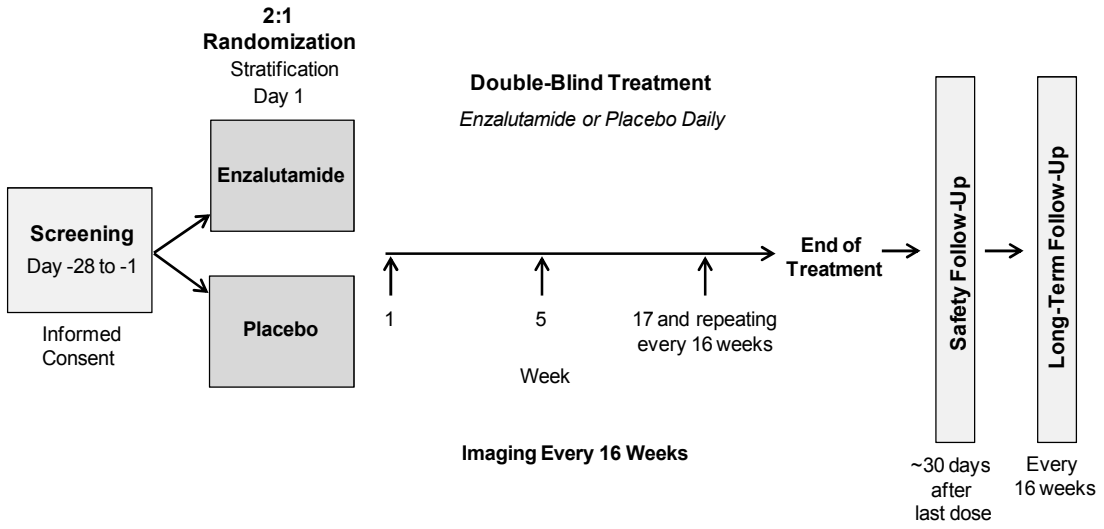
The primary efficacy endpoint is MFS assessed by blinded independent central radiology review, defined as the time from randomization to radiographic progression or death on study (death within 112 days of treatment discontinuation without evidence of radiographic progression), whichever occurs first. Assessment of bone disease will be done by whole-body radionuclide bone scan. A bone scan will consist of 5 regions including skull, thorax, spine, pelvis, and extremities. Radiographic progression for bone disease is defined as the appearance of 1 or more metastatic lesion on bone scan. When bone lesions are found in a single region on the bone scan, confirmation with a second imaging modality (plain film, computed tomography [CT], or magnetic resonance imaging [MRI]) will be required. Appearance of metastatic lesions in 2 or more of the 5 regions on a bone scan will not require confirmation with a second imaging modality. Assessment of soft tissue disease will be done by CT or MRI. Radiographic progression for soft tissue disease is defined by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) (Eisenhauer et al, 2009).[1]

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

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

Patients will have safety follow-up approximately 30 days after the last dose of study drug. If a new antineoplastic treatment is initiated before 30 days after the last dose of study drug, then safety follow-up will occur immediately before starting the new treatment. Long-term follow-up assessments will include monitoring for survival status, new antineoplastic therapies for prostate cancer, opiate medications, skeletal-related events, and interventions due to locoregional progression (eg, radiation, transurethral resection of the prostate, nephrostomy tube placement).

Study Schematic:



Key Eligibility Criteria:

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

Test Product, Dose, and Mode of Administration:

Enzalutamide; chemical name 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide. Enzalutamide, 160 mg/day, will be administered as four 40-mg soft gelatin capsules by mouth once daily with or without food.

Reference Therapy, Dose and Mode of Administration:

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

Duration of Treatment:

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

Statistical Methods:

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

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

Primary Efficacy Endpoint:

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

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

Secondary Efficacy Endpoints:

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

- Time to PSA Progression: Time to PSA progression is defined as the time from randomization to the date of the first PSA value demonstrating progression, which is subsequently confirmed. For patients with PSA decline at week 17, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline by week 17) is documented, which is confirmed by a second consecutive value obtained at least 3 weeks later.
- Time to First Use of New Antineoplastic Therapy: Time to first use of new antineoplastic therapy is defined as the time from randomization to the first use of new antineoplastic therapy for prostate cancer.
- Overall Survival: Overall survival is defined as the time from randomization to death due to any cause.

Additional secondary endpoints are as follows:

- Time to Pain Progression: Pain will be assessed using the BPI-SF. Pain progression is defined as a 2-point or more increase from baseline in the question 3 pain score. Time to this event is defined as the time from randomization to onset of pain progression.
- Time to First Use of Cytotoxic Chemotherapy: Time to first use of cytotoxic chemotherapy is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer.
- Chemotherapy-Free Disease-Specific Survival: Chemotherapy-free disease-specific survival is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer as assessed by the investigator.
- Chemotherapy-Free Survival: Chemotherapy-free survival is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer or death due to any cause.
- PSA Response: PSA response will be calculated as a decline from baseline in PSA (ng/mL) to the maximal PSA response with thresholds at 50% and 90%. Additionally, PSA response will be assessed as a decline to undetectable levels, where undetectable is defined as below the limit of quantification of the centrally assessed PSA results. A PSA response must be confirmed by a second consecutive value at least 3 weeks later. A stratified Cochran-Mantel-Haenszel mean score test will be used to compare response rates between treatment groups.
- Quality of Life as Assessed by the FACT-P questionnaire, EQ-5D-5L Health Questionnaire, and QLQ-PR25 Module: FACT-P, EQ-5D-5L, and QLQ-PR25 quality-of-life data will be summarized descriptively by study visit.

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

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

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

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

Sample Size Considerations:

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

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

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

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the curve from time zero to infinity
BPI-SF	Brief Pain Inventory Short Form
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum plasma concentration
C_{trough}	Predose trough plasma concentration
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
EC	Ethics committee (global term including institutional review boards, independent ethics committees, research ethics committees, and the like)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels health questionnaire
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone
ICH	International Council for Harmonisation
ID	Identification
INR	International normalized ratio
IXRS	Interactive voice / web recognition system
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-free survival
MRI	Magnetic resonance imaging
PFS	Progression-free survival
PK	Pharmacokinetic
PRES	Posterior reversible encephalopathy syndrome
PSA	Prostate-specific antigen
QLQ-PR25	Quality of Life Questionnaire-Prostate 25 module
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
US	United States

1. INTRODUCTION

1.1. Background

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

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

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

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

1.2. Summary of Relevant Clinical Experience With Enzalutamide

The United States (US) Food and Drug Administration (FDA) first approved Xtandi (enzalutamide) capsules in August 2012 based on a benefit in overall survival for men with metastatic CRPC who previously received docetaxel therapy.[9]

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

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

CRPC2 (AFFIRM): A phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide (160 mg daily) in patients with progressive CRPC previously treated with docetaxel-based chemotherapy was conducted in 1199 men, 800 of whom received treatment with enzalutamide.[9] The primary endpoint was overall survival. The first FDA approval of enzalutamide was based on the results of this study.

MDV3100-03 (PREVAIL): A multinational, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in chemotherapy-naïve patients with progressive metastatic after failure of androgen deprivation therapy was conducted in 1717 men, 871 of whom received treatment with enzalutamide. The coprimary endpoints were overall survival and radiographic progression-free survival (PFS). The prespecified interim analysis at the time of 540 death events demonstrated statistically significant improvements in overall survival and radiographic PFS in patients treated with enzalutamide versus placebo. Enzalutamide treatment resulted in prolongation of overall survival (hazard ratio 0.71 [95% CI: 0.60, 0.84]; $p < 0.0001$) and radiographic PFS (hazard ratio 0.19 [95% CI: 0.15, 0.23]; $p < 0.0001$). Results of an updated survival analysis performed when 784 deaths were observed was consistent with the interim analysis (hazard ratio 0.77 [95% CI: 0.67, 0.88]).

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

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

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

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

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

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

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

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

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

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

1.2.1. Pharmacokinetics and Drug Metabolism

The current enzalutamide investigator brochure provides the most up to date information on enzalutamide PK and drug metabolism. In PK investigations in men with CRPC, enzalutamide was absorbed rapidly after oral administration, with the time to maximum plasma concentration (t_{max}) after a single dose typically occurring at 1 hour postdose. No major deviations from dose proportionality were observed over the dose range 30 mg to 600 mg. Due to the long terminal half-life (approximately 5.8 days), it took approximately 1 month to reach steady state. With daily oral administration, enzalutamide accumulation was observed at steady state with an 8.3-fold higher exposure (steady-state area under the curve, AUC) relative to a single dose. Based on the mean peak-to-trough ratio, the average difference between the peak (maximum plasma concentration, C_{max}) and trough (predose plasma concentration, C_{trough}) concentrations was ≤ 25%. As a result of the low daily fluctuations, plasma profiles at steady state resembled a constant infusion. The C_{trough} values in individual patients remained constant beyond day 28 of chronic therapy, suggesting time-linear PK once steady state was achieved. At steady state, plasma concentrations of enzalutamide and the active metabolite, N-desmethyl enzalutamide, were approximately the same.

In a drug-drug interaction study in male patients with CRPC (9785-CL-0007), a single oral dose of a substrate for cytochrome P450 (CYP) 2C8, CYP2C9, CYP2C19, or CYP3A4 was administered before and concomitantly with enzalutamide (after at least 55 days of dosing at 160 mg daily). Enzalutamide at steady state reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) by 86%, 56%, and 70%, respectively. Based on the magnitude of the decreases in exposure, enzalutamide is considered a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19 (Section 7.3). Substrates of CYP3A4, CYP2C9, and CYP2C19 with a narrow therapeutic index should be avoided if possible, as enzalutamide may decrease plasma exposure of these drugs. If enzalutamide is coadministered with warfarin (CYP2C9 substrate), additional international normalized ratio (INR) monitoring should be conducted. Enzalutamide did not cause clinically meaningful changes in exposure to pioglitazone (CYP2C8 substrate).

In a drug-drug interaction study in healthy male volunteers (9785-CL-0006), a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor). Gemfibrozil increased the composite area under the curve from time zero to infinity ($AUC_{0-\infty}$) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C_{max}; therefore, strong CYP2C8 inhibitors should be avoided if possible as they can increase plasma exposure to enzalutamide plus N-desmethyl enzalutamide. If coadministration with a strong CYP2C8 inhibitor is necessary, the dose of enzalutamide should be reduced to 80 mg once daily. If coadministration of the strong

CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor. The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated in vivo (Section 7.4).

In the drug-drug interaction study in healthy male volunteers (9785-CL-0006), a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of itraconazole (strong CYP3A4 inhibitor). Itraconazole increased the composite $AUC_{0-\infty}$ of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on C_{max}. As this small change is not clinically meaningful, no starting dose adjustment is needed when coadministering enzalutamide with CYP3A4 inhibitors. The effects of CYP3A4 inducers on the PK of enzalutamide have not been evaluated in vivo (Section 7.4).

Additional information on the PK and drug metabolism of enzalutamide is provided in the enzalutamide investigator brochure.

1.3. Summary of Relevant Nonclinical Experience With Enzalutamide

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

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

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

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

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

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

1.4. Enzalutamide Benefits and Risks Assessment

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

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

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

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

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

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

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

2. STUDY OBJECTIVES

2.1. Primary Objective

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

2.2. Secondary Objectives

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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan: Description

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

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

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

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

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

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

The primary efficacy endpoint is MFS assessed by blinded independent central radiology review, defined as the time from randomization to radiographic progression or death on study (death within 112 days of treatment discontinuation without evidence of radiographic progression), whichever occurs first. Assessment of bone disease will be done by whole-body radionuclide bone scan. A bone scan will consist of 5 regions including skull, thorax, spine, pelvis, and extremities. Radiographic progression for bone disease is defined as the appearance of 1 or more metastatic lesion on bone scan. Confirmation with a second imaging modality (plain film, computed tomography [CT], or magnetic resonance imaging

[MRI]) will be required when bone lesions are found in a single region on the bone scan. Appearance of metastatic lesions in 2 or more of the 5 regions on a bone scan will not require confirmation with a second imaging modality. Assessment of soft tissue disease will be done by CT or MRI. Radiographic progression for soft tissue disease is defined by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).[1]

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

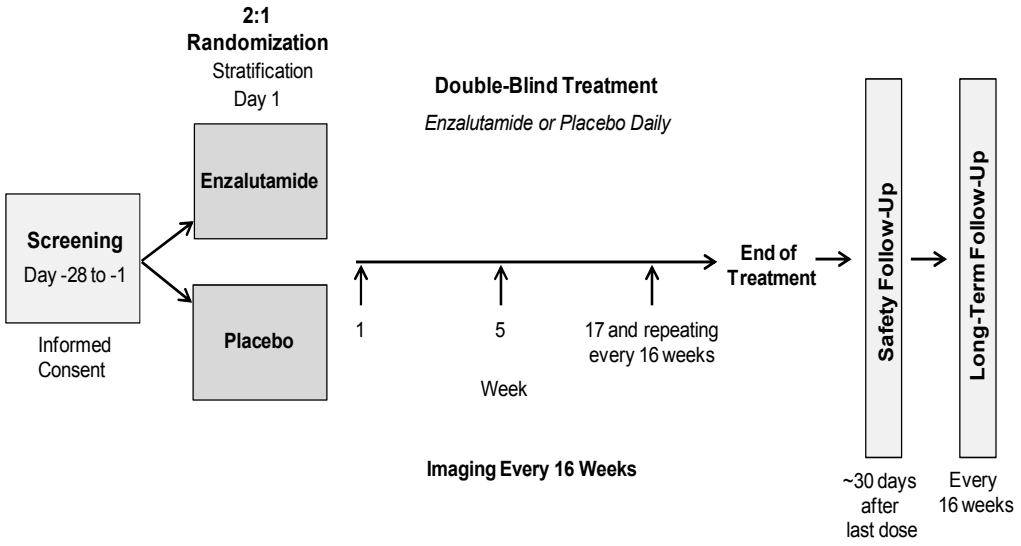
In addition to imaging, the following assessments of prostate cancer status will be made during the course of the study: survival status, pain intensity and interference using the Brief Pain Inventory Short Form (BPI-SF) (Appendix 1), PSA values, and quality of life as assessed by the FACT-P (Appendix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

Patients will have safety follow-up approximately 30 days after the last dose of study drug. If a new antineoplastic treatment is initiated before 30 days after the last dose of study drug, then safety follow-up will occur immediately before starting the new treatment. Long-term follow-up assessments will include monitoring for survival status, new antineoplastic therapies for prostate cancer, opiate medications, skeletal-related events, and interventions due to locoregional progression (eg, radiation, transurethral resection of the prostate, nephrostomy tube placement).

The study schematic is provided in Figure 1.

3.2. Study Schematic

Figure 1: Study Schematic



3.3. Blinding

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

The blinded control for this study will be placebo capsules (placebo) identical in appearance to the enzalutamide capsules.

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

3.4. Duration of Study

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

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

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

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

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

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

4. SELECTION OF STUDY POPULATION

The selected study population will have nonmetastatic CRPC with a rapid PSA doubling time. The specific eligibility criteria for selection of patients are provided in Section 4.1 and 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

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

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

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

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

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

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

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

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

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

9. No prior or present evidence of metastatic disease as assessed by CT/MRI for soft tissue disease and whole-body radionuclide bone scan for bone disease. If the screening bone scan shows a lesion suggestive of metastatic disease, the patient will be eligible only if a second imaging modality (plain film, CT, or MRI) does not show bone metastasis. If the imaging results are equivocal or consistent with metastasis, the patient is not eligible for enrollment. Patients with soft tissue pelvic disease may be eligible if lesions do not qualify as target lesions (eg, lymph nodes below aortic bifurcation are permissible if the short axis of the largest lymph node is < 15 mm).

10. Asymptomatic prostate cancer.

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

12. Estimated life expectancy ≥ 12 months.

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

14. Male patient and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration. Two acceptable methods of birth control thus include the following:

    - Condom (barrier method of contraception)

      AND

    - One of the following is required:

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

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

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

      - Tubal ligation in the female partner

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

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

4.2. Exclusion Criteria

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

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

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

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

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

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

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

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

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

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

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

11. Clinically significant cardiovascular disease including the following:

    - Myocardial infarction within 6 months before screening
    - Uncontrolled angina within 3 months before screening
    - Congestive heart failure New York Heart Association class 3 or 4, or a history of congestive heart failure New York Heart Association class 3 or 4, unless a screening echocardiogram or multigated acquisition scan performed within 3 months before randomization demonstrates a left ventricular ejection fraction ≥ 50%
    - History of clinically significant ventricular arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)
    - History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
    - Hypotension as indicated by systolic blood pressure < 86 millimeters of mercury (mm Hg) at screening
    - Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram (ECG) and on physical examination

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

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

13. Major surgery within 4 weeks of randomization.

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

15. Any concurrent disease, infection, or comorbid condition that interferes with the ability of the patient to participate in the trial, which places the patient at undue risk, or complicates the interpretation of data, in the opinion of the investigator or medical monitor.

5. ENROLLMENT AND STUDY PROCEDURES

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

5.1. Screening Period

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

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

5.1.1. Screening Identification Numbers

Study site personnel will access the interactive voice/web recognition system (IXRS) to assign a screening identification (ID) number to a potential study participant.

For patients who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent, study site personnel should ensure that the source record includes documentation for the screen failure, such as demographics, medical history, eligibility criteria reviewed, procedures performed, etc.

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

5.1.2. Screening Visit Procedures

At the screening visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless

the procedures are part of routine standard of care, and must document the informed consent process in the patient's clinical record.

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

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

Table 1: Screening Procedures

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

Table 1: Screening Procedures

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

5.2. Treatment Period

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

5.2.1. Visit Windows

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

A study visit may be scheduled on any day within a specified study week. For any given day within the study week, the visit window is ±5 or ±7 days, a 10- or 14-day period (ie, the 5- or 7-day period before or after the given day).

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

5.2.2. Day 1 (Randomization)

Day 1 procedures are listed in Table 2. Study site personnel should ensure that an approved randomization authorization form is in the patient's file before proceeding with randomization and day 1 procedures.

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

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

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

Table 2: Day 1 Procedures

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

5.2.3. Treatment Guidelines

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

5.2.4. Week 5

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

Week 5 procedures are listed in Table 3.

Table 3: Week 5 Procedures

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

5.2.5. Week 17 and Repeating Every 16 Weeks

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

Table 4: Week 17 and Repeating Every 16 Weeks Procedures

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

5.2.6. Unscheduled Visits

Unscheduled visit procedures are listed in Appendix 5.

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

5.3. Permanent Treatment Discontinuation

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

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

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

Table 5: Primary Reasons for Permanent Treatment Discontinuation

Reason	Comment
Adverse event or intercurrent illness	Any intolerable adverse event that cannot be ameliorated by the use of adequate medical intervention or that in the opinion of the investigator or medical monitor would lead to undue risk if study treatment were continued. Refer to Section 8.3.1.
Gross noncompliance with protocol (violation)	The medical monitor or investigator may request permanent discontinuation of study drug treatment in the event of a major protocol deviation, lack of cooperation, or noncompliance.
Disease progression	Study drug treatment will be discontinued after development of radiographic progression if the investigator considers continuing study drug not to be beneficial. Initiation of new therapy for prostate cancer (with the exception of cytotoxic chemotherapy, androgen receptor inhibitors, and investigational agents) at the time of radiographic progression will not mandate discontinuation of study drug if the investigator considers continuing study drug to be beneficial.
Laboratory abnormality defined by protocol	
Creatinine > 354 µmol/L (4.0 mg/dL)	
AST, ALT, or total bilirubin > 5 times the upper limit of normal (ULN) AST or ALT > 3 times ULN and total bilirubin > 2 times ULN without findings of cholestasis	
Absolute neutrophil count ≤ 750/µL	
Platelet count < 50,000/µL	
Seizure	Regardless of resolution of any identified etiology. Refer to Section 1.4.
Death	Refer to Section 8.3.6.1.
Loss to follow-up	Refer to Section 5.5.
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime as described in Section 13.6. The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.
Patient decision	Patients may permanently discontinue study treatment anytime for any reason. Following study drug discontinuation, patients should have protocol-required safety follow-up and long-term follow-up assessments unless the patient specifically declines further follow-up.

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

5.4. Follow-Up After Permanent Treatment Discontinuation

5.4.1. Safety Follow-Up

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

If treatment is discontinued due to an adverse event or serious adverse event, the event(s) must be followed up as described in Section 8.3.7. For patients who refuse further clinic study visits, telephone contact should be attempted and documented to review for adverse events through approximately 30 days after the last dose of study drug.

Safety follow-up procedures are listed in Table 6.

Table 6: Safety Follow-Up Procedures

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

5.4.2. Long-Term Follow-Up

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

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

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

Table 7: Long-Term Follow-up Procedures

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

5.5. Loss to Follow-Up

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

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

6. INVESTIGATIONAL PRODUCT INFORMATION

6.1. General Information

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

6.2. Enzalutamide Product Characteristics

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

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

6.2.1. Packaging

Blinded study drug is packaged in bottles with induction-sealed child-resistant caps labeled with the study protocol number, contents, directions for use, storage directions, clinical trial statement, and sponsor name. Each bottle contains 124 capsules (31-day supply).

6.2.2. Storage

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

6.2.3. Directions for Administration

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

Patients should self-administer blinded study drug by mouth once daily, with or without food, starting on day 1. The capsules should be swallowed whole without chewing, dissolving, or opening them.

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

6.2.4. Directions for Dose Modification

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

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

6.2.5. Treatment Compliance

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

7. PRIOR AND CONCOMITANT THERAPY

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

7.1. Prior Therapy

Medications taken within 4 weeks before randomization and any medications prescribed for chronic or intermittent use during the study, or dose adjustments of these medications, must be recorded on the case report form.

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

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

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

7.2. Concomitant Therapy

Concomitant medications will be assessed at screening and all clinic visits. All concomitant medications must be recorded on the appropriate case report form. If the use of any medication during the study is due to an adverse event, the adverse event must be recorded on the adverse event case report form and in the patient's clinical record.

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

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

- Cytotoxic chemotherapy
- Androgen receptor inhibitors
- Investigational agents

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

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

7.3. Effects of Enzalutamide on Exposure to Other Drugs

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

7.4. Drugs That May Affect Exposure to Enzalutamide

7.4.1. Drugs That Inhibit or Induce CYP2C8

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

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

7.4.2. Drugs That Induce CYP3A4

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

7.5. Precautions Regarding Concomitant Medications

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

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

8. 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, emergency unblinding of treatment assignment, and safety reporting requirements, including follow-up procedures (Section 8.2 and 8.3). Clinical laboratory safety tests are presented including estimates of blood volume to be collected during the study (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 blinded safety data during the clinical study in addition to reviewing individual safety case reports, by examining the incidence and severity of adverse events and serious adverse events, changes in laboratory results, and other data (such as aggregate analysis of data from other enzalutamide studies) as appropriate and per the sponsor's Safety Management Team Charter. Any relevant safety concerns will be communicated to the Data Monitoring Committee, investigators, and regulatory agencies, as appropriate.

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

8.2. Special Safety Considerations

8.2.1. Study Drug Dose Modification Due to Adverse Event

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

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

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

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

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

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

8.2.3. Overdose

An overdose is defined as at least 2 daily doses of study drug taken the same calendar day. In the event of an overdose, treatment with study drug should be stopped and general supportive measures initiated, taking into consideration the half-life is 5.8 days for enzalutamide. Patients may be at increased risk of seizures following an overdose of enzalutamide. The medical monitor must be contacted in the event of a study drug overdose.

All overdose events are to be reported as special events of interest within 24 hours of awareness by the study site according to Section 8.3.6, whether or not the event meets adverse event criteria. Neither the effects of overdose of enzalutamide nor an antidote to overdose are known.

8.2.4. Contraception

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

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

The 2 acceptable methods of birth control are as follows:

1. A condom (barrier method is required)

   AND

2. One of the following is required:

   - Established use of oral, injected, or implanted hormonal method
   - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
   - Additional barrier method including contraceptive sponge or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
   - Tubal ligation performed at least 6 months before screening
   - Vasectomy or other surgical castration at least 6 months before screening

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

8.3. Adverse Event Definitions and Reporting

8.3.1. Adverse Event Definitions

An adverse event is defined per FDA final rule (75 FR 59961, 29 September 2010) as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related," and per International Council for Harmonisation (ICH) Topic E2A (*Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*) as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment." An adverse event can therefore be 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.

An adverse event observed following administration of a study drug or comparator drug is considered a treatment-emergent adverse event. Adverse event terms should include a diagnosis, 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.

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 prior to 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)

8.3.2. Adverse Event Reporting

Safety reporting to regulatory authorities will be implemented according to global and country-specific regulations.

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 8.3.7.

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. Any adverse event resulting in discontinuation of study treatment must be recorded on the appropriate case report form as well as documented in the patient's clinical record.

8.3.2.1. Adverse Event Reporting Periods

Collection of nonserious adverse event information will begin at the time of first dose of study drug and continue through safety follow-up. Any nonserious adverse events occurring during the screening period must be documented on the medical history case report form and in the patient's clinical record.

Collection of serious adverse event information will begin at the time the patient signs informed consent and continue through screen failure or safety follow-up. The reporting instructions for serious adverse events are provided in Section 8.3.6. Any serious adverse event occurring during the screening period 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 randomization.

8.3.3. Assessment of Causal Relationship

The investigator will assess and document the reasonable possibility of the relationship of an adverse event to study drug using careful medical consideration at the time of evaluation of the adverse event and document the relationship in the patient's clinical record.

The criteria for determining causal relationship to study drug are presented in Table 8.

Table 8: Criteria for Determining Causal Relationship to Study Drug

Relationship	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 9 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 clinical record. Adverse events that change CTCAE grade should be reported as separate adverse events, with the start date of the event at a new grade corresponding to the stop date of the event at the previous grade. For adverse events that frequently fluctuate between 2 CTCAE grades, a single adverse event can be recorded at the higher grade.

Table 9: Criteria for Determining the Severity (Intensity) of an Adverse Event

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

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

8.3.5. Serious Adverse Event Definition

A serious adverse event or reaction is any untoward medical occurrence that at any dose meets any of the criteria in Table 10 as determined by the investigator or sponsor.

Table 10: 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 patient 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].

8.3.5.1. Adverse Events Always Considered to Be Serious

If any of the adverse events in Table 11 occur during the study, they should be considered as serious adverse events and reported as described in Section 8.3.6. NOTE: Any Hy's Law case is considered a serious adverse event. Briefly, Hy's Law cases have the following 3 components.[13]

1. Evidence of hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than a (nonhepatotoxic) control drug or placebo.

2. Among study patients showing such aminotransferase elevations, often with aminotransferases much greater than 3 times ULN, 1 or more also show elevation of serum total bilirubin to > 2-times the ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).

3. No other reason can be found to explain the combination of increased aminotransferase and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

Table 11: Adverse Events Always Considered to Be Serious

Acute liver failure	Liver necrosis
Acute renal failure	Malignant hypertension
Acute respiratory failure	Pulmonary fibrosis
Agranulocytosis	Pulmonary hypertension
Anaphylaxis	Sclerosing syndromes
Any new primary malignancy	Seizure
Aplastic anemia	Torsade de pointes
Confirmed or suspected endotoxin shock	Toxic epidermal necrolysis
Confirmed or suspected transmission of infectious agent by marketed product	Ventricular fibrillation
Congenital anomalies	Any Hy's Law case

8.3.6. Serious Adverse Event 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 safety follow-up.

Using a Pfizer Clinical Trial Serious Adverse Event (CT SAE) Report Form, serious adverse events 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 Pfizer Safety.

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

- Study number (MDV3100-14, C3431005)
- Country and site number
- Investigator name
- Patient number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the serious adverse event (event term, seriousness of the event)
- Causal relationship to the study drug

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

Reporting for a suspected serious adverse event should not be delayed in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report (preferably within 7 days of the initial report). Serious adverse events must also be reported to the responsible ethics committee (EC) per local regulatory requirements.

An **unexpected** adverse event is one for which the nature or severity is not consistent with the current enzalutamide investigator brochure. The sponsor will make this assessment for all reported serious adverse events. An adverse event that is assessed as serious, related, and unexpected is considered a suspected unexpected serious adverse reaction (SUSAR). The investigator will ensure that all requested information is provided as soon as possible to Pfizer Safety so the sponsor may meet their obligations to report any SUSAR.

The reporting of serious adverse events by the sponsor to regulatory authorities is a regulatory requirement. Each regulatory agency has a timetable for reporting serious adverse events based on established criteria. It is the responsibility of investigators to report serious adverse events to their local EC as required by the local EC. The sponsor or designee will notify all investigators responsible for ongoing clinical studies with the investigational product of all serious adverse events that may require submission to their EC within timelines and requirements set by local regional regulations.

8.3.6.1. Clarification in Reporting of Deaths

As overall survival is one of the key study endpoints, all patients must be followed for survival status until death, and information relating to the death (eg, date and primary cause) should be obtained and recorded.

Fatal events (regardless of relationship to study drug) should be reported as serious adverse events for patients until the safety follow-up visit. Fatal events occurring after this time should be reported on the designated case report form, but do not require reporting as serious adverse events.

Death is an outcome of an adverse event and not an adverse event in itself. All reports of death should include an adverse event term for the cause of death (if known).

8.3.6.2. 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. When clinical disease progression is identified, the clinical event that identifies the disease progression should be reported as the adverse event term for standard adverse event reporting, including serious adverse event reporting.

8.3.7. 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 a new antineoplastic treatment is initiated (all follow-up results are to be reported to the sponsor or designee). If a

nonserious adverse event becomes serious, or if a patient experiences a new serious adverse event, the investigator must immediately report the information to the sponsor and Pfizer Safety (Section 8.3.6).

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 8.4.1.

8.4. Clinical Laboratory Safety Tests

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

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

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

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

Table 12: Clinical Laboratory Safety Tests

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

8.4.1. Estimated Blood Volume

Blood samples will be collected for standard safety evaluations (hematology, serum chemistry), for monitoring PSA, and for the screening testosterone test according to the schedule of activities (Appendix 5). Samples will be stored until the specified analyses are completed and then they will be destroyed in accordance with standard laboratory practice and applicable local regulations.

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

8.5. Physical Examinations, Vital Signs, and Electrocardiograms

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

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

Brief physical examinations will be directed toward patient-reported symptoms and include investigating any new abnormalities.

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

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

9. ASSESSMENT OF EFFICACY AND SAFETY VARIABLES

9.1. Assessment of Efficacy

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

9.1.1. Assessments for the Primary Efficacy Endpoint

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

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

9.1.1.1. Determination of Bone Metastasis

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

9.1.1.2. Determination of Soft Tissue Metastasis

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

9.1.2. Assessments for the Secondary Efficacy Endpoints

9.1.2.1. Assessment of Survival

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

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

9.1.2.2. Assessment of Pain Progression

The assessment of pain progression will be conducted using the BPI-SF. The BPI-SF questionnaire is a validated instrument that uses a self-reported scale assessing level of pain, its effect on activities of daily living, and analgesic medication use.

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

The questionnaire is provided in Appendix 1. Study site personnel will collect the questionnaire information at the study visits. It is important that patients are fluent in reading the language used in the questionnaire and that they complete it without influence of the investigator, study site staff, or anyone else.

9.1.2.3. Assessment of New Cytotoxic Chemotherapy Use

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

9.1.2.4. Assessment of New Antineoplastic Therapy Use

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

9.1.2.5. Assessment of PSA

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

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

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

9.1.2.6. Assessment of Quality of Life

The FACT-P questionnaire is a multidimensional, self-reported, quality-of-life instrument specifically designed for use in men with prostate cancer. The questionnaire contains 27 core items to assess function in 4 domains during the prior 7 days: physical, social/family, emotional, and functional well-being, as well as 12 site-specific items to assess prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale and then combined to produce subscale scores for each domain, as well as a global quality-of-life score with higher scores representing better quality of life.

The questionnaire is provided in Appendix 2. Study site personnel will collect the questionnaire information at the study visits.

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

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

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-PR25, a module of the EORTC QLQ-30 questionnaire, was developed to assess the quality of life of patients with prostate cancer. Patients will self-rate their current state of pain as it relates to urination, ease and frequency of urination, and bowel and other problems during the past

week. Patients will also answer 5 questions about weight loss/gain and sexual interest and 4 questions about sexual activity during the past 4 weeks. Patients will choose 1 of 4 possible responses that record level of intensity (not at all, a little, quite a bit, very much) within each dimension.

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

9.2. Assessment of Safety

Assessments of safety will include adverse events, clinical laboratory tests, physical examinations, and vital signs. The reason for discontinuation of study drug will also be collected. The procedures for the investigator assessment of adverse events are presented in detail in Section 8. The procedures for clinical laboratory safety tests including estimates of blood volume are presented in Section 8.4, and for physical examinations, vital signs, and ECGs in Section 8.5.

10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

10.1. Statistical and Analytical Plans

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

10.2. Analysis Populations

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

The safety population is defined as all patients who receive 1 dose or partial dose of study drug. The safety population will be used for all safety analyses. The safety population will be analyzed based on the treatment received and not the treatment assigned.

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

10.3. Efficacy Analyses

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

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

The single MFS analysis will be performed after approximately 440 MFS events occur. All secondary endpoints will be evaluated for efficacy at this time. This will include the single

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

10.3.1. Primary Efficacy Endpoint Analysis: Metastasis-Free Survival

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

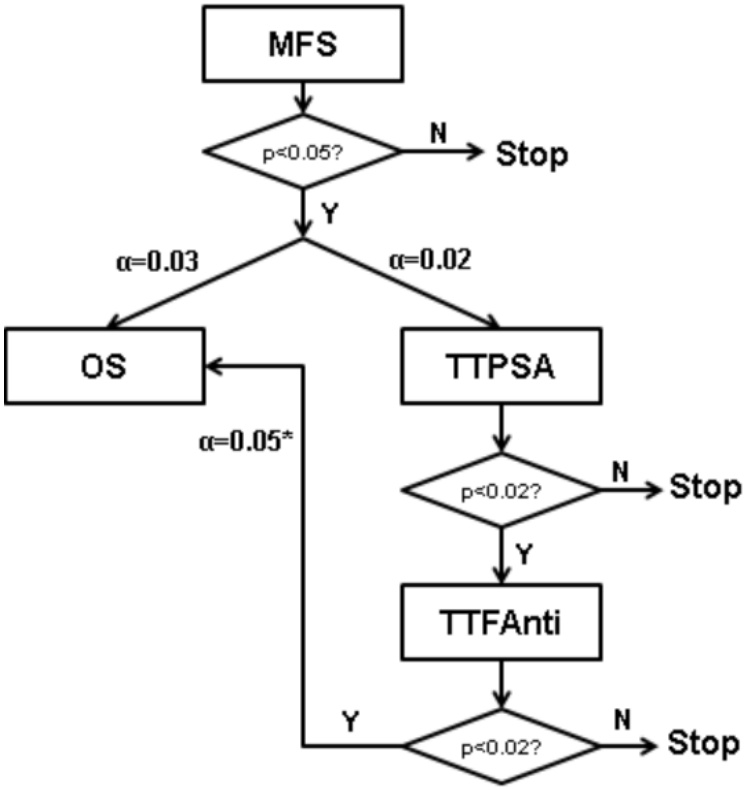
The MFS analysis will be performed when approximately 440 MFS events are observed. The primary endpoint analysis will be performed using a stratified log-rank test to compare the 2 treatment groups using a 2-sided test at the 0.05 level of significance.

10.3.2. Key Secondary Efficacy Endpoint Analyses

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

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

Figure 2: Testing Strategy for Primary and Key Secondary Endpoints



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

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

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

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

10.3.2.1. Time to PSA Progression

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

For patients with PSA decline at week 17, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir is documented, which is confirmed by a second consecutive value obtained at least 3 weeks later.

For patients with no PSA decline at week 17, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the baseline is documented, which is confirmed by a second consecutive value at least 3 weeks later.

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

10.3.2.2. Time to First Use of New Antineoplastic Therapy

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

10.3.2.3. Overall Survival

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

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

remaining type I error rate (0.029 or 0.049 depending on the outcome of time to PSA progression and time to first use of new antineoplastic therapy endpoints). If an interim analysis of overall survival is statistically significant, it will be reported as the final analysis and no subsequent analyses will be performed. The approximate number of events and corresponding significance level at each analysis based on this methodology are provided in Table 13. The interim analysis testing methodology will be described in detail in the statistical analysis plan.

Table 13: Type I Error Spending for the Overall Survival Analyses

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

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

10.3.3. Additional Secondary Endpoint Analyses

10.3.3.1. Time to Pain Progression

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

10.3.3.2. Time to First Use of Cytotoxic Chemotherapy

Time to first use of cytotoxic chemotherapy is defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer. Patients not starting treatment with a cytotoxic chemotherapy for prostate cancer at the time of analysis will be right censored on

the date of the last assessment before the analysis data cutoff date for the purposes of analysis. A stratified log-rank test will be used to compare the 2 treatment groups.

10.3.3.3. Chemotherapy-Free Disease-Specific Survival

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

10.3.3.4. Chemotherapy-Free Survival

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

10.3.3.5. PSA Response

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

10.3.3.6. Quality of Life

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

10.4. Safety Analyses

All safety analyses will use the safety population.

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

Adverse events occurring during the adverse event reporting period will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class and by preferred term within each system organ class. Tabular summaries will include the incidence overall (number and percentage of patients with treatment-emergent

adverse events classified by system organ class and preferred term); incidence by intensity (severity graded according to the CTCAE, version 4), causality, seriousness, and outcome (eg, leading to discontinuation of study drug); and other presentations as appropriate.

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

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

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

10.5. Other Analyses

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

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

10.6. Determination of Sample Size

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

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

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

The study is also powered for overall survival. Specifically, 590 death events will be required to provide 85% power to detect a target hazard ratio of 0.77 with a target difference

in Kaplan-Meier estimated median of 13.7 months (46 months for placebo vs 59.7 months for enzalutamide) at the 5% significance level. The power analysis for the remaining key secondary endpoints will be discussed in the statistical analysis plan.

11. STUDY COMMITTEES AND COMMUNICATIONS

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

12. LABORATORY REQUIREMENTS

A central laboratory will analyze the clinical laboratory safety samples (hematology, serum chemistry) as described in Section 8.4, as well as the PSA and testosterone samples for this study. The laboratory manual for this study provides details regarding sample collection procedures and laboratory tests.

13. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

Before initiating the study, the investigator must provide to the sponsor a fully executed and signed Form FDA 1572, current curriculum vitae and financial disclosure, signed protocol signature page, and signed acknowledgment of receipt of the current enzalutamide investigator brochure. Current curriculum vitae and financial disclosure must also be provided for all subinvestigator(s) listed on the Form FDA 1572. Additional documents may also be necessary per local requirements.

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

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

13.1. Ethics

13.1.1. Ethics Committee

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

The investigator will provide the EC with all appropriate material, such as the protocol, current enzalutamide investigator brochure, site-specific informed consent form, and other written information provided to the patients. The trial will not be initiated until appropriate

EC approval of the protocol, informed consent document, and all recruiting materials are obtained in writing by the investigator and copies are received by the sponsor.

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

13.1.2. Ethical Conduct of the Study

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

13.1.3. Patient Information and Informed Consent

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

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

13.1.4. Maintaining Patient Confidentiality

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

13.2. Data Quality Assurance

13.2.1. Data Management

Clinical data management will be performed by the sponsor or designee according to procedures described in a comprehensive data management plan. The data management plan will include procedures for processing the data from this study, and will describe the

responsibilities of the sponsor and designee when clinical data management is provided by an external vendor. In particular, the data management plan will include a list of the standard operating procedures that apply to this study.

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

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

13.2.2. Case Report Forms

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

13.2.3. Study Monitoring

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

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

13.2.4. Study Audits

During the course of the study and after study completion, it is likely that one or more quality assurance audits will be undertaken by authorized sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with

the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed upon time. By signing this protocol, the investigator grants permission to the sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

13.3. Investigational Product Accountability

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

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

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

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

- The investigator agrees not to supply study drug to any persons except the patients in this study.
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- The investigator/pharmacist will maintain a study drug inventory. The inventory will include details of material received and a clear record of when they were dispensed and to which patient.
- The investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the drug accountability record at the conclusion or termination of this study. It must be possible to reconcile delivery records with

those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.

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

13.4. Compensation, Insurance, and Indemnity

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

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

13.5. Retention of Records

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

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

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

13.6. Study Termination

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

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

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

14. USE OF STUDY INFORMATION AND PUBLICATION

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

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

Any formal publication of the study in which input of Medivation personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Medivation personnel. Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE) or stricter local criteria. Medivation does not compensate for authorship of a publication and all authors will be required to disclose, as part of the publication submission, any potential conflicts of interest, including pertinent financial or personal relationships with Medivation or related entities, including sponsors of competing products that might be perceived to be a source of bias.

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

15. REFERENCES

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16. INVESTIGATOR SIGNATURE

Medivation, Inc.

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

Signature of Agreement for Protocol MDV3100-14 (C3431005)
Amendment 3, v4.0 – 11 Aug 2017

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)

1903

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

Subject's Initials : _____

Study Subject #: ☐☐☐☐

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

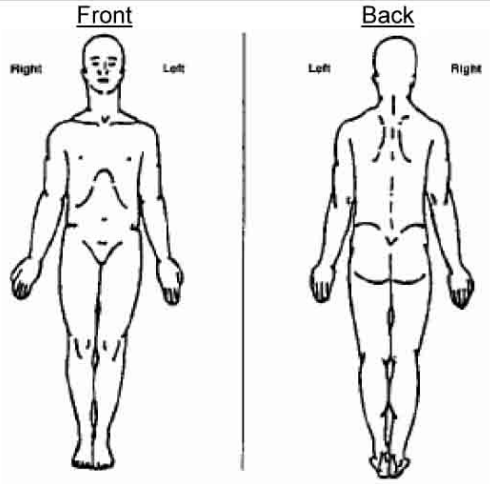
Revision: 07/01/05

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

Page 1 of 2

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1903

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

Subject's Initials : _____

Study Subject #: ☐☐☐☐

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

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

☐☐☐☐☐☐☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐☐☐☐☐
☐☐☐☐☐☐☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐☐☐☐☐

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

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

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

A. General Activity

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

B. Mood

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

C. Walking ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

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Appendix 2: Functional Assessment of Cancer Therapy - Prostate

FACT-P (Version 4)

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

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

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

Copyright 1987, 1997

FACT-P (Version 4)

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

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

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

Copyright 1987, 1997

FACT-P (Version 4)

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

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

English (Universal)
Copyright 1987, 1997

Appendix 3: European Quality of Life-5 Dimensions-5 Levels Health Questionnaire
Adapted from http://www.euroqol.org/ (UK [English] v.2 © 2009). The original EQ-5D™ is a trademark of the EuroQol Group.

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

Mobility

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

Self Care

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

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

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

Pain/Discomfort

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

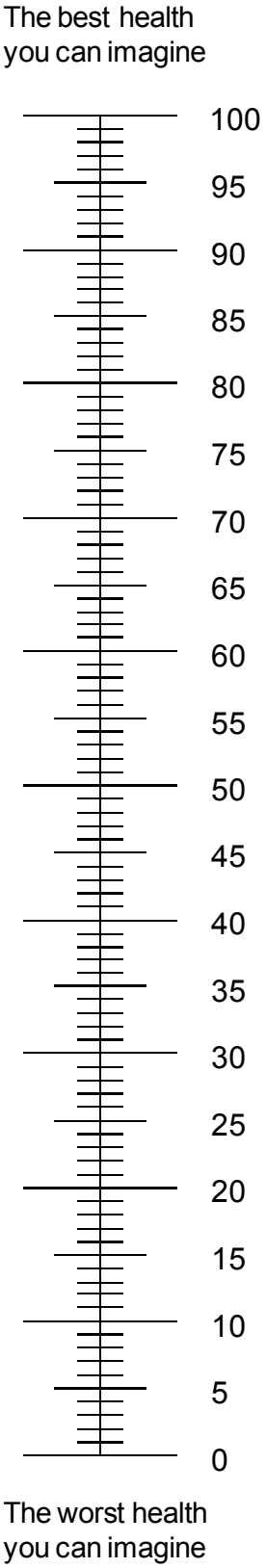
Anxiety/Depression

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

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.

  0 means the worst health you can imagine.
- Mark and X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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

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

EORTC QLQ-PR25

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

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

Please go to the next page

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

Appendix 5: Study Schedule of Activities

Study Period or Visit	Screening	Treatment			Unscheduled	Safety FU	Long-Term FU
Study Week	**−4 to −1**	**1**	**5**	**17 Then Every 16**	**Varies [1]**	**Varies [2]**	**Every 16**
Study Day	**-28 to -1**	**1**	**29**	**113**	**na**	**na**	**na**
Window (Days) [3]	**na**	**na**	**±5**	**±5**	**na**	**±7**	**±7**
General Activities							
Informed consent and screening number (IXRS) [4]	X						
Medical history	X						
Eligibility criteria	X						
12-Lead electrocardiogram (local read)	X						
Radiographic assessments	X [5]			X [6]	X opt [7]		X [6]
Randomization (IXRS) [8]		X					
Complete physical examination [9]	X					X	
Brief physical examination [10]		X	X	X	X		
ECOG performance status	X	X	X	X	X	X	
BPI-SF, FACT-P, EQ-5D-5L, QLQ-PR25 questionnaires		X		X		X	X [11]
Adverse events review [12]		X	X	X	X	X	
Concomitant medications review	X	X	X	X	X	X	
Study drug dispensing		X		X			
Study drug accountability			X	X		X	
Long-term follow-up assessments [13]							X
Central Laboratory Evaluations [14]							
Hematology, serum chemistry	X	X		X	X	X	
Testosterone	X						
Prostate-specific antigen	X	X		X		X	

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

BPI-SF, Brief Pain Inventory Short Form; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels health questionnaire; FACT-P, Functional Assessment of Cancer Therapy-Prostate; FU, follow-up; IXRS, interactive voice/web recognition system; MRI, magnetic resonance imaging; na, not applicable; opt, optional; QLQ-PR25, Quality of Life Questionnaire-Prostate 25.

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PAREXEL®

PAREXEL Informatics
Medical Imaging Services

Medivation
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ABBREVIATIONS AND ACRONYMS

CAN	Case Acceptance Notification
CFR	Code of Federal Regulations
CIL	Core Imaging Laboratory
CQN	Case Query Notification
CR	Complete Response
CT	Computed Tomography
eICRF	electronic Imaging Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IAG	Image Acquisition Guidelines
IRC	Independent Review Charter
MRI	Magnetic Resonance Imaging
ND	No Disease
NE	Inevaluable/Not Evaluable
NN	Non-CR/Non-PD
PFS	Progression Free Survival
PD	Progressive Disease
PR	Partial Response
QC	Quality Control
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	Stable Disease
SOD	Sum of Diameters
SOM	Site Operations Manual

USING CROSS-REFERENCES

The independent review charter (IRC) utilizes cross-references to link related sections of the document and reduce repetition. When in electronic format, all cross-references are hyperlinks.

1 EXECUTIVE SUMMARY

PAREXEL Informatics a subsidiary of PAREXEL International, has a contractual agreement with Medivation, Inc (Medivation) to provide the independent assessment of radiographic imaging in the Medivation MDV3100-14 clinical trial. The Independent Review Charter (IRC) describes the independent review and defines the processes, roles, and responsibilities of Medivation, PAREXEL, and the independent reviewers.

There will be a minimum of two qualified, board-eligible radiologists and two qualified, board-eligible nuclear medicine physicians assigned to the MDV3100-14 study. Independent review will be conducted as follows:

1.1 Eligibility Review

Subject eligibility for study enrollment will be based on the investigator's assessment of imaging studies done at screening. The PAREXEL Eligibility Review of screening imaging studies will provide Medivation with a monitoring tool for patients with metastatic disease at screening. One independent reviewer will assess screening images for each subject to determine the presence or absence of exclusionary disease as defined in IRC section 7.2.1 Eligibility Review Assessment Criteria. The Eligibility Review will be separate from the efficacy assessments for soft tissue disease and bone metastases. Eligibility results will be provided to Medivation or designee according to IRC section 7.4 Role of Independent Review Data.

1.2 Efficacy Review: Two Types of Review

Soft Tissue Disease Assessment: One independent radiologist will assess CT/MRI (not bone scans), for each subject on a timepoint by timepoint basis as defined in IRC section 7.3.1 Soft Tissue Disease Assessment Criteria. The assessment of soft tissue disease will be determined using modified criteria according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1). The presence of metastatic disease at baseline during the soft tissue assessment will result in discontinuation of further independent reviews for the subject. Independent reviews for a subject will also end if progression is determined at a follow-up visit. Soft Tissue Disease Assessment results will be provided to Medivation or designee according to IRC section 7.4 Role of Independent Review Data.

Bone Metastases Assessment: One independent nuclear medicine physician will assess bone scans for each subject on a timepoint by timepoint basis to determine presence or absence of any bone metastases on bone scan as defined in IRC section 7.3.6 Bone Metastases Assessment Criteria. CT/MRI and other modalities will be available to the independent nuclear medicine physician for the purpose of confirming the presence of bone metastases. The bone metastases assessment for a subject will end if any bone metastases are identified on bone scan at baseline, or if progression is determined at follow-up. Bone Metastases Assessment results will be provided to Medivation or designee according to IRC section 7.4 Role of Independent Review Data.

2 INTRODUCTION

2.1 IRC Scope and Purpose

The purpose of the IRC is to describe how the independent review of imaging and clinical data will be designed, conducted, and reported for Medivation MDV3100-14. The following are described within this document:

- Roles and responsibilities of Medivation, PAREXEL, and the independent reviewers
- Role of study imaging in relationship to trial endpoints
- Study deliverables
- Imaging schedule
- Clinical data to be collected and reviewed
- Receipt, tracking, and quality control of data
- Independent review design, assessments, and assessment criteria
- Methodology for review
- Reviewer selection and training

2.1.1 Medivation's Roles and Responsibilities

Medivation will work with PAREXEL to define in the Independent Review Charter the interpretations and criteria of the independent review. Derivation of study endpoints will be the responsibility of Medivation or designee.

2.1.2 PAREXEL's Roles and Responsibilities

PAREXEL will receive and track images from the investigative sites and/or radiology departments involved with the investigative sites and clinical data from Medivation or designee. PAREXEL is responsible for quality control, deviation identification and resolution, and storage and back-up of imaging data in Digital Imaging and Communications in Medicine (DICOM) format or other appropriate formats as needed. In cooperation with Medivation, PAREXEL will develop and write the IRC, write specifications, program and validate a Tracking Application, electronic imaging case report forms (eICRFs), and Data Export, as well as perform quality control measures on the independent review assessments including a set of post review data management checks as described in 7.10.2 Quality Monitoring. PAREXEL will also train and manage the reviewers per the PAREXEL Standard Operating Procedure (SOP). PAREXEL will notify Medivation whenever an investigative site enrolls a patient with metastatic disease at Screening. Further details for this process will be defined in the MDV3100-14 Project Plan.

2.1.3 Independent Reviewers' Roles and Responsibilities

The independent reviewers will:

- Attend training provided by PAREXEL
- Read and understand the assessment criteria, the IRC, the reviewer manual, and any other training materials
- Perform independent reviews in accordance with the assessment criteria detailed in IRC section 7 Design of Independent Review
- Abide by all other requirements described in IRC section 8 Selection and Training of Independent Reviewers

2.2 Role of Imaging in Study Design

Medivation MDV3100-14 is a multinational, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in patients with nonmetastatic castration-resistant prostate cancer (M0 CRPC).

2.2.1 Trial Endpoints

The primary endpoint is to determine the efficacy of enzalutamide compared with placebo as assessed by metastasis-free survival (MFS).

This IRC was based on Medivation protocol MDV3100-14 dated 16MAY2013. Revisions or amendments to the protocol will not require an update to the IRC unless such changes impact the independent review.

2.2.2 Imaging as a Component of Independent Review

IRC section 3 Image Acquisition and Collection describes the applicable imaging.

- Eligibility reviews will include each subject's baseline/screening imaging.
- Efficacy reviews will include baseline/screening imaging and other scheduled and unscheduled on-protocol imaging.

2.2.3 Independent Review Deliverables

2.2.3.1 Deliverables to Medivation

The assessments provided by the independent reviewers will be exported to Medivation or designee. A high-level explanation of data to be provided can be found in IRC section 7.4 Role of Independent Review Data. Further details are outlined in a separate Export Specifications document.

2.2.3.2 Deliverables to Regulatory Authorities

Medivation is responsible for submitting the independent review results to regulatory authorities. If required, PAREXEL will provide images with or without tumor markings, the redacted clinical data available to the reviewers, all eICRFs, and/or data exports.

3 IMAGE ACQUISITION AND COLLECTION

3.1 Acceptable Imaging Modalities

- CT
- MRI
- Bone Scan
- X-ray

3.2 Imaging Schedule

3.2.1 Scheduled On-Protocol Imaging

Imaging Data	Timepoint	Schedule
• Whole body bone scan and • CT or MRI (with contrast) of the chest[1] abdomen and pelvis including inguinal/femoral regions 1 The protocol allows posteroanterior and lateral x-ray of the chest to be acquired in place of CT/MRI of the chest	Baseline / Screening	Day -42 to -1
• Whole body bone scan and • CT or MRI (with contrast) of the abdomen and pelvis including inguinal/femoral regions • Other areas as clinically indicated	Post-Randomization	Every 16 weeks or sooner if radiographic progression is clinically suspected. Patients who discontinue study drug but who have not had radiographic progression will continue with their imaging schedule during the long-term follow-up period until radiographic progression.

3.2.2 Unscheduled On-Protocol Imaging

Any CT or MRI scans with i.v. contrast of the chest, abdomen and/or pelvis, x-ray of the chest, bone scans, and/or bone correlative imaging (CT, MRI or x-ray) acquired at an unscheduled timepoint will be tracked and reviewed. If CT of the chest, abdomen and pelvis are performed without i.v. contrast due to medical contraindication, they will also be tracked and independently reviewed.

Any other CT or MRI scans, x-rays of other areas (e.g., chest or brain) done for the purpose of evaluating potential progression of prostate cancer will also be tracked and independently reviewed.

3.2.3 Off-Protocol Imaging

CT, MRI, bone scan, and x-ray imaging acquired during the course of the study and received at PAREXEL is eligible for independent review. Other modalities are considered off-protocol and will not be tracked or reviewed.

3.3 Image Acquisition Parameters

The procedures entailed in image acquisition at the investigative sites will be detailed in the Image Acquisition Guidelines (IAG) and the Investigator Site Operations Manual (SOM). Sites will be instructed to acquire images in accordance with these parameters. Refer to this document for further details. Procedures concerning image retrieval and processing by PAREXEL will be detailed in the Core Imaging Laboratory (CIL) Manual.

3.4 Investigative Site Qualification Procedures

Site qualification will be conducted in a fashion agreed upon by Medivation and PAREXEL and should include the following components:

- The Site Survey, created by PAREXEL, will obtain information regarding the imaging capabilities of an investigative site (including the number and type of scanners and desired mode of image transmittal) and ensure that the site is able to meet the imaging requirements for the study.
- Test Transfers are submitted in parallel with or following the completion of the Site Survey. A successful Test Transfer will confirm that the site is able to acquire images according to the IAG and confirm PAREXEL's compatibility with the site's digital media.
    - Medivation has requested that PAREXEL not re-survey or collect test transfers from any investigative sites that overlap with the MDV3100-03 clinical trial or have been qualified by PAREXEL on other trials, as PAREXEL has previously surveyed, confirmed the capabilities of, and qualified these investigative sites. Such sites will be automatically approved for image submission. PAREXEL will provide a listing of sites that have already been qualified in either scenario to Medivation.
- The Site Approval Notification is an email notification of PAREXEL's approval of the investigative site to acquire images for the study.
- The eStart-up Package, containing electronic manuals (IAG and SOM) will be provided by PAREXEL upon approval of an investigative site. If a site will be submitting images

via courier, PAREXEL will ship hard copy manuals, Image Transmittal Forms, media labels, and pre-paid return envelopes or air bills, as required.

Please see the Project Plan and/or CIL Manual for additional information about site qualification procedures.

4 CLINICAL DATA COLLECTION

Investigative sites are instructed to submit a Baseline/Screening Clinical Information Form (Appendix 13) along with baseline/screening imaging if the subject has any benign conditions that may mimic metastases on the technetium bone scan. When received for a subject, this form will be presented to all independent reviewers along with the baseline/screening images. The purpose of this information is to identify the presence of any benign findings that may appear on screening imaging studies and confound the assessment of disease.

5 RECEIPT, TRACKING, AND QUALITY CONTROL OF IMAGING

5.1 Receipt, Storage and Back-up of Data in Image Archive

A PAREXEL project team member will be responsible for the initial handling and tracking of images received from an investigative site. Imaging data will be received in electronic format or, if not possible, in original quality hardcopy film.

Hardcopy films will be processed using a laser digitizer, converting the films to digital images. The relevant processes for laser digitization are outlined in the CIL Manual. Images received at PAREXEL as digital data will be translated from proprietary formats.

Electronic images are extracted from digital media (compact disc, magneto-optical disc, etc.) or retrieved from the 21 CFR Part 11-compliant electronic file transfer system. Images received at PAREXEL as digital data will be translated from proprietary formats or converted from hardcopy film to digital data and stored on a secure local workstation.

All production medical imaging systems will have a regular system backup completed in accordance with PAREXEL's SOPs.

5.2 Imaging Data Tracking Procedure

The Tracking Application developed for the study is used to record information about the site, subject, visit (timepoint), and images received. Images are tracked through the various steps of

preparation for independent review, as detailed in the CIL Manual. The project database audit trail captures all changes to specific site, subject, modality, visit, and image information.

Reports on the image tracking data can be accessed through the PAREXEL Portal.

5.3 Imaging Data Quality Control

Upon receipt, all images (baseline and post-baseline) will undergo two quality control (QC) reviews by two different project team members. PAREXEL's staff radiologists will be available throughout the duration of the trial to support QC activities at the discretion of the IRA and Project Manager. Further details of QC activities, query management, and query resolution will be documented in PAREXEL's Project Plan and CIL Manual.

5.3.1 First QC Inspection

The first QC inspection will include verification of proper scanning specifications in adherence to the IAG, image quality, and information completeness and accuracy.

If the study data received are complete, and adhere to the IAG and/or study protocol, a project team member will send a Case Acceptance Notification (CAN), and queue the image(s) for a second QC inspection.

If the study data are incomplete, or do not adhere to the IAG and/or study protocol, a Case Query Notification (CQN) will be sent to the investigational site. If a CQN is generated, it will be followed to resolution. Resolution of CQNs from the investigational site will be documented in the Tracking Application. When a CQN has been generated, the data will not be queued for a second QC inspection until the CQN has been resolved with a CAN or has been administratively closed.

5.3.2 Second QC Inspection

All images will undergo a second QC inspection performed by a different project team member, who verifies the images using the same methodology as the first one.

A CQN will be sent to the investigative site if the study data received are incomplete and/or do not adhere to the IAG or study protocol. If the second QC results in the generation of a CQN, the query will be followed until it is resolved. If an open query cannot be resolved after repeated attempts to do so, it may be closed administratively in some cases with Medivation's approval.

In this case, the available scans will be prepared for review regardless of image quality. Further detail on the query resolution and follow-up process will be clarified within the Project Plan.

All CANs, CQNs, and related documentation will be stored in the Tracking Application and on the fax server.

Furthermore, at the time of review the independent radiologists will assess the images for technical adequacy and quality, and record their comments on the eICRF.

5.4 De-identification and Labeling of Imaging Data

After both QC inspections are passed and query resolutions are completed, a PAREXEL project team member will prepare the imaging data for the Medivation MDV3100-14 study for independent review.

PAREXEL will ensure that all images will be handled appropriately to ensure confidentiality of any subject and site information. It is expected that all data sent to PAREXEL will be collected in compliance with local regulatory laws and that all confidential subject identifiers will be removed by the site before they are sent to PAREXEL.

All imaging received by PAREXEL will be processed with software that automatically masks any confidential patient information in order to ensure that PAREXEL is blinded to such information at all times. No such data are stored in PAREXEL's databases.

Additionally, it will be ensured that any lesion annotations or measurements documented on the images (digital markings, pencil, etc.) at the investigative sites have been masked appropriately, if possible, before any independent reviews, taking care not to obscure areas of interest in any way.

5.5 Procedures for Tracking, Documenting, and Resolving Missing Image Data

Imaging considered incomplete will be collected regardless of missing anatomy, slices, sequences, or modalities. Incomplete imaging and entirely missing scheduled on-protocol imaging timepoints will be noted in the Tracking Application. PAREXEL will query the sites for incomplete or missing imaging data as described in IRC Section 5.3 Imaging Data Quality Control.

5.6 Deviations to Required Imaging Data

Deviations with regard to required imaging are addressed with queries and are captured during the image tracking process. The escalation process for queries that are not resolved within a specified timeframe is defined in the Project Plan.

- If any of the following deviations are found, the site is queried and pertinent responses from the site are recorded via the Tracking Application and are available through a Query Report:
  - A complete set of images from the site expected as per study protocol and IAG are not received
  - The number and/or type of images received for a protocol-defined visit are inadequate or inappropriate
  - The number and/or type of views/sequences for a protocol-defined modality received for a visit are inadequate or inappropriate
  - Critical information is missing from the Image Transmittal Form
- If the site, subject, visit, and/or image information are found to be incorrect, as the result of a query or upon data reconciliation with Medivation and/or data management designee, the data will be corrected via the Tracking Application and the reason for the change will be recorded. Comments regarding the change may also be noted. If necessary, a Data Change Request will be initiated and the data corrected by the appropriate PAREXEL personnel. All changes to the data are captured in the audit trail of the database.

A Query Report accessible through the project portal includes query metrics displaying outstanding and resolved queries, identification number, date of query, reason for query, status, text of the query, recipient, resolution (if resolved), associated site, patient and timepoint information, number of days that have elapsed since the original query text that was sent to the site, and any pertinent comments. Further details regarding the Query Report will be described in the Project Plan.

6 RECEIPT, TRACKING, AND QUALITY CONTROL OF CLINICAL DATA

6.1 Receipt, Tracking, Storage, and Back-up of Clinical Data

Clinical data for the Medivation MDV3100-14 clinical trial (outlined in IRC Section 4 Clinical Data Collection) will be received from sites along with baseline/screening imaging. A project team member will be responsible for the initial handling and tracking of the clinical information received in the Tracking Application. PAREXEL will not generate queries regarding clinical data.

6.2 Clinical Data Quality Control

When received at PAREXEL, a project team member will verify that the Baseline/Screening Clinical Information Form is legible.

6.3 De-identification and Labeling of Clinical Data

PAREXEL will ensure that clinical data will be handled appropriately to ensure confidentiality of any subject and site information.

6.4 Deviations to Required Clinical Data

If a Baseline/Screening Clinical Information Form is not received with baseline imaging no action will be taken. The submission of this form is based on the sites' judgment. The clinical information will be provided to the reviewer as available.

7 DESIGN OF INDEPENDENT REVIEW

The design section describes the number and type of independent reviewers and their roles in the independent review, the subject population that each type of reviewer will assess the assessment criteria and definitions, modifications and/or clarifications to those criteria, and the rationale for any modifications and/or clarifications.

7.1 Review Paradigm, Number, and Classification of Independent Reviewers

Imaging as described in IRC Section 3 Image Acquisition and Collection will be independently read in a blinded fashion as follows:

- One independent reviewer (single-read) will review all available baseline/screening imaging during the Eligibility Review.

- A reviewer who participates in the Eligibility Review may also participate in the Soft Tissue Assessment and/or Bone Metastasis Assessment for this study.

- One independent radiologist (single review) will review all available baseline/screening and follow-up imaging, exclusive of bone scans, during the Soft Tissue Disease Assessment for efficacy.
- One independent nuclear medicine physician (single review) will review all available baseline/screening and follow-up bone scans during the Bone Metastases Assessment for efficacy. In addition to bone scan, the nuclear medicine physician will have access to all other available modalities for the purpose of confirming a new bone lesion in a single region (skull, thorax, spine, pelvis, and extremities).
- The independent reviewers will review imaging in accordance with the assessment criteria and definitions described below.

7.2 Eligibility Review Design

7.2.1 Eligibility Review Assessment Criteria

The eligibility criteria for the MDV3100-14 study prohibit inclusion of patients with evidence of metastatic disease as assessed by CT/MRI and whole-body radionuclide bone scan. Patients with soft tissue pelvic disease may be eligible if lesions do not qualify as target lesions (lymph nodes below aortic bifurcation are permissible if the short axis is <15mm and local extra-nodal disease is permissible if <10mm in long axis). If the screening bone scan shows a lesion suggestive of metastatic disease, the patient may be eligible only if a second imaging modality (plain film, CT, or MRI) does not show bone metastasis. If the imaging results are equivocal or consistent with metastasis, the patient is not eligible for enrollment.

During the Eligibility Review, the independent radiology reviewer must determine presence or absence of exclusionary disease in accordance with the follow definitions:

- Lymph nodes
    - A subject with regional pelvic lymph node(s) measuring <15mm in the short axis will be reported as eligible and the nodes will not be recorded.

- A subject with any regional pelvic lymph nodes measuring ≥ 15 mm in short axis will be reported as not eligible and the lymph nodes will be recorded as exclusionary local metastases.
- A subject with pathological lymph nodes in any other part of the body (≥10mm in short axis) will be reported as not eligible and the lymph nodes will be recorded as distant metastases.

- Extra-nodal Lesions
  - A subject with local extra-nodal lesions <10mm in long axis will be reported as eligible and the lesions will not be recorded.
  - A subject with any other extra-nodal lesions of any size will be reported as not eligible and the lesions will be recorded as distant metastases.
- Other Disease on CT/MRI
  - Fluid collections will not be considered during Eligibility Review.
- Bone Lesions (on bone scan)
  - A subject with any unequivocal bone metastases on bone scan will be reported as not eligible and the bone lesion(s) will be recorded as metastases.
    - A subject with any bone lesions suggestive of metastatic disease which cannot be proven non-metastatic by a second imaging modality (equivocal results, missing, or poor quality imaging) will be reported as not eligible and the bone lesion(s) will be recorded as metastases.
    - A subject with any bone lesions suggestive of metastatic disease, for which a second imaging modality proves the lesion(s) to be non-metastatic will be reported as eligible and no bone lesions will be recorded.
- Non-malignant findings
    - Any potential findings reported as benign on the Baseline/Screening Clinical Information Form (Appendix- Baseline/Screening Clinical Information Form) will not be considered as metastases.

7.2.2 Eligibility Review Documentation of Assessments

See IRC section 7.7.2 Eligibility Review Assessments in Accord with Study Design for details about how exclusionary disease will be identified on imaging during the Eligibility Review.

7.2.3 Limitations of Image Acquisition Parameters on Eligibility Assessments

Imaging timepoints considered incomplete will be reviewed regardless of missing anatomy, slices, sequences, or modalities and shall undergo assessment based on the available imaging.

7.2.4 Delineation of Population for Eligibility Review

Eligibility Review will occur provided the necessary imaging has been received. This requires:

- The baseline/screening exam has been received and accepted by PAREXEL

7.2.5 Independent Reviewer Blinding for Eligibility Review

In order to maintain objectivity in the evaluation of imaging and clinical data, the reviewer for eligibility will be blinded to subject name, subject initials, date of birth, randomization arm, investigative site identifiers, and imaging dates.

7.3 Efficacy Review Design

7.3.1 Soft Tissue Disease Assessment Criteria

The independent radiologist will assess available baseline and follow-up imaging, excluding bone scans, to qualitatively assess soft tissue disease using modified RECIST 1.1 criteria.

The key modifications of RECIST 1.1 for this study are as follows:

- As subjects should enter the study without metastatic disease or pelvic soft tissue disease that qualify as target lesions, no baseline assessment of target lesions will be made; only a confirmation that metastatic disease is not present and characterization of pelvic findings will be provided.
- As subjects in this study should not have target lesions at screening, no response assessments of PR, CR, or SD will be made. The only assessment options will be no disease (ND), no progression (NN), progressive disease (PD), or not evaluable (NE).

The following instructions detail the Soft Tissue Disease Assessment:

- The independent radiologist will record the presence of any pelvic lymph nodes (≥10mm and <15 mm in short axis) or extra-nodal disease (<10 mm in long axis) at baseline and follow for unequivocal progression. The assessment of unequivocal progression will be based on the assessment of all recorded disease (as a whole). Unequivocal progression of a single lesion should not drive progression unless all recorded disease has unequivocally progressed as a whole.
    - If any exclusionary disease is recorded for a subject at baseline, as defined in 7.2.1 Eligibility Review Assessment Criteria, post baseline timepoints will not undergo efficacy review.
- New disease will be recorded as equivocal new lesions or unequivocal new lesions. Only unequivocal new lesions can be a driver of progressive disease.
- Fluid collections will not be considered by the independent radiologist during the Soft Tissue Disease Assessment.
- Bone lesions will not be considered by the independent radiologist during the Soft Tissue Disease Assessment.
- Special Considerations for the Soft Tissue Disease Assessment
    - Assessment in Case of Incomplete Baseline Imaging
        - Baseline/screening imaging that is incomplete as per the imaging schedule requirements (IRC section 3.2 Imaging Schedule), including missing anatomy and/or missing sequences, will be noted as an image quality issue. All assessment options will be valid at follow-up timepoints. If at follow-up timepoint, unequivocal disease is present in the anatomy for which baseline/screening imaging was missing; such disease will be considered new for that timepoint and as evidence of new metastatic disease. The subject will be reported as having progressed.
    - If baseline imaging for a subject is completely missing, the subject will not be sent for independent review as specified in IRC section 7.3.4 Delineation of Population for Soft Tissue Disease Assessment.

- Assessments in Case of Incomplete Follow-up Imaging
  - Follow-up imaging that is incomplete as per the imaging schedule requirements (IRC section 3.2 Imaging Schedule), including missing anatomy and/or missing sequences, will be noted as an image quality issue.
  - If no disease was identified on baseline imaging, a minimum of abdomen and pelvis images must be provided to the independent reviewer for an assessment of 'no disease' at a follow-up visit. If no abdomen and pelvis images are provided, 'no disease' cannot be confirmed and NE will be reported unless progression is assessed elsewhere.
- On-Study Intervention
  - The independent reviewers shall not be notified that on-study intervention occurred for a subject. In the case that on-study intervention is suspected by the independent reviewer the review will continue, and all assessment options will be available. It will be the responsibility of Medivation to censor patients if on-study intervention occurs.

7.3.2 Soft Tissue Disease Assessment Documentation of Assessments

Efficacy assessments will be made by independent reviewers interfacing with eICRFs as described in IRC section 7.8 Efficacy Review Methodology.

7.3.3 Limitations of Image Acquisition Parameters on Soft Tissue Disease Assessments

Following the completion of the query process, imaging timepoints considered incomplete will be reviewed regardless of missing anatomy, slices, sequences, or modalities and shall undergo assessment based on the available imaging. The independent radiologists shall proceed with the review of baseline/screening and follow-up timepoint imaging as specified 7.3.1 Soft Tissue Disease Assessment Criteria.

7.3.4 Delineation of Population for Soft Tissue Disease Assessment

Soft Tissue Disease Assessment will occur for a subject provided that a baseline/screening CT/MRI and at least one follow-up CT/MRI are available.

A subject with an entirely missing baseline/screening CT/MRI shall not undergo Soft Tissue Disease Assessment. A subject with partially missing baseline/screening or follow-up CT/MRI will undergo Soft Tissue Disease Assessment. A subject with only baseline/screening CT/MRI and no follow-up CT/MRI will not undergo Soft Tissue Disease Assessment.

7.3.5 Independent Reviewer Blinding for Soft Tissue Disease Assessment

In order to maintain objectivity in the evaluation of imaging and clinical data, all independent reviewers will be blinded to subject name, date of birth, subject initials, randomization arm, and investigative site identifiers.

The independent reviewers will also be blinded to site lesion selection for tumor assessments, site determination of tumor response, exam date, and reason for exam.

7.3.6 Bone Metastases Assessment Criteria

During the Bone Metastases Assessment the independent nuclear medicine physician will assess bone scans to determine presence or absence of bone lesions. Bone scans will be used to evaluate five regions: skull, thorax, spine, pelvis, and extremities. New bone lesions in only one region require confirmation with a second imaging modality (CT, MRI, or plain film). New bone lesions in two or more of the five regions (skull, thorax, spine, pelvis, and extremities) do not require confirmation by a second imaging modality and will be considered progressive disease (PD). The nuclear medicine physician will have access to all available imaging modalities but is not expected to access other modalities unless they are needed to confirm a lesion identified on bone scan. Modalities other than bone scan should not be used to identify lesions during the bone metastasis assessment. The independent review for Bone Metastasis will be conducted as follows:

- Bone lesions, in a single region, on bone scan, that are confirmed metastatic by a second imaging modality will be recorded as new bone lesions at follow-up. Such lesions drive an assessment of PD.
- Bone lesions in two or more of five regions (skull, thorax, spine, pelvis, and extremities) do not need confirmation by a second imaging modality and will be recorded new bone lesions at follow-up. Such lesions drive an assessment of PD.

- Bone lesions confined to one of the five regions (skull, thorax, spine, pelvis, and extremities) require confirmation by a second imaging modality. If the second imaging modality is unavailable or does not confirm the bone lesions to be metastases these lesions will be recorded as new bone lesions and the subject will be reported as having unconfirmed progression (PDu). If the lesion is later confirmed to be metastasis, by a subsequent bone scan or second imaging modality, the subject will then be reported as having progressed and the timepoint the metastasis was first identified will be considered the timepoint of progression.
    - When PDu for bone metastases is reported for a subject, the independent radiologist will provide additional information describing why confirmation by a second imaging modality was not possible. The reason will be described by one of the following options or the radiologist will recording free text comments if none of the options apply:
        - Confirmatory second modality available, the necessary anatomy was present, but the bone lesion(s) was (were) not visualized
        - Confirmatory second modality available, but the necessary anatomy was NOT present; therefore the bone lesion(s) could not be confirmed
        - Confirmatory second modality NOT available as only a bone scan provided Other (comments required)
- Bone scan findings reported as benign on the Baseline/Screening Clinical Information Form (13 Appendix- Baseline/Screening Clinical Information Form) will not be considered bone lesions.

7.3.7 Documentation of Assessments

See IRC section 7.8 Efficacy Review Methodology

For details about how any evidence of disease will be identified on imaging during the Eligibility Review.

7.3.8 Limitations of Image Acquisition Parameters on Bone Metastases Assessments

Imaging timepoints considered incomplete will be reviewed regardless of missing anatomy, slices, sequences, or modalities and shall undergo assessment based on the available imaging.

7.3.9 Delineation of Population for Bone Metastases Assessment

Bone Metastases Assessment will occur provided the necessary imaging has been received. This requires:

- The baseline/screening bone scan has been received and accepted by PAREXEL
- Any required correlative imaging has been received and accepted by PAREXEL
- Any relevant prior clinical information for the imaging criteria review has been received by PAREXEL

7.3.10 Independent Reviewer Blinding for Bone Metastases Assessment

In order to maintain objectivity in the evaluation of imaging and clinical data, the reviewer for bone metastases will be blinded to subject name, subject initials, date of birth, randomization arm, investigative site identifiers, and imaging dates.

7.4 Role of Independent Review Data

Eligibility Reviews will be completed within five business days from receipt of acceptable imaging. If a patient is assessed as having exclusionary disease during the eligibility review, PAREXEL will notify Medivation. Further operational details will be stipulated in the Project Plan.

Independent review data for efficacy (Soft Tissue Disease Assessment and Bone Metastases Assessment) will be provided to Medivation multiple times during the study and for the final analysis. If a patient is assessed as having exclusionary disease at baseline during the efficacy review, the review will not continue and PAREXEL will notify Medivation. Further operational details will be stipulated in the Project Plan.

7.5 Methodology for the Independent Review

The methodology section describes the image review system, image analysis software, image and clinical data presentation, electronic case report forms (eICRFs) and function, and the image review schedule.

7.6 General Methodology

This section applies to all reviewer types (Eligibility Review, Soft Tissue Disease Assessment, and Bone Metastases Assessment).

7.6.1 Image Review System

The following will apply to all the independent reviews being performed for the study:

- The PAREXEL project code, Sponsor, Protocol, and date shall be displayed to the user in the form header
- Only authorized users have access to the image review system
- Any inserts, updates, and deletions to the database that occur while using the image review system are captured in the audit trail with date-time stamp and user identification
- All users of the image review system are required to provide electronic signatures in order to submit review information
- Independent reviewers will use PAREXEL's image viewing software to assess study images including opening and closing of study files, data entry, magnification, and using window/level and stack mode functions, as applicable
- Images will be presented to all independent reviewers electronically using PAREXEL's image viewing software, utilizing workstations with high-resolution monitors
- The software will provide magnification and panning that are linked between timepoints
- A tool will be available for measuring lesions. However, lesion measurements will not be recorded on the imaging. Only qualitative lesion markings will be saved on the imaging

7.6.2 Recording of Results of Image and Clinical Data Assessments

All assessments performed by the independent reviewers will be captured in an audit trail in keeping with International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11.

All independent reviewers will be responsible for entering the results of evaluations using eICRFs developed specifically for the MDV-3100-14 study by PAREXEL.

Re-reviews are conducted only under exceptional circumstances and pending approval by PAREXEL.

7.7 Eligibility Review Methodology

7.7.1 Data Presentation to Eligibility Reviewers

Imaging data and eICRFs will be presented on triple monitors as follows:

- Through the Independent Review Plug-in (IRP), the independent radiologist will access a list of assigned cases
- The subject number will be displayed
- The eligibility eICRF and baseline/screening images will open automatically when an independent radiologist selects a subject for review

7.7.2 Eligibility Review Assessments in Accord with Study Design

During the Eligibility Review, an independent reviewer will review images and clinical data, as applicable, in order to assess for subject eligibility according to 7.2.1 Eligibility Review Assessment Criteria. Only exclusionary disease will be marked on imaging and recorded on the eICRF.

Table 1: Eligibility Review eICRF Summary

Req	Section(s)	Parameter or Question	Possible Selections*, Values, or Calculations	Comments/Notes
1.	Subject Information	Subject Number	Read Only	
2.	Image Information	Timepoint Image Name Modality	Read Only	Timepoints labeled: Baseline, Timepoint 1, Timepoint 2 etc.
3.	Bone Scan: Image Quality	Are there Bone Scan image quality issues?	○ Yes ○ No	• If No, skip req. 4
4.	Bone Scan: Image Quality	Bone Scan Image quality issues	☐ Anatomy is not complete ☐ Poor image resolution ☐ Poor bone to background contrast ☐ Other	Comments required if Other
5.	CT/ MRI: Image Quality	Are there CT/MRI image quality issues?	○ Yes ○ No	• If No, skip req. 6
6.	CT/MRI: Image Quality	CT/MRI Image quality issues	☐ Anatomy is not complete ☐ Scan slice(s) missing ☐ Motion artifacts present ☐ Poor IV contrast ☐ No IV contrast ☐ Crucial anatomy is out of field of view ☐ Other	Comments required if Other
7.	Image Quality and Assessments	Are the quality issues preventing you from making a full assessment for this timepoint?	○ Yes ○ No	Skip this req. if there are no quality issues.
8.	Bone Scan: Existence of Metastasis	Are there any metastases on Bone Scan?	○ Yes ○ No ○ Not Evaluable	• If Yes, record mets (req. 9)
9.	Bone Scan: Existence of Metastasis	Lesion Location	Table 5: Bone Scan Lesion Location List	• Marked by an X • Unique number assigned to each
10.	Bone Scan Comments	Bone Scan Comments	Free Text	
11.	CT/MRI: Distant Metastases	Are there any distant metastases on CT/MRI?	○ Yes ○ No ○ Not Evaluable	• If Yes, record mets (req. 12)
12.	CT/MRI: Distant Metastases	Lesion Location	Table 4: Soft Tissue and New Lesion Locations	• Marked by an X • Unique number assigned to each
13.	CT/MRI: Exclusionary Local Metastases	Are exclusionary soft tissue pelvic lesions present on CT/MRI? Static Text: For pelvic disease to be considered exclusionary lymph nodes must be ≥ 15mm in short	○ Yes ○ No ○ Not Evaluable	• If Yes, record mets (req. 14)

		axis and/or extra-nodal disease must be ≥10mm in long axis.		
14.	CT/MRI: Exclusionary Local Metastases	Lesion Location	Table 4: Soft Tissue and New Lesion Locations	• Marked by an X • Unique number assigned to each
15.	Subject Eligibility	Is this subject eligible?	○ Yes ○ No ○ Not Evaluable	
16.	CT/MRI Comments	CT/MRI Comments	Free Text	
17.	General Comments	General Comments	Free text	

○ Single Select
☐ Multi Select

7.7.3 Locking the Eligibility eICRF

One eligibility eICRF will be completed for each subject. After the eICRF is completed and signed off by the reviewer, the assessment is locked, disabling the reviewer and any other users from making any modifications to the data.

7.8 Efficacy Review Methodology

7.8.1 Data Presentation during Soft Tissue Disease Assessment

Imaging data and eICRFs will be presented on triple monitors as follows:

- Through the Independent Review Plug-in (IRP), the independent radiologist will access a list of assigned cases
- The subject number will be displayed
- The slice interval for CT and MRI will be displayed
- The first eICRF and baseline/screening images, excluding bone scan, will open automatically when an independent radiologist selects a subject for review
- The subsequent eICRFs and images, excluding bone scan, will automatically launch once the current eICRF is completed and submitted by an independent radiologist
- Imaging timepoints will be displayed in chronological order one timepoint at a time
- Previous eICRFs and launched images for the current subject will be available for comparison in a read-only fashion

During the Soft Tissue Disease Assessment, the independent radiologist will not have knowledge of:

- The number or type of future timepoints
- Entirely missing timepoints
- Visit name (e.g. week 8) and/or reason for acquisition of imaging data

7.8.2 Soft Tissue Disease Assessments in Accord with Study Design

During the Soft Tissue Disease Assessment an independent radiologist will assess images and clinical data according to 7.3.1 Soft Tissue Disease Assessment Criteria. Any soft tissue disease identified at baseline and/or new disease will be recorded on the eICRF.

Table 2: Soft Tissue Disease Assessment eICRF Summary

Req	Section(s)	Parameter or Question	Possible Selections*, Values, or Calculations	Comments/Notes
1.	Subject Information	Subject Number	Read Only	
2.	Image Information	Timepoint Image Name Modality Series	Read Only	Timepoints labeled: Baseline, Timepoint 1, Timepoint 2 etc.
3.	Image Quality	Are there image quality issues?	○ Yes ○ No	• If No, proceed to req. 7.
4.	Image Quality	Image quality issues	☐ Anatomy is not complete ☐ Scan slice(s) missing ☐ Motion artifacts present ☐ Poor IV contrast ☐ No IV contrast ☐ Crucial anatomy is out of field of view ☐ Other	Comments required if Other
5.	Image Quality	Are the quality issues preventing you from making a full assessment for this timepoint?	○ Yes ○ No	
6.	Image Quality	Comments on image quality	Free text	
7.	Absence/Presence of Disease	Is there any Soft Tissue Disease at Baseline?	○ Yes ○ No	• If Yes, indicate whether disease is exclusionary (req. 8)
8.	Absence/Presence of Disease	Is the disease exclusionary?	○ Yes ○ No	• If Yes, review ends • If No, record and follow disease (req. 9-18)
9.	Soft Tissue Disease	Soft Tissue Disease Lesion Location	Table 4: Soft Tissue and New Lesion Locations	• Marked by an X • Unique number assigned to each
10.	Soft Tissue Disease	Soft Tissue Disease Lesion Description and	Free text	

		comments		
11.	Soft Tissue Disease	Individual/Group Soft Tissue Lesion Assessment at post-baseline visits	○ No Progression (NN) ○ Progressive Disease (PD) ○ Not Evaluable (NE)	
12.	Soft Tissue Disease	Individual/Group Soft Tissue Lesion Assessment: NE	○ [Single select list of corresponding image series] ○ Unable to associate the lesion to an image series	N/A
13.	Soft Tissue Disease	Individual/Group Soft Tissue Lesion Assessment: NE and Unable to associate the lesion to an image series selected	○ Missing anatomy ○ Missing modality ○ Other, specify (comments required)	Comments required if Other
14.	Soft Tissue Disease	Individual/Group Soft Tissue Lesion Assessment: NE and corresponding image series selected	○ Scan slice(s) missing ○ Poor quality ○ Other, specify (comments required)	Comments required if Other
15.	Soft Tissue Disease	Soft Tissue Lesion Comments	Free text	Baseline and post-baseline
16.	Soft Tissue Disease as a whole	Soft Tissue Disease Assessments as a whole	○ No Progression (NN) ○ Progressive Disease (PD) ○ Not Evaluable (NE)	Comments required if NE
17.	Soft Tissue Disease as a whole	Soft Tissue Disease as a whole NE Comments at post-baseline	Free text	Required when NE is selected
18.	Soft Tissue Disease as a whole	Soft Tissue Disease Assessment Comments	Free text	• Available at baseline and post-baseline • Completion is optional
19.	New Equivocal Lesions	New Equivocal Lesion Locations	Table 4: Soft Tissue and New Lesion Locations	• Marked by an X • Unique number assigned to each • Comments required if Other • Carried forward to future timepoints
20.	New Equivocal Lesions	New Equivocal Lesion Location Description	Free text	Carried forward to future timepoints
21.	New Equivocal Lesions	New Equivocal Lesion Timepoint	[Timepoint identified]	Display
22.	New Equivocal Lesions	Equivocal Lesion Assessment	○ Absent (CR) ○ Equivocal (EQ) ○ Unequivocal (UEQ) ○ Not Evaluable (NE)	
23.	New Equivocal Lesions	Equivocal Lesion Assessment: Absent or NE	○ [Single select list of corresponding image series] ○ Unable to associate the lesion to an image series	
24.	New Equivocal Lesions	Equivocal Lesion Assessment: NE and	☐ Missing anatomy ☐ Missing modality	Comments required if Other

		Unable to associate the lesion to an image series selected	☐ Other, specify (comments required)	
25.	New Equivocal Lesions	Equivocal Lesion Assessment: NE and corresponding image series selected	☐ Scan slice(s) missing ☐ Poor quality ☐ Other, specify (comments required)	Comments required if Other
26.	New Equivocal Lesions	New Equivocal Lesion NE Comments	Free text	• Post-baseline when NE is selected
27.	New Equivocal Lesions	New Equivocal Lesion Comments	Free text	
28.	New Unequivocal Lesions	New Unequivocal Lesion Locations	Table 4: Soft Tissue and New Lesion Locations	• Marked by an X • Unique number assigned to each • Comments required if Other • Carried forward to future timepoints
29.	New Unequivocal Lesions	New Unequivocal Lesion Location Description	Free text	Carried forward to future timepoints
30.	New Unequivocal Lesions	New Unequivocal Lesion Timepoint	[Timepoint identified]	Display
31.	New Unequivocal Lesions	Unequivocal Lesion Assessment	○ Unequivocal (UEQ) ○ Absent (CR) ○ Not Evaluable (NE)	
32.	New Unequivocal Lesions	Unequivocal Lesion Assessment: Absent or NE	○ [Single select list of corresponding image series] ○ Unable to associate the lesion to an image series	
33.	New Unequivocal Lesions	Unequivocal Lesion Assessment: NE and Unable to associate the lesion to an image series selected	☐ Missing anatomy ☐ Missing modality ☐ Other, specify (comments required)	Comments required if Other
34.	New Unequivocal Lesions	Unequivocal Lesion Assessment: NE and corresponding image series selected	☐ Scan slice(s) missing ☐ Poor quality ☐ Other, specify (comments required)	Comments required if Other
35.	New Unequivocal Lesions	New Unequivocal Lesion NE Comments	Free text	Post-baseline when NE is selected
36.	Assessment for Radiographic Progression	Assessment for Radiographic Progression	○ No Disease (ND) ○ No Progression (NN) ○ Progressive Disease (PD) ○ Not Evaluable (NE)	
37.	Global Assessment	Timepoint of Progression	[Select Timepoint] or N/A	
38.	General Comments	General Comments	Free text	Baseline and post-baseline

○ Single Select
☐ Multi Select

7.8.3 Locking the Soft Tissue Disease Assessment eICRF

After each timepoint is independently read and signed off by a radiologist, the assessment is locked, disabling the radiologist and any other users from making any modifications to the data.

7.8.4 Data Presentation to Bone Metastases Reviewers

Imaging data and eICRFs will be presented on triple monitors as follows:

- Through the Independent Review Plug-in (IRP), the independent nuclear medicine physician will access a list of assigned cases
- The subject number will be displayed
- The first eICRF and all available baseline/screening images will open automatically when an independent nuclear medicine physician selects a subject for review
- The subsequent eICRFs and all available images will automatically launch once the current eICRF is completed and submitted by an independent nuclear medicine physician
- Imaging timepoints will be displayed in chronological order one timepoint at a time
- Previous eICRFs and images for the current subject will be available for comparison in a read-only fashion

During the Bone Metastases Assessment, the independent nuclear medicine physician will not have knowledge of:

- The number or type of future timepoints
- Entirely missing timepoints
- Visit name (e.g. week 8) and/or reason for acquisition of imaging data

7.8.5 Bone Metastases Assessments in Accordance with Study Design

During the Bone Metastases Assessment an independent nuclear medicine physician will assess images and clinical data, as applicable, to confirm the absence of distant metastases on baseline/screening imaging, and to assess for evidence of radiological progression (presence of distant metastases) at follow-up according to 7.3.6 Bone Metastases Assessment Criteria. During the Bone Metastases Assessment lesion markings will be placed on bone scan only. Other available modalities will be provided for correlative purposes. Bone lesions requiring

confirmation by a second imaging modality will be recorded as equivocal if confirmation is not possible.

Table 3: Bone Metastases Assessment eICRF Summary

Req	Section(s)	Parameter or Question	Possible Selections*, Values, or Calculations	Comments/Notes
1.	Image Quality	Are there image quality issues?	○ Yes ○ No	If No, skip req. 4
2.	Image Quality	Image quality issues	☐ Anatomy is not complete ☐ Poor image resolution ☐ Poor bone to background contrast ☐ Other (if selected, a comment is required)	• Comments required if Other • Any CT/MRI image quality issues to be recorded as 'other'
3.	Image Quality	Are the quality issues preventing you from making a full assessment for this timepoint?	○ Yes ○ No	
4.	Image Quality	Comments on image quality	Free text	
5.	Absence/Presence of Disease	Are there any bone lesions on bone scan at baseline?	○ Yes ○ No	• If Yes, review ends
6.	New Bone Lesions	New Bone Lesion Locations	Table 5: Bone Scan Lesion Location List	• Marked by X • Unique number assigned to each • Carried forward to future timepoints
7.	New Bone Lesions	New Bone Lesion Location Description	Free text	Carried forward to future timepoints
8.	New Bone Lesions	New Bone Lesion Timepoint	[Timepoint first identified]	Display
9.	Assessment for Radiological Progression	Assessment for Progression Static text: Confirmation with a second imaging modality (plain film, CT, or MRI) will be required when bone lesions are found in a single region on the bone scan.	○ No Bone Metastases (ND) ○ Bone metastasis-unconfirmed (PDu) ○ Bone metastases (PD) ○ Not Evaluable (NE)	• Once PD is assessed, no further timepoints will be reviewed. • Free text comments required if PD or NE. See req. 10 for PDu comment options.
10.	Assessment for Radiological Progression	Bone metastases unconfirmed (PDu) Comments	○ Confirmatory second modality available, the necessary anatomy was present, but the bone lesion(s) was (were) not visualized ○ Confirmatory second modality available, but	If other is selected, the free text comment box will be required. Otherwise comments not required.

			the necessary anatomy was NOT present; therefore the bone lesion(s) could not be confirmed ○ Confirmatory second modality NOT available as only a bone scan provided ○ Other (comments required)	
11.	Global Assessment	Timepoint of Progression	[Select Timepoint] or N/A	
12.	General Comments	General Comments	Free text	

○ Single Select
☐ Multi Select

7.8.6 Locking the Bone Metastases eICRF

After each timepoint is independently read and signed off by a nuclear medicine physician, the assessment is locked, disabling the nuclear medicine physician and any other users from making any modifications to the data.

7.9 Schedule for Eligibility, Bone Metastases, and Soft Tissue Disease Assessment

Refer to 7.4 Role of Independent Review Data.

7.10 Reviewer Performance and Quality Metrics

Reviewer performance will be evaluated during the study through the following process(es).

7.10.1 Secondary Review

Secondary review is a process of re-reading by the independent reviewers. It is used for determination of intra-observer or inter-observer disagreement or variability and to monitor reviewer performance. The data from the secondary review will be used for reviewer training purposes only and this data will be maintained separately from the independent review database. The soft tissue and bone metastasis reviewers will perform secondary reviews. The eligibility reviewers will not perform secondary reviews.

7.10.1.1 Intra-Observer Secondary Review

Each reviewer will re-read 10 subjects using the same imaging data as the original read not earlier than 3 weeks after the original read in order to monitor reviewer consistency over time.

7.10.1.2 Inter-Observer Secondary Review

All soft tissue reviewers will read the same 10 previously read subjects and all bone metastasis reviewers will read the same 10 previously read subjects in order to monitor consistency across reviewers.

7.10.2 Quality Monitoring

For this study, an initial Quality Monitoring (QM) will be performed on the first five subjects per independent reviewer per review type, consisting of a review the eICRFs and images, if deemed necessary, and will be documented and monitored by PAREXEL. QM is defined as a quality control review of independent review results to ensure the correct application of criteria based on the IRC and completion of the eICRFs. Additional production reviews may be delayed when feasible until initial QM is complete.

If a lack of adherence to the IRC-defined rules and criteria and/or completion of the eICRF are identified, PAREXEL medical personnel will:

- Evaluate the discrepancy for the reviewer
- Determine its impact on the assessment results and/or study endpoints
- Formulate a recommended corrective action

Corrective actions will include the communication of the review findings to the independent reviewer. Depending on the severity and complexity of the findings, the form of communication may include:

- Phone call to the independent reviewer
- Online demonstration of the findings
- Face-to-face meeting with demonstration of the findings

Any discrepant findings will be addressed as necessary by Post-Review Data change(s) or re-review(s). Further details are provided in the Project Plan.

All discrepancies and corrective actions will be documented in a QM spreadsheet. All associated QM documents will be saved in the project files, including QM spreadsheet, training logs for reminders, and/or e-mail responses from independent reviewers.

Ongoing QM may also be performed by Data Management if required. Discrepancy level and corrective actions will be followed as described above.

7.11 Methodology for Export of Results to Medivation and Regulatory Authorities

All independent review results will be exported to Medivation or a designee as described in the Export Specifications for the study. Images with overlays will be saved to PAREXEL's secure database, and will be available to Medivation or designee and/or regulatory authorities for further study evaluation upon request. Additional details on data export will be described in the Export Specifications document.

8 SELECTION AND TRAINING OF INDEPENDENT REVIEWERS

8.1 Reviewer Qualifications

Curriculum vitae demonstrating capabilities and qualifications of all reviewers will be shared with Medivation and will be maintained in the project central files at PAREXEL. Independent reviewers shall be, at a minimum, board-eligible in the United States or have an equivalent level of certification in their respective relevant areas of expertise. The reviewers shall have no financial interest in the outcome of the study and shall not be involved in patient care or trial conduct, other than as it relates to the independent review component. Each reviewer will have signed a statement of confidentiality and/or a mutually agreeable contract with PAREXEL, as applicable, and a Financial Disclosure statement.

8.2 Reviewer Training

8.2.1 General Training Requirements

Training of the independent reviewers will be conducted prior to the start of any evaluations for the study. All training sessions will be held at PAREXEL facilities or at a secure remote location per PAREXEL SOP.

All reviewers will receive regulatory and general RECIST 1.1 training. These will include instructions on:

- 21 CFR Part 11 and required document completion
- Independent reviewer obligations
- Security regulations and policies

- Independent review data presentation
- Providing image quality assessment

In addition, the reviewers will receive project-specific training where they will be introduced to the scope of the Medivation MDV3100-14 clinical trial and to the overall functionality of the eICRFs designed for this study. All reviewers will sign and date a training log sheet. This training session will include:

- Review of trial endpoints and objectives
- Study-specific review rules as described in the independent review charter
- Definition of terms to be used in image evaluation and classification
- General requirements that constitute independent readings
- An open forum for case review and discussion regarding the applicable criteria

PAREXEL personnel with documented experience in the use of PAREXEL's image viewing software will train each reviewer to acquire an adequate understanding of the software program in order to assess study images including the opening and closing of study files, data entry, use of measuring tools if applicable, magnification, entry deletion, window/level, and stack mode functions.

Training images and any respective clinical data will be selected by PAREXEL to be most representative of the study population and review purpose. The training cases will not be part of the Medivation MDV3100-14 trial. All training results will be appropriately documented in accordance with PAREXEL's SOPs.

8.2.2 Eligibility Review Training

An appropriate mix of a minimum of five total training and/or testing cases may be used to ensure effective reviewer training for all eligibility reviewers.

8.2.3 Soft Tissue Disease Assessment Training

For radiologists performing the Soft Tissue Disease Assessment, an appropriate mix of a minimum of five total training and/or testing cases may be used to ensure effective training.

One soft tissue case will consist of at least one imaging timepoint and appropriate clinical data for a given subject. An imaging timepoint will be composed of a contrast enhanced CT of the abdomen and pelvis at each timepoint, at a minimum.

8.2.4 Bone Metastases Assessment Training

For nuclear medicine physicians performing the Bone Metastases Assessment, an appropriate mix of a minimum of five total training and/or testing cases may be used to ensure effective training.

One bone metastases case will consist of at least one imaging timepoint and appropriate clinical data for a given subject. An imaging timepoint will be composed of a whole-body bone scan, at a minimum.

8.3 Reviewer Replacement

In the event that a reviewer can no longer fulfill the responsibilities as an independent reviewer or is subsequently removed from the study, a replacement with appropriate qualifications and expertise will be provided. The replacement reviewer will undergo training as described in IRC section 8.2 Reviewer Training prior to the start of any evaluations for the study. If an independent reviewer must be replaced, any cases that have been partially reviewed must be fully re-reviewed by a replacement reviewer. The assessments made by the replacement reviewer will be considered the final review and will be the results provided to Medivation at the time of data export. Logistical details regarding reviewer replacement are documented in the Project Plan.

9 REFERENCES

Eisenhauer, E. A., P. Therasse, J. Bogaerts, L. H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, and J. Verweij. "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)." European Journal of Cancer 45 (2009): 228-47.

10 REVISION HISTORY

Revision	Section Changed	Changes Made	Author	Date
1.0	N/A	Initial issue of the document	PPD , BSN	22JUL2013
2.0	Entire Document	Perceptive changed to PAREXEL	PPD	08SEP2014

	2.2.1 3.2.1 3.2.3 7.3.6	*This IRC was based on Medivation protocol MDV3100-14 dated 16MAY2013. Revisions or amendments to the protocol will not require an update to the IRC unless such changes impact the independent review.* Follow-up CT or MRI (with contrast) of the ~~chest*~~ abdomen and pelvis including inguinal/femoral regions Follow-up ~~*The protocol allows posteroanterior and lateral x-ray of the chest to be acquired in place of CT/MRI of the chest if chest x-ray was acquired during screening.~~ All ~~modalities other than those described above will not~~ *CT, MRI, bone scan, and x-ray imaging received at PAREXEL will be independently reviewed. Other* modalities *are considered off-protocol and will not* be tracked or reviewed. ~~Single bone lesions or~~ Bone lesions confined to one of the five regions…. If the lesion is later confirmed to be metastasis, *by a subsequent bone scan or second imaging modality….* *When PDu is reported for a subject, the independent radiologist will provide additional information describing why confirmation by a second imaging modality was not possible. The reason will be described by one of the following options or the radiologist will recording free text comments if none of the options apply:* • *Confirmatory second modality available , the necessary anatomy was present, but the bone*	RN, BSN	

		lesion(s) was (were) not visualized • *Confirmatory second modality available, but the necessary anatomy was NOT present; therefore the bone lesion(s) could not be confirmed* • *Confirmatory second modality NOT available as only a bone scan provided* • *Other (comments required)*		

Italics indicates added text, strikethrough indicates deleted text

11 REVISION RATIONALE

Charter updated to version 2.0 to align imaging requirements to protocol. During this revision Perceptive was updated to PAREXEL throughout the document due to company name change. The nuclear medicine efficacy reviewer manual will be revised as a result of this charter revision and nuclear medicine reviewers will be provided with necessary guidance about the revisions. Eligibility and soft tissue reviewers will be notified of this charter revision, but eligibility and soft tissue reviewer manuals will not be updated because this charter revision does not impact them.. No re-training sessions will be required.

12 APPENDIX: INDEPENDENT REVIEW ANATOMIC LOCATION LISTS

Table 4: Soft Tissue and New Lesion Locations

Soft Tissue and New Lesion Locations
Liver - left lobe
Liver - right lobe
Liver - multiple segments - right and left lobes
Liver - multiple segments - left lobe
Liver - multiple segments - right lobe
Liver - caudate lobe, segment I
Liver - left lobe, segment II
Liver - left lobe, segment III
Liver - left lobe, segment IV
Liver - right lobe, segment V
Liver - right lobe, segment VI
Liver - right lobe, segment VII
Liver - right lobe, segment VIII
Liver - specify
Lung - left
Lung - right
Lung - multiple lobes bilaterally
Lung - multiple lobes left
Lung - multiple lobes right
Lung - left upper lobe
Lung - left lower lobe
Lung - right upper lobe
Lung - right medial lobe
Lung - right lower lobe
Lung - specify
Lymph nodes - bilateral cervical
Lymph nodes - bilateral hilar and mediastinal
Lymph nodes - bilateral supraclavicular
Lymph nodes - bilateral axillary
Lymph nodes - bilateral aorto-iliac
Lymph nodes - bilateral pelvic
Lymph nodes - bilateral inguinal
Lymph nodes - cervical left
Lymph nodes - cervical right
Lymph nodes - supraclavicular left
Lymph nodes - supraclavicular right
Lymph nodes - axillary left
Lymph nodes - axillary right
Lymph nodes - mediastinal
Lymph nodes - para-tracheal left
Lymph nodes - para-tracheal right
Lymph nodes - aortopulmonary window
Lymph nodes - hilar left
Lymph nodes - hilar right
Lymph nodes - subcarinal
Lymph nodes - peri-cardiac
Lymph nodes - retrocrural
Lymph nodes - porta hepatis
Lymph nodes - celiac axis

Soft Tissue and New Lesion Locations
Lymph nodes - portocaval
Lymph nodes - peripancreatic
Lymph nodes - mesenteric
Lymph nodes - peri-aortic
Lymph nodes - peri-caval
Lymph nodes - retroperitoneal
Lymph nodes - iliac left
Lymph nodes - iliac right
Lymph nodes - pelvic left
Lymph nodes - pelvic right
Lymph nodes - inguinal left
Lymph nodes - inguinal right
Lymph nodes - specify
Abdominal wall - left
Abdominal wall - anterior
Abdominal wall - right
Abdominal wall - posterior
Adrenal gland - left
Adrenal gland - right
Biliary tract
Bladder
Brain - bilateral
Brain - brain stem
Brain - left cerebellum
Brain - left cerebral hemisphere
Brain - right cerebellum
Brain - right cerebral hemisphere
Brain - specify
Breast - left
Breast - right
Chest wall - anterior
Chest wall - left
Chest wall - posterior
Chest wall - right
Colon
Diaphragm - bilateral
Diaphragm - left
Diaphragm - right
Heart
Kidney - left
Kidney - right
Mediastinum
Neck
Oesophagus
Ovary - left
Ovary - right
Pancreas
Pelvis
Pelvis - left
Pelvis - central
Pelvis - right
Pericardium

Soft Tissue and New Lesion Locations
Peritoneum/Omentum - central
Peritoneum/Omentum - left
Peritoneum/Omentum - right
Peritoneum/Omentum – all quadrants
Pleura - bilateral
Pleura – left
Pleura – right
Prostate
Retroperitoneum
Skin – specify
Small intestine
Spleen
Stomach
Tracheal – Bronchial Tree
Uterus
Other, specify

Table 5: Bone Scan Lesion Location List

Bone Scan Lesion Location
Skull
Thorax
Spine
Pelvis
Extremities

13 APPENDIX- BASELINE/SCREENING CLINICAL INFORMATION FORM

BASELINE/SCREENING CLINICAL INFORMATION FORM
MDV3100-14 Protocol (2011015)

This form is to be completed and shipped with SCREENING CT/ MRI and Bone Scans if there are any benign conditions in this patient that may mimic metastases on the technetium bone scan that should be communicated to the central reviewer.

To be completed by Primary Investigator or Designee:

Site Number: _____

Patient Screening Number: _____

Benign Lesions

Please provide details and specify the location(s):

Final Document Sponsor Signature Approval Page

Document Title: Medivation MDV3100-14 Independent Review Charter
Document Version: 2.0
Project: Medivation Protocol MDV3100-14

Medivation has completed a final review of this document. It is understood and approved by the following:

Document Approved By:

PPD

PPD M.D.
PPD, Clinical Development
Medivation, Inc.

PPD

Date PPD

PPD

PPD Ph.D.
PPD Biostatistics
Medivation, Inc.

PPD

Date

Final Document PAREXEL Signature Approval

Document Title: Medivation MDV3100-14 Independent Review Charter
Document Version: 2.0
Project: Medivation Protocol MDV3100-14

The following PAREXEL personnel (or supervisors, as per PAREXEL's standard operating procedures) will sign this document electronically via P-MED attesting to their understanding and approval:

PPD, BSN
Medical Writer
PAREXEL Informatics

PPD PhD
PPD
PAREXEL Informatics

PPD M.D., M.M.Sc.
PPD
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PPD
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PPD, CNMT, RT(N)
PPD
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Medivation, Inc.

CHARTER FOR THE INDEPENDENT DATA MONITORING COMMITTEE

Study Title:	PROSPER: A Multinational, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer
Protocol Identifier:	MDV3100-14
Phase:	3
Investigational Product:	Enzalutamide (formerly MDV3100)
Indication:	Prostate Cancer
Sponsor:	Medivation, Inc. 525 Market Street, 36th Floor San Francisco, CA 94105 Telephone: +1 (415) 543-3470 Fax: +1 (415) 543-3411
Sponsor Medical Monitor:	PPD, MD Telephone: PPD Mobile: PPD Email: PPD
Sponsor Statistician:	PPD, MS
Charter Version:	v1.0 – FINAL 12 Aug 2013

This study will be conducted according to the principles of Good Clinical Practice as described in International Conference on Harmonisation guidelines, including the archiving of essential documents.

FINAL CHARTER APPROVAL SHEET

CHARTER FOR THE INDEPENDENT DATA MONITORING COMMITTEE

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

Data Monitoring Committee Approvals:

PPD _____ PPD _____
PPD , MD Date PPD
PPD
PPD
New Orleans, LA
DMC Chair

PPD _____ PPD _____
PPD , PhD PPD Date
PPD
Rochester, MN

PPD _____ PPD _____
PPD , MD Date
PPD
Cleveland, OH

PPD _____ PPD _____
PPD MD Date
PPD
Baltimore, MD

FINAL CHARTER APPROVAL SHEET

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

Medivation, Inc. Approvals:

PPD _____ PPD
PPD MD Date PPD
PPD Clinical Development

PPD _____ PPD
PPD PhD Date
PPD Biostatistics

PPD _____ PPD
PPD RAC Date
PPD, Regulatory Affairs

FINAL CHARTER APPROVAL SHEET

CHARTER FOR THE INDEPENDENT DATA MONITORING COMMITTEE

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

Independent Statistician Acknowledgement of Responsibilities:

PPD

PPD

PPD

, PhD

PPD

Date

San Mateo, CA 94403

Independent DMC Support Statistician

PPD

PPD

PPD

Date

San Mateo, CA 94403

Independent DMC Support Statistician

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1 INTRODUCTION AND BACKGROUND

1.1 Introduction

This charter describes the roles, responsibilities, and operating procedures of the independent Data Monitoring Committee (DMC) for the MDV3100-14 (PROSPER) protocol: A Multinational, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer. The DMC procedures will be in accordance with the Food and Drug Administration (FDA) Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The MDV3100-14 protocol is a placebo-controlled study designed to evaluate the efficacy and safety of enzalutamide compared with placebo and will be conducted globally in approximately 250 centers. The DMC will provide additional safety oversight to ensure that any significant and serious safety concerns are identified expeditiously. The DMC comprises individuals with relevant expertise who are external to the study and are not involved with the study conduct or with the sponsor. The DMC will provide independent safety oversight for the MDV3100-14 protocol patients and will advise the sponsor of the need for study modification or termination based on regular reviews of accumulating safety data.

An independent statistics unit that is external to the sponsor and not otherwise involved in the conduct of the study will analyze and report MDV3100-14 data to the DMC.

1.2 Background

Prostate cancer progresses through a series of characteristic clinical states that reflect both the natural history of the disease and response to treatment.[1] Following the initial evaluation and diagnosis of prostate cancer, approximately 90% of men undergo primary localized treatment with curative intent.[2] After initiation of androgen deprivation therapy in men with rising prostate-specific antigen (PSA) after primary therapy, the next clinical state in the current model of prostate cancer progression is that of castration-resistant prostate cancer (CRPC), defined as progression despite castrate hormone levels (testosterone < 50 ng/dL). CRPC is present in 10% to 20% of all men with prostate cancer, and is associated with a high risk of bone metastases, bone pain, pathologic fractures, spinal cord compression, decreased quality of life, and death from prostate cancer.

Currently, although continued use of androgen deprivation therapy is part of clinical practice, no medicine is approved for treatment of patients with nonmetastatic CRPC or for prevention of metastasis, and the results of several studies designed to address these needs have been disappointing.[3,4,5,6] Therefore, no standard of care is defined for nonmetastatic CRPC and accordingly, patients are encouraged to participate in clinical trials.[7]

The androgen receptor remains the main driver of prostate cancer progression in CRPC. Enzalutamide is a potent androgen receptor inhibitor that significantly prolonged overall survival in men with metastatic CRPC previously treated with docetaxel.[8] Patients with

nonmetastatic CRPC at high risk for metastatic disease may, therefore, also derive significant benefit from treatment with enzalutamide.

2 COMPOSITION AND RESPONSIBILITIES OF THE DMC

2.1 Composition of the DMC

The DMC is a multidisciplinary group that is external to the sponsor and consists of clinicians and a statistician. Collectively, these professionals have experience in the treatment of patients with prostate cancer, as well as experience in the conduct and monitoring of randomized clinical studies. In addition to its core membership, the DMC may request that outside consultants with specialized expertise (ie, a neurologist, cardiologist, hepatologist, etc) participate in 1 or more DMC meetings, or be available for consultation by the DMC chairperson (chair). The sponsor will facilitate access to the appropriate specialists by providing the DMC chair with the appropriate contact information.

DMC members must be free of apparent or actual conflicts of interest, which may be financial, scientific, personal, or regulatory in nature. DMC members may not own stock, stock options, or any equity position in the sponsor. For this purpose, the sponsor is defined as Medivation, Inc. and Astellas, Inc. DMC members must submit a financial disclosure form to the sponsor on an annual basis. The DMC members as a group will be responsible for deciding whether consultant agreements or financial interests of the members have the potential for conflict of interest. DMC members will be responsible for advising the sponsor of any changes that may lead to potential conflict of interest during the course of the study. If such changes have the potential to materially impact objectivity, the DMC member will be asked to resign and a replacement DMC member will be appointed by the sponsor in consultation with the DMC.

Every effort will be made to maintain the stability and continuity of the DMC throughout the study. However, if a member leaves the DMC, the sponsor will consult with the DMC chair and select a replacement. The departing member must return all study-related documents to the chair (or acting chair), and the incoming member will receive all information on previous DMC activities from the chair. The intended duration of DMC membership extends from the organizational meeting at the start of the study through study closure, database lock, and treatment unblinding.

2.2 Responsibilities of the DMC

The DMC is responsible for providing an independent and ongoing review of accumulated safety data approximately every 6 months during the study by blinded treatment group (ie, treatment A and B), unless a specific request to unblind is made by the DMC chair. Unscheduled ad hoc DMC meetings will be held if requested by the DMC chair or the sponsor. The DMC chair will also receive an updated summary of serious adverse events in the study by email on a monthly basis.

2.2.1 General Recommendations to the Sponsor

Through these safety reviews, the primary role of the DMC is to provide recommendations to the sponsor after each meeting in order to safeguard the interests and safety of participating and future study patients. These recommendations will be conveyed to the sponsor representative, Mohammad Hirmand MD, or designee, both verbally and in writing, and will generally consist of one of the following options:

- Continue the study as planned (with or without a request for additional data);
- Modify the study eligibility criteria or protocol procedures to enhance safety (with or without a request for additional data);
- Halt study enrollment or discontinue the study (with or without a request for additional data) for serious and unequivocal safety reasons.

To guide the committee recommendations regarding study discontinuation when mortality results are unfavorable, the independent statistics unit will be prepared to provide the results of a 1-sided unstratified log rank test at the 0.025 level for harm. The results of this test will be provided upon request of the DMC chair. This guideline will be nonbinding to allow complete interpretation of all safety results prior to the DMC issuing a recommendation on study continuance. Results of this interim testing will be used for assessing harm only and will not impact the type I error allocated for testing the primary endpoint.

It is important to note that the DMC may require additional analyses to make decisions regarding early study termination, and statistical methods alone may not be adequate to guide the decisions. The totality of the safety data will need to be taken into account in order for the DMC to make specific recommendations based on their collective expertise and judgment.

2.2.2 Data for DMC Review

At least 1 week before each DMC meeting, an unblinded statistician from the independent statistics unit will generate an electronic data package to send to the DMC members using password-protected files to maintain data confidentiality.

The independent statistics unit will receive aggregate study data from the sponsor and will prepare the appropriate tables by blinded treatment group according to the DMC statistical analysis plan. Specifically, the following safety variables will be monitored:

- Adverse events;
- Deaths;
- Serious adverse events;
- Adverse events leading to study drug discontinuation;
- Study drug discontinuations and reasons for discontinuation;
- Concomitant medications;

- Vital signs;
- Laboratory value shift tables;
- Abnormal laboratory values classified as grade ≥ 3 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4;
- Occurrences of accidental or intentional treatment unblinding;
- Study accrual and baseline data.

Although the data will be presented by blinded treatment group, the DMC may request treatment group unblinding if such information will materially affect recommendations regarding study continuation or protocol modification. In such a case, the treatment assignment will come from the independent statistics unit to the DMC chair electronically using password-protected files to maintain data confidentiality. Other study personnel, including study site investigators, will not be given the treatment assignment information unless required for urgent and optimal medical management of a study patient.

In addition to safety data, the DMC data package will also contain aggregate study data on overall enrollment and enrollment by region.

2.3 Responsibilities of the DMC Chair

In addition to the general responsibilities outlined above, the DMC chair will also be responsible for the following:

- Ensuring that the data received from the independent statistics unit is complete and in the appropriate form;
- Leading and facilitating discussions during both open and closed sessions and seeking consensus for DMC recommendations;
- Deciding whether a safety concern warrants an unscheduled ad hoc DMC meeting;
- Determining whether an outside consultant is required to fully assess a particular safety concern (eg, a cardiologist, hepatologist, or other specialist);
- Ensuring that the DMC recommendations or requests for additional data are clearly documented and communicated to the sponsor within 24 hours of the meeting;
- Upon request from the sponsor, providing a formal letter of recommendations from the DMC that can be used by study sites to obtain institutional review board/ethics committee renewals;
- Approving minutes to appropriately document both the open and closed sessions of the DMC meetings;
- Maintaining confidentiality of closed session reports and DMC data packages until after the study concludes, the database is locked, and the study blind is broken.

2.4 Responsibilities of DMC Members

In addition to the general responsibilities outlined above, the DMC members will also be responsible for the following:

- Approving minutes to appropriately document both the open and closed sessions of the DMC meetings;
- Maintaining confidentiality of closed session reports and DMC data packages until after the study concludes, the database is locked, and the study blind is broken.

2.5 Responsibilities of the Sponsor

The sponsor will ensure that data packages are distributed to the DMC members at least 1 week in advance of a scheduled DMC meeting. In the event an in-person face-to-face meeting is requested by the DMC, the sponsor is responsible for selecting the meeting venue, arranging transportation, and providing accommodations.

The sponsor will be responsible for providing the DMC with general information about study progress and for alerting the DMC about any new data arising from other clinical or nonclinical studies of enzalutamide that may have safety implications for study participants.

2.6 Responsibilities of the Independent Statistics Unit

At the time of each safety meeting, the independent statistics unit will execute the statistical analysis plan as specified by the DMC and the sponsor. The independent statistics unit will prepare and distribute the data reports for the open and closed sessions within a prespecified timeline agreed upon with the sponsor, by courier or by secured electronic transfer with password protection. All distributed material will be clearly marked as confidential.

The independent statistics unit will be responsible for providing secure teleconference numbers, including one each for the open and closed sessions, in advance of each meeting to be conducted by phone. The teleconference number for the closed session will be provided to the DMC members only and not to the sponsor.

An independent statistician from the independent statistics unit (or designee) will attend scheduled and unscheduled DMC meetings as a nonvoting participant. This participant will record minutes and provide them to the DMC members for editing and approval. The independent statistics unit will keep a log of all materials provided to the DMC members. This log will be provided to the sponsor at the conclusion of the study. In addition, the independent statistics unit will keep all closed session reports and DMC packages until the study has concluded, the database is locked and the study blind is broken.

3 DMC MEETING SCHEDULE

3.1 Initial Organizational Meeting

The first DMC meeting will be an organizational meeting. At this meeting, the DMC will review the background information on enzalutamide, the MDV3100-14 protocol, the draft DMC charter, and the DMC statistical analysis plan.

3.2 Scheduled Safety Review Meetings

Approximately every 6 months after the first 50 patients are enrolled and have reached the week 17 assessment, the DMC will review all available safety data. Data packages will be prepared and sent in a secure manner to the DMC members in advance of meetings. All members should review the materials before the meetings. Meetings may occur via teleconference or in person at the discretion of the DMC chair or sponsor; however, if a safety concern arises such that termination or substantial modification of the study is likely to be discussed, then the meeting should be in person.

3.3 Unscheduled Safety Review Meetings

The DMC chair may request an ad hoc DMC meeting and will outline the specific data required for review, and will clarify whether unblinding is necessary. The sponsor will then alert the independent statistics unit to prepare the requested data as promptly as possible and deliver it to the DMC members.

4 DMC MEETING FORMAT

4.1 Meeting Quorum

The DMC will begin each scheduled and ad hoc safety review meeting by determining whether there is sufficient representation and expertise for a quorum. For this study, a quorum will be defined as a minimum of 3 DMC members including the chair, a statistician, and 1 other committee member. If the DMC chair is unable to attend a specific meeting, the chair may appoint another DMC member to temporarily assume the chair responsibilities to ensure a quorum. Unless unforeseen, the sponsor should be notified of this change in advance of the DMC meeting.

4.2 Open Session

Each scheduled and ad hoc safety review meeting will begin with an open session. The primary purpose of this session is for the sponsor to provide up-to-date enrollment information to the DMC and answer any questions about study conduct. The sponsor will inform the DMC of any additional clinical or nonclinical data generated in other studies that may have safety implications relevant to MDV3100-14. Non-DMC member participants in the open session may include sponsor study team members as appropriate and an independent statistician from the independent statistics unit. The independent statistician will document the topics discussed in the open session report, which will be provided to the sponsor.

4.3 Closed Session

The second part of each meeting will be a closed session, with only DMC members and the nonvoting statistician from the independent statistics unit in attendance. The primary purpose of the closed session is to discuss the safety data package and formulate recommendations regarding study conduct. The DMC chair will strive to generate consensus among DMC members regarding the formal recommendation; however, if the decision is not unanimous, then recommendations will be based on majority vote. The independent statistician will document the topics discussed during the closed session in the closed session report, which will be kept confidential from the study sponsor until after the study has concluded and the randomization code blind is broken. The nonvoting independent statistics unit statistician will record minutes and provide them to the DMC members for review and approval by the chair.

4.4 Recommendations

Once the DMC concludes and the closed session reaches a decision, the DMC chair will contact the sponsor and verbally convey the committee recommendation as well as request any follow-up information. Within 24 hours of the DMC meeting, this verbal communication will be followed by written communication to the sponsor representative as noted in Section 2.2.1.

5 COMMUNICATIONS

All communication should be appropriately documented, and the DMC members as well as the independent statistics unit should maintain all documentation between parties until after the sponsor breaks the study blind. After study data unblinding, all documentation will then be transferred to the sponsor for final archiving.

5.1 Between the DMC and the Independent Statistics Unit

Any communication between the DMC and the independent statistics unit that includes unblinded information or aggregate data by treatment group will occur in the absence of the sponsor or other personnel involved with the study. Aside from submission of regular safety data reports, communication may include clarification of the safety reports, as well as any requests for additional statistical analyses that may aid the interpretation of the data presented. The independent statistics unit will provide any additional information that the DMC requests to the DMC in a timely fashion. The DMC chair and the statistician from the independent statistics unit are the primary points of contact.

5.2 Between the DMC and the Sponsor

Communication between the DMC and the sponsor may not involve any unblinded study information or aggregate information by treatment group. Communication may include any administrative or procedural issues relating to the DMC, information on study conduct and enrollment, blinded safety information, and DMC recommendations. The DMC chair and the sponsor medical monitor are the primary points of contact.

5.3 Between the Sponsor and the Independent Statistics Unit

Communication between the independent statistics unit and the sponsor may not involve any unblinded study information or aggregate information by treatment group. For scheduled and unscheduled meetings, the sponsor will work with the independent statistics unit to set up meetings and associated logistics, and to facilitate the transfer of blinded study data. If the DMC chair requests additional data or analyses, the sponsor may facilitate the performance of the analyses by the independent statistics unit or provide any needed data in a blinded fashion. The sponsor statistician and the independent statistician are the primary points of contact.

5.4 Between the DMC Chair and the FDA or Other Competent Authority

If for any reason, the DMC desires a direct communication between the DMC chair and the FDA or other regulatory authority, then the DMC chair must first communicate and discuss such a desire with the sponsor.

6 REFERENCES

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