Study Title: PREVAIL: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients with Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy

Protocol Number: MDV3100-03

Investigational Product: Enzalutamide (formerly MDV3100)

Indication: Prostate Cancer

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Original Protocol Date: Version 1.0 – 09 June 2010
Amendment 1: Version 2.0 – 27 August 2010
Amendment 2: Version 3.0 – 29 March 2011
Amendment 3: Version 4.0 – 23 July 2012
Amendment 4: Version 5.0 – 14 March 2013

Confidentiality Statement:
The information contained in this document and all information provided to you related to MDV3100 are the confidential and proprietary information of Medivation, Inc. (“Medivation”) and except as may be required by federal, state or local laws or regulations, may not be disclosed to others without prior written permission of Medivation. The Principal Investigator may, however, disclose such information to supervised individuals working on the Drug, provided such individuals agree to be bound to maintain the confidentiality of such Drug information.

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.
Medivation, Inc.
CLINICAL RESEARCH PROTOCOL

PREVAIL: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients with Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy

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2. SYNOPSIS

<table>
<thead>
<tr>
<th>TITLE OF STUDY:</th>
<th>PREVAIL: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients with Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTOCOL NUMBER:</td>
<td>MDV3100-03</td>
</tr>
<tr>
<td>LOCATION:</td>
<td>Multinational</td>
</tr>
<tr>
<td>STUDY CENTERS:</td>
<td>Approximately 225</td>
</tr>
<tr>
<td>PHASE:</td>
<td>3</td>
</tr>
<tr>
<td>OPEN-LABEL PERIOD:</td>
<td>Following the independent Data Monitoring Committee recommendation to halt the double-blind period of the study due to compelling clinical benefit of MDV3100 (enzalutamide) over placebo for the coprimary endpoints of overall survival (hazard ratio 0.70, p &lt; 0.0001) and radiographic progression-free survival (hazard ratio 0.19, p &lt; 0.0001), all ongoing enzalutamide-treated patients and ongoing and previous placebo-treated patients will be offered the opportunity to receive open-label study drug and continue in this protocol. The data collected during the open-label period will be limited to safety assessments, survival status, skeletal-related events, and new prostate cancer therapies. Long-term follow-up data (survival status, skeletal-related events, and new prostate cancer therapies) will be collected every 12 weeks up to at least 5 years after the last patient randomized or until the study average survival follow-up time from randomization is 5 years, whichever is first. These data will be used to perform a 5-year landmark analysis of survival rate. The complete details for the conduct of the open-label period are provided in Supplement 1: Open-Label Period. Patients who do not participate in the open-label period or withdraw consent for further treatment will continue long-term follow-up assessments per protocol.</td>
</tr>
<tr>
<td>DOUBLE-BLIND PERIOD:</td>
<td>The completed double-blind protocol remains unchanged. The double-blind period will conclude at the time of database lock and the open-label period will commence at the time of data unblinding.</td>
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<tr>
<td>STUDY OBJECTIVES:</td>
<td>Co-Primary Objectives: \n</td>
</tr>
<tr>
<td>Primary:</td>
<td></td>
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<tr>
<td>Secondary:</td>
<td></td>
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</table>
Exploratory Objectives:

- To determine the safety of treatment with MDV3100 as compared to placebo.
- To evaluate quality of life using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and the European Quality of Life 5-Domain Scale (EQ-5D) instruments;
- To evaluate emergence of pain relative to baseline at 6 months using the Brief Pain Inventory for MDV3100 versus placebo;
- To determine the benefit of MDV3100 as compared to placebo as assessed by time to first subsequent antineoplastic therapy (cytotoxic or hormonal);
- To determine the benefit of MDV3100 as compared to placebo as assessed by PSA response ≥ 90%;
- To characterize MDV3100 exposure (e.g., minimum or trough plasma concentrations [C_{min}]);
- To collect pharmacokinetics (PK) data that will be combined with data from other studies in a population PK model.

STUDY SCHEMATIC:

METHODS:

This study is a multinational Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral enzalutamide (formerly MDV3100, as used throughout this protocol) (160 mg/day) in asymptomatic or mildly symptomatic patients with progressive metastatic prostate cancer who have disease progression despite androgen deprivation therapy. Patients must not have been previously treated with cytotoxic chemotherapy. Approximately 1,680 patients will be centrally randomized 1:1. Randomization will be stratified by investigative site. Study drug therapy should be continued as long as the patient is tolerating the study drug and continues androgen deprivation therapy (i.e., surgical castration or ongoing gonadotropin releasing hormone [GnRH] analogue therapy) until confirmed radiographic disease progression or a skeletal-related event AND one of the two following events: 1) initiation of cytotoxic chemotherapy; or 2) initiation of an investigational agent or cytotoxic chemotherapy, whichever comes first. Study visits will occur every 12 weeks beginning at Week 49. Long Term Follow-Up visits will occur after Study Drug discontinuation per frequency of scheduled visits.

The following assessments of prostate cancer status will be collected during the course of the trial: overall survival, soft tissue disease on computed tomography (CT) scan or on magnetic resonance imaging (MRI), bone disease on radionuclide bone scans, skeletal-related events, Brief Pain Inventory, FACT-P and EQ-5D quality of life questionnaires, and PSA.
The consensus guidelines of the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) and the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) have been taken into consideration for the determination of radiographic disease progression. Radiographic disease progression is defined by RECIST 1.1 for soft tissue disease, or the appearance of two or more new bone lesions on bone scan (PCWG2). The documentation required for the determination of radiographic disease progression is listed in Table 1.

<table>
<thead>
<tr>
<th>Date Progression Detected (Visit)</th>
<th>Criteria for Progression</th>
<th>Criteria for Confirmation of Progression (requirement and timing)</th>
<th>Criteria for Documentation of Disease Progression on Confirmatory Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 9</strong></td>
<td>Bone lesions: 2 or more new lesions compared to baseline bone scan by PCWG2.</td>
<td>Timing: at least 6 weeks after progression identified or at Week 17 visit.</td>
<td>Two or more new bone lesions on bone scan (compared to Week 9 scan).</td>
</tr>
<tr>
<td></td>
<td>Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.</td>
<td>Confirmation required for soft tissue disease (scan of same modality as demonstrated progression).</td>
<td>Confirmation of progressive soft tissue disease by RECIST 1.1.</td>
</tr>
<tr>
<td><strong>Week 17</strong></td>
<td>Bone lesions: Two or more new lesions on bone scan compared to Week 9 bone scan.</td>
<td>Timing: at least 6 weeks after progression identified or at Week 25 visit. Required for bone lesions observed on bone scan.</td>
<td>Persistent or increase in number of bone lesions on bone scan compared to Week 17 scan.</td>
</tr>
<tr>
<td></td>
<td>Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.</td>
<td>No confirmatory scan required for soft tissue disease progression.</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Week 25 or later</strong></td>
<td>Bone lesions: Two or more new lesions compared to Week 9 bone scan.</td>
<td>Timing: at least 6 weeks after progression identified. Required for bone lesions observed on bone scan.</td>
<td>Persistent or increase in number of lesions on bone scan compared to prior scan.</td>
</tr>
<tr>
<td></td>
<td>Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.</td>
<td>No confirmatory scan required for soft tissue disease.</td>
<td>n/a</td>
</tr>
</tbody>
</table>

* Progression detected by bone scan at an unscheduled visit either prior to Week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan. Progression detected by CT/MRI at an unscheduled visit prior to Week 13 will require a confirmatory scan at least 6 weeks later whereas progression on or after Week 13 does not require confirmation.

* Confirmation must occur at the next available scan.

* For confirmation, at least two of the lesions first identified as new must be present at the next available scan (confirmation scan).

n/a, not applicable.

Study films (CT/MRI and bone scan) should be read on site and also be submitted in digital format to the central imaging contract research organization for an independent central radiology review. Each site should designate a radiologist or investigator to ensure that all images are read according to RECIST 1.1 and PCWG2, as specified by the protocol. Radiographic imaging is not required after radiographic progression has been confirmed according to protocol specifications. Note that determination of radiographic progression should be confirmed by the central independent radiology review prior to stopping radiographic imaging until the time that at least 410 rPFS events are confirmed as required for the primary PFS analysis. After this time, radiographic progression should be confirmed by the local radiology review prior to stopping radiographic imaging. However, scans should continue to be sent to the central imaging contract research organization for archiving.
Throughout the study, safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs). An independent Data Monitoring Committee will monitor safety data on an ongoing basis.

Patients will have a Safety Follow-up visit 28 days after their last dose of study drug or prior to initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first. All patients are to be followed for survival status, skeletal-related events, and subsequent treatments for prostate cancer.

**Number of Patients:** Approximately 1,680 (840 MDV3100 and 840 placebo)

### Inclusion Criteria:
Patients eligible to participate in this study are those who meet all of the following inclusion criteria:

1. Age 18 or older and willing and able to provide informed consent;
2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features;
3. Ongoing androgen deprivation therapy with a GnRH analogue or bilateral orchiectomy (i.e., surgical or medical castration);
4. Patients who have not had a bilateral orchiectomy, must have a plan to maintain effective GnRH-analogue therapy for the duration of the trial;
5. Serum testosterone level $\leq 1.73$ nmol/L (50 ng/dL) at the Screening visit;
6. Patients receiving bisphosphonate therapy must have been on stable doses for at least 4 weeks;
7. Progressive disease at study entry defined as one or more of the following three criteria that occurred while the patient was on androgen deprivation therapy as defined in eligibility criterion #3:
   - PSA progression defined by a minimum of two rising PSA levels with an interval of $\geq 1$ week between each determination. Patients who received an anti-androgen must have progression after withdrawal ($\geq$ 4 weeks since last flutamide or $\geq$ 6 weeks since last bicalutamide or nilutamide). The PSA value at the Screening visit should be $\geq 2 \mu g/L$ (2 ng/mL);
   - Soft tissue disease progression defined by RECIST 1.1;
   - Bone disease progression defined by PCWG2 with two or more new lesions on bone scan;
8. Metastatic disease documented by bone lesions on bone scan or by measurable soft tissue disease by CT/MRI. Patients whose disease spread is limited to regional pelvic lymph nodes are not eligible;
9. No prior cytotoxic chemotherapy for prostate cancer;
10. Asymptomatic or mildly symptomatic from prostate cancer (i.e., the score on Brief Pain Inventory – Short Form Question #3 must be $< 4$);
11. Eastern Cooperative Oncology Group (ECOG) performance status of 0–1;
12. Estimated life expectancy of $\geq 6$ months;
13. Able to swallow the study drug and comply with study requirements.

### Exclusion Criteria:
Patients must NOT meet any of the following exclusion criteria:

1. Severe concurrent disease, infection, or co-morbidity that, in the judgment of the Investigator, would make the patient inappropriate for enrollment;
2. Known or suspected brain metastasis or active leptomeningeal disease;
3. History of another malignancy within the previous 5 years other than curatively treated non-melanomatous skin cancer;
4. Absolute neutrophil count $< 1,500/\mu L$, or platelet count $< 100,000/\mu L$, or hemoglobin $< 5.6$ mmol/L (9 g/dL) at the Screening visit (NOTE: patients may not have received any growth factors within 7 days or blood transfusions within 28 days of the hematologic laboratory values obtained at the Screening visit);
5. Total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 2.5$ times the upper limit of normal at the Screening visit;
6. Creatinine $> 177$ μmol/L (2 mg/dL) at the Screening visit;
7. Albumin $< 30$ g/L (3.0 g/dL) at the Screening visit;
8. History of seizure or any condition that may predispose to seizure. Also, history of loss of consciousness
or transient ischemic attack within 12 months of enrollment (Day 1 visit);

9. Clinically significant cardiovascular disease including:
   - Myocardial infarction within 6 months;
   - Uncontrolled angina within 3 months;
   - Congestive heart failure New York Heart Association (NYHA) class III or IV, or patients with
     history of congestive heart failure NYHA class III or IV in the past, unless a screening
     echocardiogram or multi-gated acquisition scan performed within 3 months results in a left
     ventricular ejection fraction that is ≥ 45%;
   - History of clinically significant ventricular arrhythmias (e.g., 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 the
     Screening visit;
   - Bradycardia as indicated by a heart rate of < 50 beats per minute on the Screening ECG;
   - Uncontrolled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood
     pressure > 105 mm Hg at the Screening visit;

10. Gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease within last
    3 months);

11. Major surgery within 4 weeks of enrollment (Day 1 visit);

12. Use of opiate analgesics for pain from prostate cancer within 4 weeks of enrollment (Day 1 visit);

13. Radiation therapy for treatment of the primary tumor within 3 weeks of enrollment (Day 1 visit);

14. Radiation or radionuclide therapy for treatment of metastasis;

15. Treatment with flutamide within 4 weeks of enrollment (Day 1 visit);

16. Treatment with bicalutamide or nilutamide within 6 weeks of enrollment (Day 1 visit);

17. Treatment with 5-α reductase inhibitors (finasteride, dutasteride), estrogens, cyproterone within 4 weeks
    of enrollment (Day 1 visit);

18. Treatment with systemic biologic therapy for prostate cancer (other than approved bone targeted agents
    and GnRH-analogue therapy) or other agents with anti-tumor activity within 4 weeks of enrollment
    (Day 1 visit);

19. History of prostate cancer progression on ketoconazole;

20. Prior use, or participation in a clinical trial, of an investigational agent that blocks androgen synthesis
    (e.g., abiraterone acetate, TAK-700, TAK-683, TAK-448) or targets the androgen receptor (e.g., BMS
    641988);

21. Participation in a previous clinical trial of MDV3100;

22. Use of an investigational agent within 4 weeks of enrollment (Day 1 visit);

23. Use of herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease
    PSA levels (e.g., saw palmetto) or systemic corticosteroids greater than the equivalent of 10 mg of
    prednisone per day within 4 weeks of enrollment (Day 1 visit);

24. Any condition or reason that, in the opinion of the Investigator, interferes with the ability of the patient to
    participate in the trial, which places the patient at undue risk, or complicates the interpretation of safety
    data.

**TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:**

The investigational product evaluated in this study is MDV3100; the chemical name is 3-(4-cyano-3-
trifluoromethylphenyl)-1-[3-fluoro-4-(methylcarbamoyl)phenyl]-5,5-dimethyl-2-thioxoimidazolin-4-one.
MDV3100 is provided as 40 mg soft gelatin capsules and is indicated at a dose of 160 mg/day administered
orally once daily in this protocol. MDV3100 can be taken with or without food.
DURATION OF TREATMENT:
Study drug therapy should be continued as long as the patient is tolerating the study drug and continues androgen deprivation therapy (i.e., surgical castration or ongoing GnRH-analogue therapy) until confirmed radiographic disease progression or a skeletal-related event AND one of the two following events:
1) initiation of cytotoxic chemotherapy; or 2) initiation of an investigational agent for treatment of prostate cancer.

Reference Therapy, Dose, and Mode of Administration:
Placebo capsules that are identical in appearance to MDV3100 will be administered in the same manner and frequency as MDV3100.

CRITERIA FOR EVALUATION:
Efficacy:
The co-primary efficacy outcomes include:
- A comparison of overall survival between the MDV3100-treated and the placebo groups;
- A comparison of rPFS between the MDV3100-treated and the placebo groups.
Secondary efficacy outcomes include:
- A comparison of the time to first skeletal-related event between the MDV3100-treated and the placebo groups;
- A comparison of the time to initiation of cytotoxic chemotherapy between the MDV3100-treated and the placebo groups;
- A comparison of the time to PSA progression between the MDV3100-treated and the placebo groups;
- A comparison of PSA response ≥ 50% between the MDV3100-treated and the placebo groups;
- A comparison of best overall soft tissue response between the MDV3100-treated and the placebo groups.
Exploratory efficacy outcomes include:
- FACT-P and EQ-5D data summarized descriptively;
- A comparison of the rate of pain progression, defined as increase of ≥ 30% from baseline in the average of Brief Pain Inventory pain intensity item scores (items 3, 4, 5, and 6) at 6 months between the MDV3100-treated and the placebo groups;
- A comparison of the time to first subsequent antineoplastic therapy (cytotoxic or hormonal) between the MDV3100-treated and the placebo groups;
- A comparison of PSA response ≥ 90% between the MDV3100-treated and the placebo groups.

Safety:
The safety of MDV3100 will be assessed by the frequency of serious adverse events, frequency and severity of adverse events, frequency of study drug discontinuation due to adverse events, as well as the frequency of new clinically significant changes in physical exam findings, vital signs, laboratory values, and ECGs.

Pharmacokinetics:
Exposure to MDV3100 and possibly its metabolites will be evaluated by analysis of $C_{min}$ data.

STATISTICAL METHODS:
Efficacy Analyses:
The efficacy analyses will be conducted using an Intent-to-Treat (ITT) population defined as all randomized patients.
Co-Primary Efficacy Endpoints:
The total type I error rate for this study is 0.05 (two-sided) and will be allocated between two co-primary efficacy endpoints: 0.049 for overall survival and 0.001 for rPFS.
Overall Survival: Time from randomization to death due to any cause will be assessed. The primary analysis of overall survival will be performed when at least a total of 765 deaths have been reported. A formal interim analysis for overall survival will be performed at approximately 516 deaths or 67% of the required total number of death events for the primary overall survival analysis. A two-stage group sequential design with Lan-DeMets alpha-spending function determined by means of the O'Brien-Fleming approach will be used to allocate the overall type I error rate, 0.049, between the single interim analysis and the primary analysis of overall survival. An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups for both the interim and final analyses.

Radiographic Progression-Free Survival: Time from randomization to the first objective evidence of radiologic progression or death due to any cause within 168 days after treatment discontinuation, (whichever occurs first) will be assessed. Radiographic disease progression is defined by the criteria in Table 1. The primary analysis of rPFS will be based upon at least the first 410 rPFS events observed and will be conducted at the time of the formal interim analysis of overall survival. An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups at the significance level of 0.001 (two-sided). The trial will be continued until the primary analysis of the overall survival co-primary endpoint has been completed.

Secondary Efficacy Endpoints:

1. Time to First Skeletal-Related Event: Time from randomization to first skeletal-related event will be assessed. A skeletal-related event is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups;

2. Time to Initiation of Cytotoxic Chemotherapy: Time from randomization to initiation of cytotoxic chemotherapy will be assessed. An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups;

3. Time to PSA Progression: PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 μg/L (2 ng/mL) above the nadir (or baseline value for patients who did not have a decline in PSA value at Week 13). This increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later. Time from randomization to first observation of PSA progression will be assessed. An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups;

4. PSA Response ≥ 50%: Confirmed PSA responses will be defined as ≥ 50% reductions in PSA from baseline to lowest postbaseline PSA result, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response. PSA response ≥ 50% will be calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment. An unstratified Cochran-Mantel-Haenszel mean score test will be used to compare the response rates between the MDV3100-treated and the placebo groups;

5. Best Overall Soft Tissue Response: The best overall soft tissue response as assessed by investigators using RECIST 1.1 will be summarized. Only patients with measurable soft tissue disease at screening (i.e., at least 1 target lesion per RECIST 1.1) will be included in this analysis. A Cochran-Mantel-Haenszel mean score test will be used to compare the proportion of patients with an objective response (complete response or partial response) per RECIST 1.1 between the MDV3100-treated and the placebo groups.

Exploratory Efficacy Endpoints:

1. FACT-P Quality of Life: The FACT-P data will be summarized descriptively by study visit;

2. EQ-5D Quality of Life: The EQ-5D data will be summarized descriptively by study visit;

3. Pain Score per Brief Pain Inventory: The rate of pain progression, defined as increase of ≥ 30% from baseline in the average of Brief Pain Inventory pain intensity item scores (items 3, 4, 5, and 6) at 6 months will be used to compare the MDV3100-treated and the placebo groups. The Brief Pain Inventory pain score will be summarized descriptively at baseline, 3 months, and 6 months;

4. Time to First Subsequent Antineoplastic Therapy (Cytotoxic or Hormonal): An unstratified log-rank test will be used to compare this endpoint between the MDV3100-treated and the placebo groups at the significance level of 0.05 (two-sided);

5. PSA Response ≥ 90%: Defined similarly to PSA response ≥ 50%, an unstratified Cochran-Mantel-Haenszel mean score test at the significance level of 0.05 (two-sided) will be used to compare this endpoint between the MDV3100-treated and the placebo groups.
Safety Analyses:
Safety will be assessed through summaries of adverse events, laboratory evaluations, vital signs, physical examinations, and ECGs. Safety analyses will be based on all randomized patients who receive at least 1 dose or partial dose of study drug (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all adverse events is to be evaluated by the Investigator based on the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 and will be coded to preferred term, higher level 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 rather than inferential statistics.

Laboratory values also will be classified by toxicity grade based on the National Cancer Institute’s CTCAE, version 4.0. Laboratory shift tables of the baseline results to each of the subsequent visits will be produced.

An independent Data Monitoring Committee will monitor all available safety data, including survival data, on an ongoing basis during this trial.

Other Analyses:
The PK data analyses will include calculation of parametric and/or non-parametric descriptive statistics of the $C_{min}$ data for MDV3100 and possibly one or more metabolites. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately.
## 2.1 Study Schedule of Activities

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Screening Visit</th>
<th>1</th>
<th>29</th>
<th>57</th>
<th>85</th>
<th>113</th>
<th>141</th>
<th>169</th>
<th>197 &amp; 225</th>
<th>253</th>
<th>281 &amp; 309</th>
<th>337 &amp; every subsequent 84 days</th>
<th>Safety F/U</th>
<th>Unscheduled Visit</th>
<th>Long-Term F/U</th>
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<tbody>
<tr>
<td>Week</td>
<td>~4 to ~1 (28 days)</td>
<td>1</td>
<td>5</td>
<td>9</td>
<td>13</td>
<td>17</td>
<td>21</td>
<td>25</td>
<td>29 &amp; 33</td>
<td>37</td>
<td>41 &amp; 45</td>
<td>49 and every subsequent 12 weeks</td>
<td>n/a</td>
<td>n/a</td>
<td>± 7</td>
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<td>Window (days)</td>
<td>± 3</td>
<td>± 3</td>
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<td>± 7</td>
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<td>± 7</td>
<td>28 Days after last dose</td>
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<th>169</th>
<th>197 &amp; 225&lt;sup&gt;c&lt;/sup&gt;</th>
<th>253</th>
<th>281 &amp; 309&lt;sup&gt;e&lt;/sup&gt;</th>
<th>337 &amp; every subsequent 84 days</th>
<th>Safety F/U</th>
<th>Unscheduled Visit&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>29 &amp; 33</td>
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<td>41 &amp; 45</td>
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<sup>a</sup> Assessment may be completed by telephone.

<sup>b</sup> Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient’s request or if deemed necessary by the Investigator.

<sup>c</sup> Beginning after Study Drug discontinuation, all patients MUST undergo long-term follow-up to assess for survival, subsequent treatments for prostate cancer, skeletal-related events, and radiographic progression. Visit schedule will follow schedule of events.

<sup>d</sup> Or prior to initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first.

<sup>e</sup> The informed consent must be signed within 6 weeks of randomization; otherwise the Screening visit must be repeated.

<sup>f</sup> A brief physical examination is required at each visit, with the exception of the Screening visit during which a complete physical examination will be completed.

<sup>g</sup> A single ECG will be taken at specified study visits, with the exception of the Day 1 visit during which three ECGs will be obtained during a 15-minute interval.

<sup>h</sup> If medically indicated.

<sup>i</sup> Laboratory assessments include serum chemistries, urinalysis, and hematology.

<sup>j</sup> Genotyping samples will only be collected from patients who agree to provide genotyping samples as documented by signing a separate Genotyping informed consent form.

<sup>k</sup> In the event of unusual PK patterns or safety findings, genotype analysis of relevant drug metabolism and transporter genes will be conducted. If there is no requirement for analysis, the whole blood sample will be destroyed.

<sup>l</sup> All protocol-specified PSAs are to be done at local laboratories.

<sup>m</sup> PK samples will be drawn pre-dose at Week 5, 13, 25, and at adverse event-related unscheduled visits prior to Week 25. Patients should hold their dose of study drug on these visit days and should be instructed to take their study drug after the PK sample is drawn. At each study visit with a PK draw, patients will be asked the time that study drug was taken on the preceding 2 days.

<sup>n</sup> The abdominopelvic CT scan or MRI, bone scan, chest x-ray or chest CT must occur within 6 weeks of randomization; otherwise the Screening visit must be repeated.

<sup{o}</sup> The window for all radiological (CT/MRI) assessments is ± 7 days. At Weeks 9, 17, and 25 all other procedures must be completed within the ± 3 day window.

<sup>p</sup> Disease progression observed by CT or MRI for soft tissue disease on Week 17 or later (or Week 13 or later if done during an unscheduled visit) does not require a confirmatory scan.

<sup>q</sup> Chest CT is required at all imaging time points, if screening chest x-ray demonstrates metastatic chest disease.

<sup>r</sup> The Brief Pain Inventory will assess pain related to prostate cancer only.

<sup>s</sup> Serious adverse events will be collected from the time the patient signs the consent form until the end of the safety reporting period (or until screen failure). Non-serious adverse events will be collected from the time of first study drug dosing until the end of the safety reporting period. The safety reporting period ends at the time of the Safety Follow-up visit, 28 days after last dose of study drug, or initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first.

<sup>t</sup> For study visit days, patients will self administer study drug upon instruction from the staff.
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<td>Liter</td>
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<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<td>mg</td>
<td>Milligram</td>
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<td>Abbreviation</td>
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<td>mL</td>
<td>Milliliter</td>
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<td>mm Hg</td>
<td>Millimeters of Mercury</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>ng</td>
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<td>New York Heart Association</td>
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<td>PCWG2</td>
<td>Prostate Cancer Clinical Trials Working Group 2</td>
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<td>Prostate-Specific Antigen</td>
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<td>Pregnane X Receptor</td>
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<td>Red Blood Cells</td>
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<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumors</td>
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<td>rPFS</td>
<td>Radiographic Progression-Free Survival</td>
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<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<td>(t_{1/2})</td>
<td>Half-Life</td>
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<td>(\mu g)</td>
<td>Microgram</td>
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<td>UGT</td>
<td>Uridine 5'-diphospho-glucuronosyltransferase</td>
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<td>Micromoles per Liter</td>
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<td>WBC</td>
<td>White Blood Cell Count</td>
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<td>WHO-DD</td>
<td>World Health Organization Drug Dictionary</td>
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<td>WMA</td>
<td>World Medical Association</td>
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5. ETHICS

5.1 Institutional Review Board or Independent Ethics Committee

Prior to initiating the study, the Investigator will obtain written confirmation from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that the IRB/IEC is properly constituted and compliant with all requirements and all local regulations. A copy of the confirmation will be provided to the sponsor, Medivation, Inc. The Investigator will provide the IRB/IEC with all appropriate material, including the protocol, current Investigator’s Brochure, the informed consent document, and other written information provided to the patients. The trial will not be initiated until appropriate IRB/IEC approval of the protocol and the informed consent document and all recruiting materials are obtained in writing by the Investigator and copies are received by Medivation. IRB/IEC approval will be obtained for any protocol amendments and informed consent revisions before implementing the changes. Appropriate reports on the progress of the study will be made to the IRB/IEC and to Medivation (or designee) by the Investigator in accordance with applicable governmental regulations and in agreement with policy established by Medivation and the IRB/IEC.

5.2 Ethical Conduct of the Study

This study will be conducted under the principles of the World Medical Association (WMA) Declaration of Helsinki under its most recent amendment (by the 59th WMA General Assembly, Seoul, Korea October 2008, noting the prior Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002 and on Paragraph 30 added by the WMA General Assembly, Tokyo 2004), and including Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines. Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an IRB/IEC; the study will be conducted by scientifically and medically qualified persons; the 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; each patient will give his or her written, informed consent before any protocol-specific tests or evaluations are performed.

5.3 Patient Information and Informed Consent

A properly executed, written, informed consent, in compliance with the Declaration of Helsinki, ICH GCP, United States (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 prior to entering the patient into the trial. The Investigator will prepare the informed consent form and provide the documents to Medivation (or designee) for approval prior to submission to the IRB/IEC. Medivation and the IRB/IEC must approve the documents before they are implemented. The Investigator will provide copies of the signed informed consent form to each patient and will maintain copies in the patient’s record file.
6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to study initiation, the Investigator at each site will have provided to Medivation or designee a fully executed and signed Food and Drug Administration (FDA) Form 1572, current curriculum vitae, and a Financial Disclosure Form. Financial Disclosure Forms must also be completed for all Sub-Investigators listed on the Form 1572 who will be directly involved in the treatment or evaluation of research patients in this study.

The study will be managed and monitored by employees or authorized representatives of Medivation, Inc. The Study Monitor will visit the study sites on a periodic basis and perform verification of source documentation for each patient as described in the monitoring plan. Medivation will be responsible for the timely reporting of serious adverse events to applicable regulatory authorities.

7. INTRODUCTION

7.1 Prostate Cancer

Worldwide, prostate cancer ranks third in cancer incidence and sixth in cancer mortality in men. Prostate cancer growth is dependent on androgens, and depleting or blocking androgen action has been a mainstay of treatment for over 6 decades. Hormonal therapies include gonadotropin-releasing hormone (GnRH) analogues, anti-androgens, ketoconazole, and estrogenic compounds. Despite the early sensitivity of tumors to hormonal strategies, tumors that progress despite androgen deprivation generally represent a transition to the lethal variant of the illness, and most patients ultimately succumb to this disease.1, 2

Results of clinical investigations and studies on the molecular profiles of these progressing tumors show that the androgen receptor remains functional and that the tumors should respond to strategies directed at the androgen receptor signaling axis. Overexpression of the androgen receptor has been documented in upwards of 50% of such prostate cancer specimens and is believed to contribute to tumor progression.3, 4 In addition, currently approved anti-androgens have the potential to act as a partial agonist and stimulate androgen receptor signaling in the setting of androgen receptor overexpression, therefore exacerbating or accelerating tumor growth. The decline in serum levels of prostate-specific antigen (PSA) seen upon discontinuation of these agents is consistent with the agonist effects (“anti-androgen withdrawal syndrome”).

In clinical practice, treatment of advanced prostate cancer is therefore limited by the development of resistance to anti-androgen therapies. Most patients receive two or more hormonal manipulations and are then offered chemotherapy as they continue to progress and develop symptoms.5 A randomized trial comparing docetaxel administered every 3 weeks vs. docetaxel weekly vs. mitoxantrone has shown a modest survival benefit for docetaxel every 3 weeks, but this response is not durable.6 In addition, cytotoxic chemotherapy has significant treatment-related toxicities when compared to hormonal and other non-cytotoxic therapies. Once patients progress on docetaxel, there is currently no approved second-line therapy. Because overexpression of the androgen receptor is a common feature of progressive prostate cancer, second generation anti-androgen therapies that are more potent and that are pure antagonists may be effective in such patients.
The purpose of this study is to evaluate the efficacy and safety of enzalutamide (formerly MDV3100, as used throughout this protocol), a novel potent androgen-receptor antagonist without known agonist activity, in asymptomatic or mildly symptomatic patients with progressive metastatic prostate cancer who have disease progression despite androgen deprivation therapy.

7.2 MDV3100

MDV3100 is an oral androgen-receptor antagonist with clinically relevant therapeutic potential in prostate cancer that has progressed despite androgen deprivation therapy.

7.2.1 Pharmacology

MDV3100 is a novel small molecule androgen-receptor antagonist selected for its activity against prostate cancer cells overexpressing the androgen receptor. MDV3100 has a novel mechanism of action that is unlike that of bicalutamide. MDV3100 has been shown in preclinical studies to provide a more complete suppression of the androgen receptor pathway than bicalutamide. MDV3100 slows growth and induces cell death in bicalutamide-resistant cancers via three complementary actions – MDV3100 blocks testosterone binding to the androgen receptor, impedes movement of the androgen receptor to the nucleus of prostate cancer cells (nuclear translocation), and inhibits binding of DNA. Preclinical data have demonstrated that MDV3100 is superior to bicalutamide in each of these three actions. MDV3100 has no known agonist activity when the androgen receptor is overexpressed.

In a mouse xenograft model of prostate cancer using an androgen receptor overexpressing cell line, MDV3100 treatment resulted in a dose-dependent reduction in tumor volume (p < 0.05 and p < 0.01 for mid- and high-dose groups vs. vehicle, respectively). MDV3100 treatment decreased tumor volume, resulting in unmeasurable tumors in 1/7 animals in the low-dose group and 3/7 animals in the high-dose group. As expected, bicalutamide had little effect on tumor growth.

MDV3100 binds with high affinity to the human androgen receptor (K_i = 13 nM). Other targets for which measurable MDV3100 binding was detected included the human progesterone receptor with a 50% inhibitory concentration (IC_{50}) of 10–25 μM and the rat gamma amino butyric acid-gated chloride channel (IC_{50} = 2.6 μM; K_i = 2.1 μM [1.0 μg/mL]). Binding of MDV3100 at 25 μM to the human progesterone receptor was too weak to derive a K_i value. No significant binding was detected with the remaining 70 receptors.

7.2.2 Nonclinical Pharmacokinetics and Metabolism

In mice, rats, and dogs, oral MDV3100 had a half-life (t_{1/2}) of approximately 0.25 to 3 days. The t_{1/2} did not appear to be affected by the dose size; however, the bioavailability appeared to decrease with increasing dose size. In vitro drug metabolism studies suggest that MDV3100 undergoes very slow rates of metabolism. Plasma protein binding of MDV3100 in human plasma ranged from 97% to 98% and was similar in mice, rats, rabbits, and dogs.
7.2.3 Nonclinical Toxicology

MDV3100 was not mutagenic or clastogenic as measured by bacterial reverse mutation or mouse lymphoma assays, respectively.

MDV3100 has also been tested in repeat dose toxicity studies in rats and dogs. In male and female rats, MDV3100 caused no deaths or clinical signs that were considered likely to be related to MDV3100 at oral doses as high as 100 mg/kg/day for 26 weeks. In studies in male and female dogs, repeated oral MDV3100 doses ≥ 60 mg/kg/day in Labrasol® for up to 4 weeks were associated with a moribund condition in some animals. At these doses, many dogs exhibited behavioral resistance to dosing not observed in vehicle control animals. Other clinical signs associated with oral MDV3100 at doses ≥ 60 mg/kg/day in dogs, but of uncertain direct relationship to MDV3100, included ataxia, hypoactivity, and a single instance of convulsions. In contrast, MDV3100 doses ≤ 20 mg/kg/day were well-tolerated in male dogs for up to 13 weeks. Clinical signs of emesis, fecal changes, and/or salivation seen in all of the canine studies were most likely related to the vehicle, Labrasol.

Consistent with the expected anti-androgen pharmacology of MDV3100, the most salient effects of MDV3100 in rats and dogs were on male sex organs. Reductions in prostate, epididymis, and/or seminal vesicle weight were observed, and these were associated with corresponding histopathological findings of prostatic and seminal vesicle secretory depletion and/or atrophy, and with epididymal atrophy in dogs only. Hypospermatogenesis and degeneration of seminiferous tubules in testes were observed in dogs, but not in rats. Reversible hepatocellular hypertrophy, associated with liver weight increases, has been a consistent finding of MDV3100 in rats, but not in dogs. Additional histopathological findings definitively related to MDV3100 treatment in males in the 26-week study in rats included hypertrophy/hyperplasia in adrenals, pituitary, and thyroid, and atrophy in the mammary gland. Chronic progressive nephropathy was also observed in rats. The relationship of this common background finding in rats to MDV3100 cannot be entirely excluded, but no significant changes in renal function were evident from clinical pathology parameters.

7.2.4 Previous Human Experience

The tolerability, pharmacokinetics (PK), and antitumor activity of MDV3100 were studied in a multi-center, open-label, dose-escalation study of MDV3100 in 140 patients with advanced prostate cancer (Study S1-3100-01). Patients were treated with MDV3100 at doses of 30–600 mg/day until disease progression or intolerable side effects developed.

The antitumor activity of MDV3100 was assessed by post-therapy changes in PSA, soft tissue and osseous disease, and circulating tumor cell count. PSA declines of ≥ 50% from baseline were observed in 62% of chemotherapy-naïve and 51% of postchemotherapy patients. At the time of the analyses, the median time to PSA progression was not yet reached for chemotherapy-naïve patients and was 186 days for postchemotherapy patients. Among the chemotherapy-naïve patients, there was evidence of radiographic control (no progression) in 80% of patients with evaluable soft tissue disease and 63% of patients with bone lesions. Among the postchemotherapy patients, there was evidence of radiographic
control in 65% of patients with evaluable soft tissue disease and 51% of patients with bone lesions. The median time to radiographic progression was not yet reached for chemotherapy-naive patients and was 201 days for postchemotherapy patients. Enumeration of circulating tumor cells demonstrated that 91% of patients with favorable pretreatment counts (i.e., < 5 circulating tumor cells/7.5 mL of blood) maintained favorable post-treatment counts, while 49% of patients converted from unfavorable pretreatment counts (i.e., ≥ 5 circulating tumor cells/7.5 mL of blood) to favorable post-treatment counts.

At the highest dose of 600 mg/day, two of three patients had dose-limiting toxicities (seizure, rash, respectively). One witnessed seizure at 360 mg/day and a possible seizure at 480 mg/day were also reported. No deaths and no other drug-related serious adverse events were reported. Fatigue was the most frequently reported adverse event, with dose-dependent increases of Grade 3 fatigue (0% at 150, 9% at 240, 15% at 360, and 20% at 480 mg/day groups). Only one patient discontinued treatment due to fatigue with an onset coinciding with PSA rise. The dose of 240 mg/day was defined as the maximum tolerated dose.

MDV3100 was absorbed rapidly after oral administration, with maximum plasma concentration (C_{max}) occurring approximately 30 minutes to four hours after dosing. The t_{1/2} in patients was approximately 1 week (range 3 to 13 days) and did not appear to be affected by the dose size. MDV3100 plasma concentrations exhibited a low degree of inter- and intra-patient variability and increased linearly with dose. The PK remained linear with time, and there was no evidence of inhibition or autoinduction of metabolism during chronic administration. In accordance with a 1 week t_{1/2}, it took approximately 1 month to reach steady state. The daily fluctuation in steady-state plasma concentrations (i.e., the difference between C_{max} and minimum plasma concentration [C_{min}]) was low, and PK profiles approximated a constant infusion. At 160 mg/day, the mean steady-state C_{min} is expected to be approximately 12 ± 4 μg/mL.

Refer to the Investigator’s Brochure for additional information about MDV3100.

8. STUDY OBJECTIVES

Co-Primary Objectives

- To determine the benefit of MDV3100 as compared to placebo as assessed by overall survival;
- To determine the benefit of MDV3100 as compared to placebo as assessed by radiographic progression-free survival (rPFS).

Secondary Objectives

- To determine the benefit of MDV3100 as compared to placebo as assessed by time to first skeletal-related event;
- To determine the benefit of MDV3100 as compared to placebo as assessed by time to initiation of cytotoxic chemotherapy;
- To determine the benefit of MDV3100 as compared to placebo as assessed by time to PSA progression;
- To determine the benefit of MDV3100 as compared to placebo as assessed by PSA response $\geq 50\%$;
- To determine the benefit of MDV3100 as compared to placebo as assessed by best overall soft tissue response;
- To determine the safety of treatment with MDV3100 as compared to placebo.

**Exploratory Objectives**

- To evaluate quality of life using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) *(APPENDIX E)* and the European Quality of Life 5-Domain Scale (EQ-5D) *(APPENDIX F)* instruments;
- To evaluate emergence of pain relative to baseline at 6 months using the Brief Pain Inventory for MDV3100 versus placebo;
- To determine the benefit of MDV3100 as compared to placebo as assessed by time to first subsequent antineoplastic therapy (cytotoxic or hormonal);
- To determine the benefit of MDV3100 as compared to placebo as assessed by PSA response $\geq 90\%$;
- To characterize MDV3100 exposure (e.g., $C_{\text{min}}$);
- To collect PK data that will be combined with data from other studies in a population PK model.

9. **INVESTIGATIONAL PLAN**

9.1 **Overall Study Design and Plan**

This study is a multinational Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 (160 mg/day) in asymptomatic or mildly symptomatic patients with progressive metastatic prostate cancer who have disease progression despite androgen deprivation therapy. Patients must not have been previously treated with cytotoxic chemotherapy. Approximately 1,680 patients will be centrally randomized 1:1. Randomization will be stratified by investigative site.

Study drug therapy should be continued as long as the patient is tolerating the study drug and continues androgen deprivation therapy (i.e., surgical castration or ongoing gonadotropin GnRH-analogue therapy) until confirmed radiographic disease progression or a skeletal-related event AND one of the two following events: 1) initiation of cytotoxic chemotherapy; or 2) initiation of an investigational agent for treatment of prostate cancer. PSA rise, without evidence of confirmed radiographic progression or a skeletal-related event, is strongly discouraged as a criterion to start a new systemic antineoplastic therapy during the first 12 weeks of therapy and is discouraged as a criterion to start a new systemic antineoplastic therapy throughout the study. Radiation therapy, vaccine therapy, and initiation of bisphosphonates or other approved bone targeting agents, and standard of care steroid and pain management are allowed and should not result in discontinuation of study drug therapy. Study drug should be discontinued prior to initiation of a cytotoxic chemotherapy or another investigational agent.
The following assessments of prostate cancer status will be collected during the course of the trial: overall survival, soft tissue disease on computed tomography (CT) scan or on magnetic resonance imaging (MRI), bone disease on radionuclide bone scans, skeletal-related events, Brief Pain Inventory, FACT-P and EQ-5D quality of life questionnaires, and PSA.

The consensus guidelines of the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) (APPENDIX A) and the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) have been taken into consideration for the determination of radiographic disease progression. Radiographic disease progression is defined by RECIST 1.1 for soft tissue disease, or the appearance of two or more new bone lesions on bone scan (PCWG2).

Progression at the first scheduled reassessment at Week 9 requires a confirmatory scan at least 6 weeks later or at the next scheduled scan (Week 17). The confirmatory scan should show progressively worsening disease on bone scan (e.g., two additional new lesions on bone scan) or confirm progressive soft tissue disease by RECIST 1.1 criteria as outlined in this protocol. Progression on bone scan first determined at time points after Week 9 also requires a confirmatory scan at least 6 weeks later (e.g., if progression is noted at Week 17 then the confirmatory scan may be performed at Week 23 or at the scheduled Week 25 scan). If progression is noted at Week 25 or later then a confirmatory scan will need to be performed at least 6 or more weeks later. This confirmatory scan should demonstrate persistence of the new bone lesions. Disease progression observed by CT or MRI for soft tissue disease on Week 17 or later (or Week 13 or later if done during an unscheduled visit) does not require a confirmatory scan.

Study films (CT/MRI and bone scan) should be read on site and also be submitted in digital format to the central imaging contract research organization, Perceptive Informatics, Inc., for an independent central radiology review. Each site should designate a radiologist or investigator to ensure that all images are read according to RECIST 1.1 and PCWG2 as specified by the protocol. Radiographic imaging is not required after radiographic progression is confirmed according to protocol specifications. Note that determination of radiographic progression should be confirmed by the central independent radiology review prior to stopping radiographic imaging until the time that at least 410 rPFS events are confirmed as required for the primary PFS analysis. After this time, radiographic progression should be confirmed by the local radiology review prior to stopping radiographic imaging. However, scans should continue to be sent to the central imaging contract research organization for archiving.

Throughout the study, safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs). An independent Data Monitoring Committee will monitor safety data on an ongoing basis.

Patients will have a Safety Follow-up visit 28 days after their last dose of study drug or prior to initiation of cytotoxic chemotherapy or another investigational agent, whichever occurs first. All patients are to be followed for survival status, skeletal-related events, and subsequent treatments for prostate cancer.
9.2 Discussion of Study Design, including Choice of Control Group

This randomized, placebo-controlled trial is designed as an adequate and well-controlled study to demonstrate the efficacy and safety of MDV3100 in the treatment of patients with asymptomatic or mildly symptomatic progressive metastatic prostate cancer who have failed androgen deprivation therapy.

MDV3100 at a dose of 160 mg/day will be compared to placebo. All enrolled patients will be allowed standard of care background treatment. A placebo-controlled design is considered ethical because there is no one standard of care treatment for the patient population under investigation in this trial. MDV3100 and placebo are being studied on top of a background of various standard of care treatments as selected by the individual treating physicians. Patients will be allowed to be treated with prednisone (or prednisone equivalent) at doses up to 10 mg per day. Supportive care with bisphosphonates or other approved bone stabilization agents, palliative therapy including radiation therapy, and transfusions or growth factors are allowed.

In this study, patients will be removed from study drug therapy once they are confirmed to have radiographic disease progression or a skeletal-related event AND one of the two following events: 1) initiation of cytotoxic chemotherapy; or 2) initiation of an investigational agent for treatment of prostate cancer. Maintenance of study drug while the patient remains castrated is indicated as MDV3100 is a pure androgen receptor antagonist with no known agonist activity and is consistent with the treatment paradigm to continue androgen deprivation therapy in these patients.

The primary outcome measures will be overall survival and rPFS which are the optimal endpoints to demonstrate clinical risk/benefit in a Phase 3 prostate cancer trial.

9.3 Selection of Study Population

The study population will include men with asymptomatic or mildly symptomatic progressive metastatic prostate cancer who have failed androgen deprivation therapy. Asymptomatic or mildly symptomatic from prostate cancer is defined in this protocol as having a score of < 4 on Brief Pain Inventory – Short Form Question #3.

9.3.1 Inclusion Criteria

Patients eligible to participate in this study are those who meet all of the following inclusion criteria:

1. Age 18 or older and willing and able to provide informed consent;
2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features;
3. Ongoing androgen deprivation therapy with a GnRH analogue or bilateral orchiectomy (i.e., surgical or medical castration);
4. Patients who have not had a bilateral orchiectomy, must have a plan to maintain effective GnRH-analogue therapy for the duration of the trial;
5. Serum testosterone level ≤ 1.73 nmol/L (50 ng/dL) at the Screening visit;
6. Patients receiving bisphosphonate therapy must have been on stable doses for at least 4 weeks;
7. Progressive disease at study entry defined as one or more of the following three criteria that occurred while the patient was on androgen deprivation therapy as defined in eligibility criterion #3:
   - PSA progression defined by a minimum of two rising PSA levels with an interval of ≥ 1 week between each determination. Patients who received an anti-androgen must have progression after withdrawal (≥ 4 weeks since last flutamide or ≥ 6 weeks since last bicalutamide or nilutamide). The PSA value at the Screening visit should be ≥ 2 μg/L (2 ng/mL);
   - Soft tissue disease progression defined by RECIST 1.1;
   - Bone disease progression defined by PCWG2 with two or more new lesions on bone scan;
8. Metastatic disease documented by bone lesions on bone scan or by measurable soft tissue disease by CT/MRI. Patients whose disease spread is limited to regional pelvic lymph nodes are not eligible;
9. No prior cytotoxic chemotherapy for prostate cancer;
10. Asymptomatic or mildly symptomatic from prostate cancer (i.e., the score on the Brief Pain Inventory – Short Form (APPENDIX C) Question #3 must be < 4);
11. Eastern Cooperative Oncology Group (ECOG) performance status 0–1;
12. Estimated life expectancy of ≥ 6 months;
13. Able to swallow the study drug and comply with study requirements.

9.3.2 Exclusion Criteria
1. Patients must NOT meet any of the following exclusion criteria:
   1. Severe concurrent disease, infection, or co-morbidity that, in the judgment of the Investigator, would make the patient inappropriate for enrollment;
   2. Known or suspected brain metastasis or active leptomeningeal disease;
   3. History of another malignancy within the previous 5 years other than curatively treated non melanomatous skin cancer;
   4. Absolute neutrophil count < 1,500/μL, or platelet count < 100,000/μL, or hemoglobin < 5.6 mmol/L (9 g/dL) at the Screening visit. (NOTE: patients may not have received any growth factors within 7 days or blood transfusions within 28 days of the hematologic laboratory values obtained at the Screening visit);
   5. Total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal at the Screening visit;
   6. Creatinine > 177 μmol/L (2 mg/dL) at the Screening visit;
   7. Albumin < 30 g/L (3.0 g/dL) at the Screening visit;
8. History of seizure or any condition that may predispose to seizure. Also, history of loss of consciousness or transient ischemic attack within 12 months of enrollment (Day 1 visit);

9. Clinically significant cardiovascular disease including:
   - Myocardial infarction within 6 months;
   - Uncontrolled angina within 3 months;
   - Congestive heart failure New York Heart Association (NYHA) class III or IV, or patients with history of congestive heart failure NYHA class III or IV in the past, unless a screening echocardiogram or multi-gated acquisition scan performed within 3 months results in a left ventricular ejection fraction that is ≥ 45%;
   - History of clinically significant ventricular arrhythmias (e.g., 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 the Screening visit;
   - Bradycardia as indicated by a heart rate of < 50 beats per minute on the Screening ECG;
   - Uncontrolled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at the Screening visit;

10. Gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease within last 3 months);

11. Major surgery within 4 weeks of enrollment (Day 1 visit);

12. Use of opiate analgesics for pain from prostate cancer within 4 weeks of enrollment (Day 1 visit);

13. Radiation therapy for treatment of the primary tumor within 3 weeks of enrollment (Day 1 visit);

14. Radiation or radionuclide therapy for treatment of metastasis;

15. Treatment with flutamide within 4 weeks of enrollment (Day 1 visit);

16. Treatment with bicalutamide or nilutamide within 6 weeks of enrollment (Day 1 visit);

17. Treatment with 5-α reductase inhibitors (finasteride, dutasteride), estrogens, cyproterone within 4 weeks of enrollment (Day 1 visit);

18. Treatment with systemic biologic therapy for prostate cancer (other than approved bone targeted agents and GnRH-analogue therapy) or other agents with anti-tumor activity within 4 weeks of enrollment (Day 1 visit);

19. History of prostate cancer progression on ketoconazole;
20. Prior use, or participation in a clinical trial, of an investigational agent that blocks androgen synthesis (e.g., abiraterone acetate, TAK-700, TAK-683, TAK-448) or blocks the androgen receptor (e.g., BMS 641988);

21. Participation in a previous clinical trial of MDV3100;

22. Use of an investigational agent within 4 weeks of enrollment (Day 1 visit);

23. Use of herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (e.g., saw palmetto) or systemic corticosteroids greater than the equivalent of 10 mg of prednisone per day within 4 weeks of enrollment (Day 1 visit);

24. Any condition or reason that, in the opinion of the Investigator, interferes with the ability of the patient to participate in the trial, which places the patient at undue risk, or complicates the interpretation of safety data.

9.3.3 Removal of Patients from Therapy

Patients may withdraw consent to participate in the trial at any time for any reason and discontinue treatment. Investigators or the Medical Monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the Safety Follow-up visit. Patients who discontinue treatment will continue to be followed for radiographic progression (until disease progression has been confirmed), skeletal-related event, additional treatments for prostate cancer, and survival. Note that determination of radiographic progression should be confirmed by the central independent radiology review prior to stopping radiographic imaging until the time that at least 410 rPFS events are confirmed as required for the primary PFS analysis. After this time, radiographic progression should be confirmed by the local radiology review prior to stopping radiographic imaging. However, scans should continue to be sent to the central imaging contract research organization for archiving.

9.3.3.1 Removal of Patients from Therapy for Adverse Events or Lack of Compliance

The following safety/compliance events will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved:

- Any adverse event that is intolerable to the patient and 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 to the patient if dosing continued;
- Any seizure;
- Creatinine > 354 μmol/L (4.0 mg/dL);
- Liver function tests (AST, ALT, or total bilirubin) > 5 times the upper limit of normal;
- An absolute neutrophil count of ≤ 750 /μL;
- A platelet count of < 50,000/μL;
- Patients who are, in the opinion of the Investigator or the Medical Monitor, grossly non-compliant with the protocol’s requirements.
9.3.3.2 Maintenance of Study Drug Therapy in the Setting of Disease Progression and Initiation of Other Non-Investigational Antineoplastic Agents

Study drug therapy should be continued as long as the patient is tolerating the study drug and continues androgen deprivation therapy (i.e., surgical castration or ongoing GnRH analogue therapy) until confirmed radiographic disease progression or a skeletal-related event AND one of the two following events: 1) initiation of cytotoxic chemotherapy; or 2) initiation of an investigational agent for treatment of prostate cancer. PSA rise without evidence of confirmed radiographic progression or a skeletal-related event is strongly discouraged as a criterion to start a new systemic antineoplastic therapy during the first 12 weeks of therapy and is discouraged as a criterion to start a new systemic antineoplastic therapy throughout the study. Radiation therapy and initiation of bisphosphonates or other approved bone targeting agents are allowed and should not result in discontinuation of study drug therapy.

9.4 Treatments

9.4.1 Treatments Administered

In this study, patients will be randomized to receive blinded oral doses of study drug (MDV3100 160 mg/day or placebo) which will be administered as four capsules per day.

9.4.2 Identity of Investigational Product

The study drug, MDV3100, has the chemical name 3-(4-cyano-3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylcarbamoyl) phenyl]-5,5-dimethyl-2-thioxoimidazolin-4-one. The drug substance has no chiral centers and no salt forms are available at ~ pH 2 to 10. It is essentially insoluble in water, but partially soluble in lipid-based solutions.

9.4.2.1 Product Characteristics

The drug substance is formulated in the surfactant Labrasol to create a self-emulsifying (or microemulsifying) dosage form. The product is provided as 40 mg soft gelatin capsules in bottles with induction-sealed child-resistant caps. The placebo consists of Labrasol in identical capsules.

9.4.2.2 Directions for Administration

Study drug doses should be taken as close as possible to the same time each day. Study patients will take four capsules of study drug once daily. If dosing is missed on one day for any reason, double-dosing should NOT occur the following day. Patients will hold their dose of study drug prior to the visit on clinic visit days; on PK visit days they will be instructed to take their study medication after PK samples are drawn. The study drug can be taken with or without food.

9.4.2.3 Dose Reduction/Dose Adjustment

Patients who experience a Grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a Grade 2 or lower severity. Patients may subsequently be re-started on study drug, including at a reduced dose, with the written approval of Medivation (or designee).
9.4.2.4 Storage and Labeling

Study drug should be handled and stored safely and properly in accordance with the study drug label. Bottles will be labeled with the study protocol number, medication or bottle number, contents, directions for use, storage directions, clinical trial statement, and Medivation as Sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children.

9.4.3 Method of Assigning Patients to Treatment Group and Patient ID Number

After a patient is screened and the Investigator determines that the patient is eligible for enrollment, the site staff will complete the Randomization Authorization Form and fax it to Medivation or designee. Medivation or designee will approve the patient’s enrollment in writing. Once the site has approval, the patient may undergo his Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met on Day 1, the site will randomize the patient to treatment by using the Interactive Voice/Web Recognition Service (IVRS/IWRS) during the patient’s Day 1 visit. The IVRS/IWRS will assign the patient a study drug bottle number available at the site according to the randomization code. The IVRS/IWRS will also assign the Patient ID Number.

9.4.4 Selection of Doses Used in the Study

The dose of 160 mg/day was selected for evaluation in this study. The durability of disease suppression was found to be similar between the 150 mg/day and the 240 mg/day dose cohorts in the Phase 1-2 study. Given this comparable efficacy, dose-dependent increases of Grade 3 fatigue (0% at 150 mg/day vs. 9% at 240 mg/day), and reports of seizure at high doses (one witnessed event at 360 mg/day and another at 600 mg/day), a dose of 160 mg/day is believed to have the optimal risk/benefit profile and is selected for investigation in the Phase 3 program.

9.4.5 Selection and Timing of Dose for Each Patient

MDV3100 is administered orally once daily. MDV3100 should be taken as close as possible to the same time each day. Patients will be instructed to take their study medication in the clinic on study visit days.

9.4.6 Blinding

The control for this blinded study will be placebo capsules that appear identical to the MDV3100 capsules. All patients, Investigators, and Medivation staff or representatives involved in the conduct of the study will be blinded to treatment assignment. Unblinding should occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. The Principal Investigator should make every effort to contact the Medivation Medical Monitor or designee before unblinding a patient in IVRS/IWRS. To unblind a patient, the Principal Investigator will access the Unblinding Module in IVRS/IWRS. Patients whose treatment assignment has been unblinded will be permanently discontinued from treatment.
9.4.7 Prior and Concomitant Therapy

All concomitant medication(s), including any medications taken within 4 weeks (28 days) prior to the Day 1 visit, must be reported on the appropriate case report form. Concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications. If an intermittent or as needed (prn) use of any medication during the study is due to an adverse event, then the adverse event must also be recorded on the adverse event case report form.

APPENDIX G provides a list of medicinal products that have a potential for drug-drug interactions with MDV3100. Cytochrome P450 (CYP) 2C8 plays an important role in the metabolism of MDV3100; therefore, use caution when co-administering MDV3100 with strong inhibitors (e.g., gemfibrozil) or inducers (e.g., rifampicin) of CYP2C8 as they can affect MDV3100 plasma exposure. Concomitant use of strong CYP2C8 inhibitors should be avoided if possible as they may result in higher plasma exposure to MDV3100. If concomitant use of strong CYP2C8 inhibitors cannot be avoided, then the dose of study drug should be reduced to 80 mg per day (2 capsules).

MDV3100 can induce CYP2C9, CYP2C19, CYP3A4, uridine 5’-diphospho-glucuronosyltransferase (UGT), and the efflux transporter P-glycoprotein (P-gp) via activation of the nuclear pregnane X receptor (PXR). Co-administration of MDV3100 with substrates of these enzymes or transporter may reduce the oral bioavailability and/or increase the clearance of the substrate, resulting in decreased exposures. In consideration of the half-life of MDV3100 (approximately 1 week), effects on enzymes and transporters may persist for one month or longer after stopping MDV3100.

Patients in this study will not have had any prior cytotoxic chemotherapy for prostate cancer. In addition, they will not have had any opiate analgesics for pain from prostate cancer within 4 weeks of enrollment (Day 1 visit). The following medications are prohibited within 4 weeks of enrollment, unless otherwise indicated below:

- Flutamide;
- Bicalutamide or nilutamide (6 weeks washout required for these two agents);
- 5 α-reductase inhibitors (finasteride, dutasteride);
- Estrogens;
- Cyproterone acetate;
- Biologic, or other agents with anti-tumor activity against prostate cancer;
- Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone;
- Herbal medications that have known hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (i.e., saw palmetto);
- Androgens (testosterone, dihydroepiandrosterone [DHEA], etc.);
- Patients with a history of prostate cancer progression on ketoconazole will not be enrolled in this study;
• Investigational agents: Patients who have participated in a previous clinical trial of an investigational agent that blocks androgen synthesis (e.g., abiraterone acetate, TAK-700, TAK-683, TAK-448) or androgen receptor (e.g., BMS-641988) will not be enrolled in this study. Patients who have participated in a previous clinical trial of MDV3100 will also not be enrolled in this study.

Hormonal treatment for treating complications of LHRH treatment (e.g., hot flashes) will be allowed with Medical Monitor approval.

The doses of the following medication classes should be maintained during the Screening Period and while actively treated with study drug:

• Bisphosphonates or other approved bone targeting agents for the treatment of metastatic prostate cancer;
• GnRH analogues.

The following treatments are allowed during the study (and do not require study drug discontinuation) including, but not limited to:

• Blood transfusions and growth factor support per standard of care and institutional guidelines;
• Steroid use per standard of care;
• Pain therapy per standard of care and institutional guidelines;
• Radiation therapy including external beam radiotherapy or systemic radionuclides (e.g., Samarium or Strontium);
• Vaccine therapy that has prior market authorization;
• Palliative surgical procedures to treat skeletal-related events.

The following additional therapies are allowed during treatment with study medication but only once the patient has confirmed radiographic progression or has a skeletal-related event:

• Hormonal therapies including other anti-androgens;
• Biological anti-tumor treatments.

Androgen deprivation therapy (either bilateral orchiectomy or LHRH agonist/antagonist) must be continued during the trial. If androgen deprivation therapy is discontinued, the patient must be withdrawn from study treatment.

Deviation from the above guidelines should occur only if absolutely necessary for the well-being of the patient. Any deviation to the medication/treatment guidelines are to be recorded on the concomitant medication case report form. Additionally the Medical Monitor is to be notified to determine the patient’s continued eligibility in the study.
9.4.8 Treatment Compliance

Study drug accountability will be performed to document compliance with the dosing regimen. Patients will be asked to bring back all remaining study drug and all study drug packaging at each study visit. Treatment compliance will be defined as the number of capsules taken during the study divided by the expected number of capsules, multiplied by 100%. Capsules that are not returned will be considered to have been taken.

9.5 Efficacy Assessments and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed

9.5.1.1 Co-Primary Efficacy Assessments

9.5.1.1.1 Overall Survival

Deaths from any cause comprise the overall survival events.

9.5.1.1.2 Radiographic Progression-Free Survival

Deaths due to any cause within 168 days after treatment discontinuation and radiographic progression comprise the rPFS events.

The consensus guidelines of RECIST 1.1 and PCWG2 have been taken into consideration for the determination of radiographic disease progression. Radiographic disease progression is defined by RECIST 1.1 for soft tissue disease, or the appearance of two or more new bone lesions on bone scan (PCWG2). The documentation required for the determination of radiographic disease progression is listed in Table 9.5.1.1.2-1.
### Table 9.5.1.2-1: Protocol-Specified Documentation for Radiographic Evidence of Disease Progression

<table>
<thead>
<tr>
<th>Date Progression Detected (Visit)</th>
<th>Criteria for Progression</th>
<th>Criteria for Confirmation of Progression (requirement and timing)</th>
<th>Criteria for Documentation of Disease Progression on Confirmatory Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 9</td>
<td>Bone lesions: Two or more new lesions compared to <strong>baseline</strong> bone scan by PCWG2.</td>
<td>Timing: at least 6 weeks after progression identified or at Week 17 visit.</td>
<td>Two or more new bone lesions on bone scan (compared to Week 9 scan).</td>
</tr>
<tr>
<td></td>
<td>Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.</td>
<td>Confirmation required for soft tissue disease (scan of same modality as demonstrated progression).</td>
<td>Confirmation of progressive soft tissue disease by RECIST 1.1.</td>
</tr>
<tr>
<td>Week 17</td>
<td>Bone lesions: Two or more new lesions on bone scan compared to Week 9 bone scan.</td>
<td>Timing: at least 6 weeks after progression identified or at Week 25 visit. Required for bone lesions observed on bone scan.</td>
<td>Persistent or increase in number of bone lesions on bone scan compared to Week 17 scan.</td>
</tr>
<tr>
<td></td>
<td>Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.</td>
<td>No confirmatory scan required for soft tissue disease progression.</td>
<td>n/a</td>
</tr>
<tr>
<td>Week 25 or later</td>
<td>Bone lesions: Two or more new lesions compared to Week 9 bone scan.</td>
<td>Timing: at least 6 weeks after progression identified. Required for bone lesions observed on bone scan.</td>
<td>Persistent or increase in number of lesions on bone scan compared to prior scan.</td>
</tr>
<tr>
<td></td>
<td>Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.</td>
<td>No confirmatory scan required for soft tissue disease.</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*a Progression detected by bone scan at an unscheduled visit either prior to Week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan. Progression detected by CT/MRI at an unscheduled visit prior to Week 13 will require a confirmatory scan at least 6 weeks later whereas progression on or after Week 13 does not require confirmation.

*b Confirmation must occur at the next available scan.

*c For confirmation, at least two of the lesions first identified as new must be present at that next available scan (confirmation scan).

n/a, not applicable.

### 9.5.1.2 Secondary Efficacy Assessments

#### 9.5.1.2.1 Time to First Skeletal-Related Event

A skeletal-related event is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.
9.5.1.2.2 Time to Initiation of Cytotoxic Chemotherapy

Initiation of cytotoxic chemotherapy will comprise this event.

9.5.1.2.3 Time to PSA Progression

PSA progression will be defined according to the consensus guidelines of PCWG2. For patients with PSA declines at Week 13, the PSA progression date is defined as the date that a \$\geq 25\%$ increase and an absolute increase of \$\geq 2 \text{ng/mL}$ above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later. For patients with no PSA decline at Week 13, the PSA progression date is defined as the date that a \$\geq 25\%$ increase and an absolute increase of \$\geq 2 \text{ng/mL}$ above the baseline is documented, which is confirmed by a second consecutive value 3 or more weeks later.

9.5.1.2.4 PSA Response $\geq 50\%$

Confirmed PSA responses will be defined as $\geq 50\%$ reductions in PSA from baseline to lowest postbaseline PSA result as determined by the central laboratory, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response.

9.5.1.2.5 Best Overall Soft Tissue Response

Patients with measurable soft tissue disease at screening (i.e., at least 1 target lesion per RECIST 1.1) who have an objective response (complete response or partial response) per RECIST 1.1 by independent review during the study will be included in this assessment.

9.5.1.3 Exploratory Efficacy Assessments

9.5.1.3.1 Functional Assessment of Cancer Therapy – Prostate

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

9.5.1.3.2 European Quality of Life 5-Domain Scale

The EQ-5D is a standardized instrument for use as a measure of health outcome. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 3-point categorical scales ranging from “no problem” to “severe problem.”

9.5.1.3.3 Brief Pain Inventory

The Brief Pain Inventory questionnaire is a validated instrument that is a patient self-rated scale assessing level of pain, effect of the pain on activities of daily living, and analgesic use. The short form of the Brief Pain Inventory is used in this study and contains nine main questions. For this study, the Brief Pain Inventory will assess pain related to prostate cancer only.
9.5.1.3.4 **Time to First Subsequent Antineoplastic Therapy**

All antineoplastic therapies, including cytotoxic and hormonal therapies, will be considered for this assessment.

9.5.1.3.5 **PSA Response ≥ 90%**

Confirmed PSA responses will be defined as ≥ 90% reductions in PSA from baseline to lowest postbaseline PSA result as determined by the central laboratory, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response.

9.5.1.4 **Adverse Events**

An adverse event or experience is defined as any symptom, sign, illness, or untoward experience (including a clinically significant laboratory finding classified as Grade 3 or higher by the National Cancer Institute’s Common Terminology Criteria for Adverse Events [CTCAE] v4.0) that develops or worsens during the course of the study, whether or not the event is considered related to study drug.

When a diagnosis is possible, it is preferable to record it, rather than a series of signs or symptoms relating to the diagnosis, on the case report form.

Examples of adverse events include:

- A worsening, 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 which may or may not be related to the use of a concomitant medication or study drug;
- 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 two separate medical events (e.g., for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately).

Adverse events are detected in two ways:

- Clinical: symptoms reported by the patient or signs detected on examination;
- Ancillary Tests: clinically significant abnormalities of vital signs, ECG, laboratory tests, and other diagnostic procedures.

An adverse event **does not** include:

- Medical or surgical procedures (e.g., 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 (e.g., hospitalization for elective surgery, social and/or convenience admissions);

• Overdose of either study drug or concomitant medication without any signs or symptoms.

**Relationship to Study Drug:** The reasonable possibility of an adverse event’s relationship to study drug is to be assessed with careful medical consideration at the time of evaluation of the adverse event. The Medical Monitor’s opinion may be sought in those cases in which the site Investigator is unable to make an independent judgment. The following definitions are to be used:

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>Adverse event is <em>clearly not</em> related to the investigational drug (s)</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Adverse event is <em>doubtfully</em> related to the investigational drug (s)</td>
</tr>
<tr>
<td>Possible</td>
<td>Adverse event <em>may be</em> related to the investigational drug (s)</td>
</tr>
<tr>
<td>Probable</td>
<td>Adverse event is <em>likely</em> related to the investigational drug (s)</td>
</tr>
<tr>
<td>Definite</td>
<td>Adverse event is <em>clearly</em> related to the investigational drug (s)</td>
</tr>
</tbody>
</table>

The following criteria will be used as guidelines for determining the attribution of an adverse event to the study drug:

**Unrelated**
There is no possible relationship to the study drug. The temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible.

**Unlikely**
The study drug is believed to be not reasonably related to the adverse event, although a causal relationship cannot be ruled out. While the temporal relationship between drug exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug.

**Possible**
The causal relationship to the study drug is uncertain. The temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, dechallenge or rechallenge information is either unknown or equivocal, and while other potential causes may not exist, a causal relationship to the study drug does not appear probable.
Probable  There is a high degree of certainty for a causal relationship between the study drug and the adverse event. The temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to dechallenge, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Definite  Causal relationship is certain. The temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to dechallenge, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Adverse Event Documentation: All adverse events, whether or not related to the study drug, must be fully and completely documented on the adverse event page of the case report form and in the patient’s clinical chart. In the event that a patient is withdrawn from the study because of an adverse event, it must be recorded on the case report forms as such. Adverse events will be monitored until resolution or until the event has stabilized and/or reached a new baseline. If an adverse event remains unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator and Medical Monitor whether continued follow-up of the adverse event is warranted.

The site Investigator must record all directly observed adverse events and all spontaneously reported adverse events. At each visit the site Investigator will ask the patient a non-specific question (e.g., “Have you noticed anything different since your last visit?”) to assess whether any adverse event has been experienced since the last report or visit. Adverse events will be identified and documented on the adverse event case report form in appropriate medical terminology. The severity and the relationship to the study drug will be determined and reported on the case report form (see below).

Note that any intermittent or as needed use of any medication (and specifically any newly prescribed medication) during the course of a study may indicate the occurrence of an adverse event that may need to be recorded on both the adverse event case report form and on the concomitant medication case report form.

Serious adverse events will be collected and reported on the Adverse Event Case Report Form from the time the patient signs the informed consent form until the Safety Follow-up Visit, 28 days after the last dose of study drug, or until the initiation of an investigational agent or cytotoxic chemotherapy, whichever comes first. Non-serious adverse events will be collected and reported on the Adverse Event Case Report Form from the time of first study drug dosing until the Safety Follow-up visit, 28 days after the last dose of study drug, or until the initiation of an investigational agent or cytotoxic chemotherapy, whichever comes first.
9.5.1.4.1 Adverse Event Severity Rating

Severity describes the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria. The severity of an adverse event will be graded following the CTCAE v4.0. The severity of the adverse event should be recorded in the appropriate section of the adverse event case report form.

9.5.1.4.2 Disease Progression as an Adverse Event

It is anticipated that a proportion of patients will experience disease progression. The term “disease progression” itself should not be reported as an adverse event. When clinical disease progression is identified, the clinical event which marks or identifies the disease progression should be reported as the adverse event term for standard adverse event reporting, including serious adverse event reporting, as per ICH criteria reviewed in Sections 9.5.1.4 and 9.5.1.5 of this protocol.

9.5.1.5 Serious Adverse Events

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

- Results in death;
- Is life threatening (i.e., the patient was at immediate risk of death at the time of the event). “Life-threatening” does not include an event that hypothetically might have caused death if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of the patient’s ability to carry out normal life functions);
- Is a congenital anomaly/birth defect.

In addition, medical and scientific judgment should be exercised in deciding whether other situations should be considered a serious adverse event (i.e., important medical events that may not be immediately life-threatening or result in death, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above). Examples of such medical events include (but are not limited to) allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. In this study, a documented or suspected seizure should be reported within 24 hours of the site’s knowledge of the event (as a medically-important serious adverse event).
Reports of serious adverse events, as defined above require immediate notification (within 24 hours of the site’s knowledge of the event) to the Medivation designated Drug Safety Reporting contact whether or not the Investigator believes that the experience is related to study drug.

9.5.1.5.1 Serious Adverse Events – Reporting

The reporting of serious adverse events by Medivation to Regulatory Authorities (e.g., US FDA) is a regulatory requirement. Each Regulatory Agency has established a timetable for reporting serious adverse events based upon established criteria. Likewise, it is the responsibility of the Investigator to report serious adverse events to their local Institutional Review Boards or Ethics Committees.

All serious adverse events should be recorded once the informed consent form is signed and must be reported immediately (within 24 hours of the site’s knowledge of the event) by facsimile to the company listed below.

Name: ProductLife, Ltd.
SAE Fax: +44 (0) 1223 413689 (GMT) OR regional fax number provided to sites
Email: safety@verius.co.uk
Phone: +44 (0)1223 402660

The initial report should include the site name and number, the name of the Investigator, the Patient ID Number and initials, the patient demographic information, the details of study drug administration, and as many details of the serious adverse event as are known, including the date of onset, the intensity, the treatment, and the relationship to study drug. If the patient died, the report should include the cause of death and whether or not the death was related to study drug, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report.

A completed serious adverse event report form signed by the Investigator must be faxed to ProductLife within 24 hours of the site’s knowledge of the event. This will include: an identification that one or more serious adverse event criteria have been met; a detailed description of the experience, relevant medical records (without names or other patient identifiers), the date of death and autopsy report (as applicable and available), the Investigator’s current assessment of the relationship between the serious adverse event and the study drug and action taken. Serious adverse events must also be reported to the responsible IRB/IECs as per regulatory requirements.

The Investigator is responsible for complying with the responsible IRB’s/IEC’s procedures regarding the reporting of adverse events.

All serious adverse events will be followed until resolution, until the event has stabilized and/or reached a new baseline. All serious adverse events continuing at the completion of
the study must be followed to determine outcome. Serious adverse events will be collected and reported from the time the patient signs the informed consent form until the Safety Follow-up visit, 28 days after the last dose of study drug, or until the initiation of an investigational agent or cytotoxic chemotherapy, whichever comes first.

9.5.1.5.2 Clarification in Reporting of Deaths

As overall survival is one of the co-primary endpoints of the study, all patients must be followed for survival until death and information relating to a patient’s death (e.g., date of death and primary cause of death) should be recorded. Fatal events (regardless of relationship to study drug) should be reported as serious adverse events for patients until the Safety Follow-up visit until 28 days after study drug discontinuation, or until the initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first. Fatal events occurring after the Safety Follow-up visit until 28 days after study drug discontinuation, or until the initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first will not be reported as serious adverse events, and will be captured on the designated case report form.

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

9.5.1.6 Clinical Laboratory Tests

All patients will be assessed for safety with specimen sampling at specified visits, and at Unscheduled visits if necessary, including serum chemistries, urinalysis, and hematology (see Study Schedule of Activities in the Protocol Synopsis).
Clinical laboratory tests will be performed by a central laboratory specified in Section 4 of the Form FDA 1572 for the study and the reference ranges of this laboratory will be used. Prostate Specific Antigen (PSA) testing will be completed by local laboratory specified in Section 4 of the Form FDA 1572 for the study and the reference ranges of this laboratory will be used. For Unscheduled visits, another clinical laboratory may be used, if necessary or for the urgent management of an adverse event. If a clinical laboratory not listed on the Form FDA 1572 is used, the reference ranges of the lab must be provided to Medivation or designee. All samples for laboratory analysis must be collected, prepared, labeled, and shipped according to the laboratory’s requirements.

9.5.1.7 Physical Examinations, Vital Signs, and Electrocardiograms

The safety of patients enrolled in the trial will also be assessed with regular evaluation of vital signs, physical examinations, and 12-lead ECGs.

There will be both complete and brief physical examinations. The complete physical examination will include head, ears, eyes, nose, mouth, skin, heart, and lung examinations, lymph nodes, genito-urinary, gastrointestinal, skeletal, and neurological systems. The brief physical exams will be directed towards patient reported symptoms and areas of cancer spread, and to the cardiac, respiratory, and gastrointestinal systems.

Standard 12-lead ECGs with rhythm strips will be collected. ECGs will be obtained after the patient has rested quietly and awake in a fully supine position (or semi-recumbent, if supine not tolerated) for 5–10 minutes. The Investigator or designee will be responsible for the initial reading of the ECGs prior to the patient being dismissed from the clinic at each applicable visit; however, all ECGs will also be read centrally at an ECG laboratory.
9.5.2 Drug Concentration Measurements

Pre-dose blood samples (4 mL) for PK will be collected in K2-EDTA tubes at most study visits, including visits scheduled for Weeks 5, 13, 25, and for any adverse event related unscheduled visits prior to Week 25. After collection, the tube will be gently inverted 8 to 10 times to ensure adequate mixing of the tube contents, and the whole blood will be processed to plasma within 1 hour of collection as described in detail in the study manual. The shipment address and assay lab contact information will be provided to the investigative site prior to initiation of the study.

Samples will be analyzed for MDV3100 and possibly MDV3100 metabolites using a validated analytical method. PK samples will be collected from all patients to maintain blinding; however, the PK samples from placebo patients will not be assayed unless requested by Medivation or designee. As the primary goal of the PK analysis is to define the steady-state exposure of MDV3100, all samples from a given patient may not need to be assayed.

The PK samples may be used for future metabolite identification and/or further evaluation of bioanalytical methods. These data will be used for internal exploratory purposes and will not be included in the clinical study report. Selected samples may be analyzed for concurrent medications. These data may be used to assess pharmacokinetic drug-drug interactions.

**On PK sample collection days, it is important to take all reasonable measures to ensure accurate recording of information on dosing and timing of sample collections relative to dosing history. Patients should hold their dose of study drug on these visit days and should be instructed to take their study drug after the PK sample is drawn. At each study visit with a PK draw, patients will be asked the time that study drug was taken on the preceding 2 days.**

9.5.3 Pharmacogenomic Measurements

Genotyping samples will only be collected from patients who agree to provide genotyping samples as documented by signing a separate Genotyping consent form. Prior to dosing, a blood sample (3 mL) will be obtained for potential genotyping analysis. This blood sample will be collected into a plastic K2EDTA tube and gently inverted 8 to 10 times to ensure adequate mixing. The blood sample will be stored upright in the original tube in a −20°C or colder freezer (cannot be self-defrosting type) within 30 minutes of collection. This sample will be identified with the patient’s initials and date of collection and will not contain any personal identification information. The sample will be shipped to a secure long-term storage facility and retained for up to 10 years for possible genotyping analysis of PK and ADME genes. If there is no requirement within this timeframe for genotyping analysis, the blood sample will be destroyed.

Details pertaining to the collection, handling, and shipment of blood samples for potential genotyping analysis are located in the Study Manual.
9.5.4 Appropriate Measurements

The co-primary outcome measures of efficacy used in this study of overall survival and rPFS are endpoints widely used to assess patients with progressive metastatic prostate cancer and are widely recognized as clinically relevant. The safety measures used in this study are standard and include measurement of adverse events, vital signs, physical examinations, ECGs, and clinical laboratory testing.

9.5.5 Primary Efficacy Variables

The co-primary efficacy variables are accepted measures in subjects with asymptomatic or mildly symptomatic patients with progressive metastatic prostate cancer who have disease progression despite androgen deprivation therapy.

- To determine the benefit of MDV3100 as compared to placebo as assessed by overall survival;
- To determine the benefit of MDV3100 as compared to placebo as assessed by rPFS.

9.5.6 Study Procedures

Study procedures are summarized in tabular form in the Study Schedule of Activities.

9.5.6.1 Screening (Days -42 to -1) and (Days -28 to -1)

During this visit, the patient will be thoroughly informed about all aspects of the study, including all scheduled visits and activities, and will be requested to sign and date the informed consent form prior to any study-specific procedures. The informed consent must be signed within 6 weeks of randomization; otherwise the Screening visit must be repeated. The original signed and dated informed consent form must be retained by the Investigator in the patient’s file and a copy must be provided to the patient.

The abdominopelvic CT scan or MRI, bone scan, and postero-anterior and lateral chest x-ray (and chest CT also if suspected or documented chest metastatic disease is demonstrated on plain chest x-ray) must occur within 6 weeks of randomization; otherwise the Screening visit must be repeated.

Patient eligibility will be assessed and confirmed by the Investigator. All the inclusion criteria must be met and none of the exclusion criteria may apply. All the results from the screening procedures must be available before determining a patient’s eligibility for the study.

All protocol-specified procedures at the Screening visit listed below must occur within 28 days of randomization; otherwise the Screening visit must be repeated.
The following procedures will be performed at the Screening visit:

- Medical history;
- 12-lead ECG;
- Vital signs (blood pressure, heart rate, temperature);
- Complete physical examination, including weight and height;
- Laboratory assessments (central: hematology, chemistry, and urinalysis; and local: PSA);
- ECOG performance status (see APPENDIX B);
- Record concomitant medications;
- Brief Pain Inventory (Short Form), to assess pain related to prostate cancer only;
- At least two business days prior to Study Day 1, complete and sign the Randomization Authorization Form;
- Fax the Randomization Authorization Form to the study Medical Monitor together with a copy of the screening ECG Analysis Report, screening central laboratory reports, and concomitant medication list (may be completed on the Randomization Authorization Form);
- The patient may undergo his Day 1 visit only after receipt of the signed Randomization Authorization Form, or confirmation email that has been approved by a study Medical Monitor or designee.

9.5.7 Study Evaluations

9.5.7.1 Study Day 1 (Week 1)

The following procedures should be performed prior to randomization:

- Triplicate 12-lead ECGs during a 15-minute interval;
- Vital signs (blood pressure, heart rate, temperature);
- Brief physical examination including weight;
- ECOG performance status;
- Brief Pain Inventory (Short Form), to assess pain related to prostate cancer only;
- Brief Fatigue Inventory (APPENDIX D) and assessment of the severity of the patient’s fatigue;
- FACT-P and EQ-5D quality of life questionnaires;
- Review and record concomitant medications and any interval new medical history since Screening;
- Review and record any serious adverse events that occurred from the time the patient signed the informed consent form (if not already reported) and report as applicable and required by the protocol;

- Review of inclusion and exclusion criteria and confirmation that the patient is eligible for the study;

- Randomize the patient using the IVRS/IWRS.

The following procedures should be performed after randomization and prior to the administration of study drug:

- Laboratory assessments (central: hematology, chemistry, and urinalysis; and local: PSA). Repeat laboratory assessments are not required if within 3 days of screening central laboratory draw date;

- Whole blood sample for potential genotype analysis. Genotyping samples will only be collected from patients who agree to provide genotyping samples as documented by signing a separate Genotyping informed consent form;

- Instruct patient to self administer study drug (dosing must occur within 3 days of randomization);

- Dispense study drug for the first 28 days (One bottle).

9.5.7.2 Study Day 29 (Week 5) (± 3 days)

The following procedures should be performed:

- 12-lead ECG;

- Vital signs (blood pressure, heart rate, temperature);

- Central laboratory assessment (hematology, urinalysis, and chemistry);

- Ask the patient and record the time that study medication was taken on the preceding 2 days. (Patients should hold study drug administration prior to this visit and take study drug after the PK blood draw. PK sample should be taken even if patient did not hold study drug);

- PK sample;

- Brief physical examination including weight;

- ECOG performance status;

- Record concomitant medications;

- Record adverse events;

- Instruct patient to self administer study drug after PK sample;

- Dispense study drug for next 28 days (One bottle);

- FACT-P quality of life questionnaire.
9.5.7.3 Study Day 57 (Week 9) (± 3 days)

The following procedures should be performed:

- Vital signs (blood pressure, heart rate, temperature);
- Brief physical examination including weight;
- ECOG performance status;
- Record concomitant medications;
- Record adverse events;
- Instruct patient to self administer study drug;
- Dispense study drug for next 28 days (One bottle);
- Abdominopelvic (and chest if screening demonstrated metastatic chest disease) CT scan or MRI (whichever imaging study was conducted at the Screening visit). The window for radiological (CT/MRI) assessments at this visit is ± 7 days;
- Bone scan. The window for the bone scan at this visit is ± 7 days.

If there is evidence of radiographic soft tissue or bone progression, a confirmatory scan using the same modality that detected disease progression must be performed at least 6 weeks later or at the next scheduled scan (Week 17).

9.5.7.4 Study Day 85 (Week 13) (± 3 days)

The following procedures should be performed:

- 12-lead ECG;
- Vital signs (blood pressure, heart rate, temperature);
- Laboratory assessment (central: hematology, chemistry, and urinalysis; and local: PSA);
- Ask the patient and record the time that study medication was taken on the preceding 2 days. (Patients should hold study drug administration prior to this visit and take study drug after the PK blood draw. PK sample should be taken even if patient did not hold study drug);
- PK sample;
- Brief physical examination including weight;
- ECOG performance status;
- Record concomitant medications;
- Record adverse events;
- Instruct patient to self administer study drug;
- Dispense study drug for next 28 days (One bottle);
- Brief Pain Inventory (Short Form), to assess pain related to prostate cancer only;
- FACT-P and EQ-5D quality of life questionnaires.
9.5.7.5 **Study Day 113 (Week 17) (± 3 days)**

The following procedures should be performed:

- Vital signs (blood pressure, heart rate, temperature);
- Local laboratory assessment (PSA);
- Brief physical examination including weight;
- ECOG performance status;
- Record concomitant medications;
- Record adverse events;
- Instruct patient to self administer study drug;
- Dispense study drug for next 28 days (One bottle);
- Abdominopelvic (and chest if screening demonstrated metastatic chest disease) CT scan or MRI using the same modality as at the Screening visit. The window for radiological (CT/MRI) assessments at this visit is ± 7 days;
- Bone scan. The window for the bone scan at this visit is ± 7 days.

If there is evidence of radiographic bone progression on bone scan only, a confirmatory bone scan must be performed at least 6 weeks later or at the next scheduled scan (Week 25).

9.5.7.6 **Study Day 141 (Week 21) (± 3 days)**

The following procedures should be performed:

- Vital signs (blood pressure, heart rate, temperature);
- Local laboratory assessment (PSA);
- Brief physical examination including weight;
- ECOG performance status;
- Record concomitant medications;
- Record adverse events;
- Instruct patient to self administer study drug;
- Dispense study drug for next 28 days (One bottle).

9.5.7.7 **Study Day 169 (Week 25) (± 3 days)**

The following procedures should be performed:

- 12-lead ECG;
- Vital signs (blood pressure, heart rate, temperature);
- Laboratory assessment (central: hematology, chemistry, and urinalysis; and local: PSA);
• Ask the patient and record the time that study medication was taken on the preceding 2
days. (Patients should hold study drug administration prior to this visit and take study
drug after the PK blood draw. PK sample should be taken even if patient did not hold
study drug);
• PK sample;
• Brief physical examination including weight;
• ECOG performance status;
• Record concomitant medications;
• Record adverse events;
• Instruct patient to self administer study drug;
• Dispense study drug for next 84 days (three bottles);
• Brief Pain Inventory (Short Form), to assess pain related to prostate cancer only;
• FACT-P and EQ-5D quality of life questionnaires;
• Abdominopelvic (and chest if screening demonstrated metastatic chest disease) CT scan
or MRI using the same modality as at the Screening visit The window for radiological
(CT/MRI) assessments at this visit is ± 7 days;
• Bone scan. The window for the bone scan at this visit is ± 7 days.
If there is evidence of radiographic bone progression on bone scan, a confirmatory bone scan
must be performed at least 6 or more weeks later.

9.5.7.8 Study Day 197 (Week 29), and Day 225 (Week 33) (± 7 days)
The following procedures should be performed but may be conducted via a phone call with
the patient.
• ECOG performance status;
• Record concomitant medications;
• Record adverse events.

If this visit is done at the site then vital signs (blood pressure, heart rate, temperature) should
be recorded.

9.5.7.9 Study Day 253 (Week 37) (± 7 days)
The following procedures should be performed:
• 12-lead ECG;
• Vital signs (blood pressure, heart rate, temperature);
• Laboratory assessment (central: hematology, chemistry, and urinalysis; and local: PSA);
- Brief physical examination including weight;
- ECOG performance status;
- Record concomitant medications;
- Record adverse events;
- Instruct patient to self administer study drug;
- Dispense study drug for next 84 days (three bottles);
- FACT-P and EQ-5D quality of life questionnaires;
- Abdominopelvic (and chest if screening demonstrated metastatic chest disease) CT scan or MRI using the same modality as at the Screening visit;
- Bone scan.

If there is evidence of radiographic bone progression on bone scan only, a confirmatory bone scan must be performed at least 6 or more weeks later.

### 9.5.7.10 Study Day 281 (Week 41), and Day 309 (Week 45) (± 7 days)

The following procedures should be performed but may be conducted via a phone call with the patient:
- ECOG performance status;
- Record concomitant medications;
- Record adverse events.

If this visit is done at the site then vital signs (blood pressure, heart rate, temperature) should be recorded.

### 9.5.7.11 Study Day 337 (Week 49) and every subsequent 84 days (± 7 days)

The following procedures should be performed:
- 12-lead ECG;
- Vital signs (blood pressure, heart rate, temperature);
- Laboratory assessment (central: hematology, chemistry, and urinalysis; and local: PSA);
- Brief physical examination including weight;
- ECOG performance status;
- Record concomitant medications;
- Record adverse events;
- Instruct patient to self administer study drug;
- Dispense study drug for next 84 days (three bottles);
- FACT-P and EQ-5D quality of life questionnaires;
• Abdominopelvic (and chest if screening demonstrated metastatic chest disease) CT scan or MRI using the same modality as at the Screening visit;

• Bone scan.

If there is evidence of radiographic bone progression on bone scan only, a confirmatory bone scan must be performed at least six or more weeks later.

9.5.7.12 Safety Follow-Up Visit

All patients terminating study drug treatment will be seen 28 days (± 7 days) following the last dose of study drug or prior to the start of cytotoxic chemotherapy or an investigational agent, whichever occurs first.

The following procedures will be performed during the Safety Follow-up visit:

• 12-lead ECG;

• Vital signs (blood pressure, heart rate, temperature);

• Laboratory assessment (central: hematology, chemistry, and urinalysis; and local: PSA);

• Brief physical examination including weight;

• ECOG performance status;

• Record concomitant medications;

• Record adverse events.

9.5.7.13 Long-Term Follow-Up (± 7 days)

All patients terminating study drug treatment MUST undergo long-term follow-up to assess for survival, subsequent therapy for prostate cancer, skeletal-related events, and radiographic progression. All long-term follow-ups will be performed per schedule of events every 4 weeks until Week 49 and then every 12 weeks. The following assessments will be performed during the long-term follow-up:

• Survival status:
  • If the patient has died, date of death should be obtained;

• Subsequent therapy for prostate cancer;

• Skeletal-related events;

• Radiographic progression (until confirmed) via CT or MRI, using the same modality as at the Screening visit, and bone scan. Imaging for assessment of radiographic progression is not required if radiographic progression has been previously determined (including the protocol-specified confirmatory scans). Note that determination of radiographic progression should be confirmed by the central independent radiology review prior to stopping radiographic imaging until the time that at least 410 rPFS events are confirmed as required for the primary PFS analysis. After this time, radiographic progression should be confirmed by the local radiology review prior to stopping radiographic imaging. However, scans should continue to be sent to the central imaging contract research organization for archiving.
If imaging is not required as described above, the other assessments may be obtained with a telephone contact. Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete study-related assessments and retrieve any outstanding data and study drug. Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Contact via an alternate, pre-approved contact is permissible if the patient is not reachable. Such efforts should be documented in the source documents.

9.5.7.14 Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient’s request, or as deemed necessary by the Investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities will be completed at Unscheduled visits (other than those exclusively for return or re-supply of study drug):

- 12-lead ECG (if medically indicated);
- Vital signs (blood pressure, heart rate, temperature);
- Central laboratory assessment (hematology, urinalysis, and chemistry);
- Brief physical examination including weight;
- ECOG performance status;
- Record concomitant medications;
- Record adverse events.

If the Unscheduled visit occurs prior to Week 25 and the unscheduled visit is due to an adverse event then the following procedures should also be performed:

- Ask the patient and record the time that study medication was taken on the preceding 2 days. (Patients should hold study drug administration for this day prior to this visit and take study drug after the PK blood draw. PK sample should be taken even if patient did not hold study drug);
- PK sample.

9.6 Data Quality Assurance

9.6.1 Clinical Procedures

Medivation, Inc. personnel or their designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, case report forms, monitoring requirements, and reporting of serious adverse events with the site personnel.

9.6.2 Monitoring

This study will be monitored by Medivation (or designee) in accordance with current GCP regulations. By signing this protocol, the Investigator grants permission to Medivation (or designee), and appropriate regulatory authorities to conduct on-site monitoring of all
appropriate study documentation. In order to assure the accuracy of data collected in the case report forms, it is mandatory that representatives of Medivation or designee have access to original source documents (e.g., patient records, patient charts, and laboratory reports). 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 records of the study. It will be the Study Monitor’s responsibility to inspect the case report forms at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all case report form entries. The Study Monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the case report forms. The Investigator agrees to cooperate with the Study Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.6.3 Data Management

Clinical data management will be performed by Medivation or designee according to procedures described in a comprehensive Data Management Plan that will be subject to review and approval by Medivation. The Data Management Plan will include procedures for all aspects of the processing of the data from this study and, where clinical data management is outsourced, the responsibilities of Medivation and its selected designee. 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 Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary (WHO-DD), respectively. The Data Management Plan will include specific details of which version of these dictionaries has been used.

Perceptive Informatics, Inc. will be responsible for managing the blinded independent review of radiographic data as described in the independent review charter. Perceptive Informatics will assist with the collection of images from the investigator sites and will be responsible for reviewing those images and maintaining the database, including entry of the independently read imaging data.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

A statistical analysis plan will describe the statistical methods and analyses used to analyze this study for submission to the US FDA and to the European Medicines Agency. The analysis populations to be used include:

Intent-to-Treat Population:

The Intent-to-Treat (ITT) population is defined as all patients who were randomized in this study. The ITT population will be analyzed by treatment arm as randomized (i.e., treatment arm based on randomization assignment). The ITT population will be used to conduct efficacy analyses.
Safety Population:

The safety population is defined as all randomized patients who received at least 1 dose or partial dose of study drug. The safety population will be analyzed by treatment arm as treated (i.e., based on the treatment the patient actually received rather than the treatment to which the patient was randomized). The safety population will be used to conduct safety analyses.

9.7.1.1 Efficacy Analyses

Overall survival and rPFS are the two co-primary efficacy endpoints for the study. The overall type I error rate is 0.05 (two-sided) for the study and will be allocated to the two co-primary endpoints as follows: 0.049 for overall survival and 0.001 for rPFS. The study will be continued until the primary analysis for the OS co-primary endpoint has been completed.

9.7.1.1.1 Overall Survival

The duration of overall survival will be calculated for all randomized patients from the date of randomization to the date of death due to any cause. Conventions for censoring will be described in the statistical analysis plan. There will be a formal interim analysis and a primary analysis for overall survival. The primary analysis of overall survival will be performed when at least a total of 765 deaths have been reported.

A formal interim analysis for overall survival will be performed at approximately 67% of the required total number of death events (516 of 765) for the primary overall survival analysis. A two-stage group-sequential design with Lan-DeMets alpha-spending function based upon the O’Brien-Fleming approach will be used to preserve the associated two-sided type I error rate of 0.049. Alpha-spending for the interim overall survival analysis and the primary overall survival analysis will be 0.012 and 0.045 (both two-sided), respectively. If the actual number of events for the interim analysis is not 516, alpha-spending between the two overall survival analyses will be adjusted accordingly. The interim analysis of overall survival will be conducted by an independent statistician under the charter of the Data Monitoring Committee.

The effect of MDV3100 compared to placebo based on overall survival will be tested with an unstratified log-rank test.

9.7.1.1.2 Radiographic Progression-Free Survival

The duration of rPFS will be calculated for all randomized patients from the date of randomization to the date of first objective evidence of radiographic progression (soft tissue or bone lesion) as assessed by independent review or date of death on study due to any cause, whichever occurs first. Death on study is defined as death due to any cause within 168 days after treatment discontinuation. This 168-day interval represents 2 consecutive tumor assessments, 12 weeks apart. Conventions for censoring will be described in the statistical analysis plan. This analysis will be based upon at least the first 410 rPFS events observed in the trial.
Radiographic disease progression is defined as progressive disease by RECIST 1.1 for soft tissue disease or by appearance of two or more new lesions on bone scan for bone disease. The radiological assessment by the Independent Central Imaging Review will be used as the primary data source to conduct the analysis. However, the radiological assessment by the Investigator will also be used in sensitivity analyses. The number of concordant and discordant cases will be summarized.

The effect of MDV3100 compared to placebo based on rPFS will be tested with an unstratified log-rank test at the significance level of 0.001 (two-sided).

The primary analysis of rPFS will be conducted by an independent statistician and reviewed by the external Data Monitoring Committee. The study will not be discontinued based upon the primary analysis of rPFS.

9.7.1.1.3 Secondary Efficacy Endpoints

All secondary efficacy endpoint analyses will be performed by adjusting for multiple comparisons. All planned secondary endpoint analyses will maintain a study-wide type I error of 5%. The detailed methodology will be presented in the statistical analysis plan.

9.7.1.1.3.1 Time to First Skeletal-Related Event

Skeletal-related events include radiotherapy to the bone, surgery to the bone, pathological bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.

Time to first skeletal-related event will be calculated for all randomized patients from the date of randomization to the date of first skeletal-related event. Conventions for censoring will be described in the statistical analysis plan.

The effect of MDV3100 compared to placebo based on time to first skeletal-related event will be tested with an unstratified log-rank test.

9.7.1.1.3.2 Time to Initiation of Cytotoxic Chemotherapy

Time to initiation of cytotoxic chemotherapy will be calculated for all randomized patients from the date of randomization to the date of initiation of cytotoxic chemotherapy. Conventions for censoring will be described in the statistical analysis plan.

The statistical analysis for time initiation of cytotoxic chemotherapy will be the same as that described for time to first skeletal-related event.

9.7.1.1.3.3 Time to PSA Progression

PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 μg/L (2 ng/mL) above the nadir (or baseline value for patients who did not have a decline in PSA value at Week 13). This increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later.
Time to PSA progression will be calculated for all randomized patients from the date of randomization to the date of first observation of PSA progression. Conventions for censoring will be described in the statistical analysis plan.

The statistical analysis for time to PSA progression will be the same as that described for time to initiation of cytotoxic chemotherapy.

9.7.1.1.3.4 PSA Response ≥ 50%

Confirmed PSA responses will be defined as ≥ 50% reductions in PSA from baseline to lowest postbaseline PSA result as determined by the local laboratory, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response. PSA response ≥ 50% will be calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment. An unstratified Cochran-Mantel-Haenszel mean score test will be used to compare the response rates between the MDV3100-treated and the placebo groups.

9.7.1.1.3.5 Best Overall Soft Tissue Response

The best overall soft tissue response as assessed by investigators using RECIST 1.1 will be summarized. Only patients with measurable soft tissue disease at screening (i.e., at least 1 target lesion per RECIST 1.1) will be included in this analysis. A Cochran-Mantel-Haenszel mean score test will be used to compare the proportion of patients with an objective response (complete response or partial response) per RECIST 1.1 between the MDV3100-treated and the placebo groups.

9.7.1.1.4 Exploratory Efficacy Endpoints

Other exploratory efficacy endpoints include assessments of FACT-P, EQ-5D, Brief Pain Inventory, time to first subsequent antineoplastic therapy (cytotoxic or hormonal), and PSA response ≥ 90%. No adjustment will be made for multiple comparisons.

9.7.1.1.4.2 FACT-P

The FACT-P data will be summarized descriptively by treatment group and study visit.

9.7.1.1.4.3 EQ-5D

The EQ-5D data will be summarized descriptively by treatment group and study visit.

9.7.1.1.4.4 Brief Pain Inventory

The rate of pain progression, defined as increase of ≥ 30% from baseline in the average of Brief Pain Inventory pain intensity item scores (items 3, 4, 5, and 6) at 6 months will be used to compare the MDV3100-treated and the placebo groups. Pain assessment by the Brief Pain Inventory will be summarized descriptively by treatment group at baseline, 3 months, and 6 months.
9.7.1.1.4.5 Time to First Subsequent Antineoplastic Therapy

All antineoplastic therapies, including cytotoxic and hormonal therapies, will be considered for this endpoint. Time to first subsequent antineoplastic therapy will be compared between the MDV3100-treated and the placebo groups using an unstratified log-rank test at the significance level of 0.05 (two-sided).

9.7.1.1.4.6 PSA Response ≥ 90%

Confirmed PSA responses will be defined as ≥ 90% reductions in PSA from baseline to lowest postbaseline PSA result as determined by the local laboratory, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response. PSA response ≥ 90% will be calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment. An unstratified Cochran-Mantel-Haenszel mean score test at the significance level of 0.05 (two-sided) will be used to compare the response rates between the MDV3100-treated and the placebo groups.

9.7.1.2 Safety Analyses

Safety analyses will be conducted using the safety population and summarized by treatment arm as treated. The treatment emergent period will be defined as the period of time from the first dose date of study drug up to 28 days after last dose date of study drug or the date of initiation of investigational agent, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and ECGs. Descriptive statistics will be used rather than inferential statistics.

The severity of all adverse events is to be evaluated by the Investigator based on the National Cancer Institute’s CTCAE, version 4.0. All adverse events will be coded to preferred term and system organ class using MedDRA 12.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment, when calculating incidence.

Laboratory data consist of hematology, urinalysis, and chemistry laboratory tests. The National Cancer Institute’s CTCAE, version 4.0, will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus postbaseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based on the normal range (low, normal, and high) will be provided for each parameter 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 first dose date of study drug. The percentage of patients in each treatment group with new abnormal and clinically significant ECG findings will be summarized by study visit.
9.7.1.3 Pharmacokinetic Analyses

The PK data analyses will include calculation of parametric and/or non-parametric descriptive statistics of the $C_{\text{min}}$ data for MDV3100 and possibly one or more metabolites. In addition, the PK data from this study will be combined with PK data from other studies to build a population PK model, which will be reported separately.

9.7.1.4 Randomization

Patients will be centrally randomized through an IVRS/IWRS to receive MDV3100 or placebo in a 1:1 ratio using a computer-generated permuted block randomization schedule. Randomization will be stratified by investigative site.

9.7.2 Determination of Sample Size

This study is powered to evaluate both overall survival and rPFS. The overall type I error rate (two-sided) for the study is 0.05 with 0.049 allocated to overall survival and 0.001 allocated to rPFS. The desired operating characteristics for the overall survival endpoint were used to determine the study’s total sample size and overall duration. The timing of the primary analysis of each endpoint was determined separately based on the considerations described below.

The study is planned to randomize approximately 1,680 patients (840 patients per treatment arm) in order to observe at least 765 deaths due to any cause. This sample size includes a 5% increase adjustment for patients lost to follow-up. The sample size calculations for the overall survival endpoint are based on the following considerations:

- A 1:1 randomization ratio between the two treatment arms (MDV3100 versus placebo);
- A target hazard ratio of 0.815. The expected median overall survival for the placebo arm is 28 months as measured from the date of randomization. A target hazard ratio of 0.815 corresponds to a 22.7% increase in median overall survival for the MDV3100 arm relative to the placebo arm (approximately 34.4 versus 28 months);
- A minimum of 765 death events provides 80% power to detect the target hazard ratio of 0.815 based on a two-sided log-rank test and significance level of 0.049.

The co-primary analysis of rPFS was determined from the following considerations:

- A target hazard ratio of 0.57. The expected median rPFS for the placebo arm is 8 months as measured from the date of randomization. A target hazard ratio of 0.57 corresponds to a 75% increase in median rPFS for the MDV3100 arm relative to the placebo arm (approximately 14 versus 8 months);
- The required minimum of 410 rPFS events (radiographic progression or death on study, defined as death from any cause within 168 days after treatment discontinuation, whichever occurs first) provides $\geq 99\%$ power to detect a target hazard ratio of 0.57 based on a two-sided log-rank test and significance level of 0.001.
9.8 Changes in the Conduct of the Study or Planned Analyses

The Investigator will not deviate from the protocol without first obtaining approval from Medivation (or designee) and the IRB/IEC, if required. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard, then notify Medivation (or designee) and the IRB/IEC immediately regarding the type of emergency and course of action taken. Any other changes or deviations in the protocol will be made as an amendment to the protocol and approved by Medivation (or designee) and the IRB/IEC before they are implemented. The Principal Investigator or designee must notify Medivation (or designee) of any inadvertent protocol violations upon their discovery, and document the violations appropriately in the study files and/or in the case report forms.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB/IEC, and all patients on treatment will again provide informed consent.

9.9 Study Committees and Communication

There will be two formal committees for this study.

9.9.1 Steering Committee

The study will be overseen by a Steering Committee consisting of experts in prostate cancer and members of Medivation staff. The Steering Committee will participate in the design, conduct, analyses, and publication of the study. The Steering Committee will remain blinded to patients’ treatment assignment until the database is officially locked and unblinded.

9.9.2 Data Monitoring Committee

An independent Data Monitoring Committee consisting of experts in prostate cancer, clinical trial safety monitoring, and statistics will evaluate the safety of the trial on an ongoing basis. Approximately every 4 months after the first 50 patients have been enrolled into the trial, members of the Data Monitoring Committee will review all available safety data including survival. Further details on the composition and responsibility of the Data Monitoring Committee will be outlined in a separate charter.

10. COMPENSATION, INSURANCE, AND INDEMNITY

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

If a bodily injury is sustained, resulting directly from the use of the study drug or by required study procedures, Medivation will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which 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 his/her staff. No other compensation of any type will be provided by Medivation. Financial compensation for lost wages, disability or discomfort due to the study participation or procedures is not available.
11. INVESTIGATIONAL PRODUCT ACCOUNTABILITY

The Investigator must maintain accurate records (including dates and lot numbers) of all study drug supplies received. All study drug supplies issued to, used by, and returned by each patient must be recorded on a Drug Accountability Log completed by the Investigator, study coordinator, or pharmacist. All remaining study supplies, opened or unopened, must be returned to Medivation (or designee) at the end of the study or destroyed on site according to the site’s standard operating procedures only after study drug accountability has been completed and with approval of the Study Monitor. All records must be made available to Medivation or authorized representatives and appropriate regulatory agencies, upon request.

12. LABORATORY REQUIREMENTS

A central laboratory will be used for clinical laboratory sample processing for this study except for PSA testing which will be conducted locally. Details regarding safety laboratory tests are presented in the laboratory manual for this study.

A central laboratory will also be used for ECG analyses.

13. CASE REPORT FORMS

The study will be using an electronic data capture system. All electronic case report forms will be designed and provided electronically to the site by Medivation (or designee) and electronic data capture system vendor. All case report forms are to be completely filled out and reviewed and signed by the Investigator or Sub-Investigators listed on the Form FDA 1572 and/or other appropriate local health authority documents. Every effort should be made to have the case report forms completed and signed as soon as possible following a patient’s study visit.

Perceptive Informatics, Inc. is responsible for designing and managing the case report forms for the blinded independent review of radiographic tumor scans as described in the independent review charter. Treatment assignment blinding will be maintained until the study is unblinded after database lock.

14. STUDY MONITORING AND AUDITING

All aspects of the study will be monitored by qualified individuals designated by Medivation. Monitoring will be conducted according to GCP and standard operating procedures for compliance with applicable government regulations. The Investigator agrees to allow these monitors access to the clinical supplies, dispensing, and storage areas and to the clinical files of the study patients, and, if requested, agrees to assist the monitors.

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 representatives of Medivation. The purpose of the audit is to ensure that the study is being, 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 subsequent regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed upon time.
15. RETENTION OF RECORDS

The Investigator must make study data accessible to the Study Monitor or other authorized representatives of Medivation (or designee) and Regulatory Agency (e.g., FDA) inspectors 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 on the Patient Confidentiality Log for a duration in accordance with local requirements but for a minimum period of 15 years.

Investigators must maintain all study documentation for at least a period of 2 years following the approval of the drug, or until 2 years after the investigational drug program is discontinued; or in accordance with local requirements (if longer). Study documentation includes all Essential Documents as defined in ICH E6 Guidelines for Good Clinical Practice. Medivation or designee will notify the Investigator when any records may be discarded.

16. USE OF INFORMATION AND PUBLICATION

Medivation recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Study Agreement.
17. REFERENCES


18. SIGNATURE PAGE

Medivation, Inc.

A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients with Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy

Signature of Agreement for Protocol MDV3100-03

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practices (GCPs) 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.

__________________________________________
Site Number   Print Site Name

__________________________________________
Investigator Signature   Date

__________________________________________
Print Investigator Name and Title
APPENDIX A: Soft Tissue Assessment (RECIST 1.1)

Table 1 – Time point response: patients with target (+/- non-target) disease.

<table>
<thead>
<tr>
<th>Target lesions</th>
<th>Non-target lesions</th>
<th>New lesions</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD or not all evaluated</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD or not all evaluated</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>Non-PD</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

<table>
<thead>
<tr>
<th>Non-target lesions</th>
<th>New lesions</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>Non-CR/non-PD a</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>Unequivocal PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

CR = complete response, PD = progressive disease, and NE = inevaluable.
a ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

## APPENDIX B: ECOG Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG Performance Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
APPENDIX C: 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?
   1. Yes
   2. No

2. Or 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 circling the one number that best describes your pain at its worst in the last 24 hours.
   0 = No Pain
   10 = Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.
   0 = No Pain
   10 = Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.
   0 = No Pain
   10 = Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.
   0 = No Pain
   10 = Pain as bad as you can imagine
<table>
<thead>
<tr>
<th>STUDY ID #</th>
<th>HOSPITAL #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>Name:</td>
<td></td>
</tr>
<tr>
<td>Last</td>
<td>First</td>
</tr>
<tr>
<td>Middle Initial</td>
<td></td>
</tr>
</tbody>
</table>

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 circle the one percentage that most shows how much relief you have received.

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

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

<table>
<thead>
<tr>
<th>General Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Does not Interfer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mood</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Does not Interfer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Walking Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Does not Interfer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normal Work (includes both work outside the home and housework)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Does not Interfer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relations with other people</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Does not Interfer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Does not Interfer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enjoyment of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Does not Interfer</td>
</tr>
</tbody>
</table>
APPENDIX D: Brief Fatigue Inventory

Brief Fatigue Inventory

Date

First Name

Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ___ No ___

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

   0 1 2 3 4 5 6 7 8 9 10

   No

   Fatigue

   As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

   0 1 2 3 4 5 6 7 8 9 10

   No

   Fatigue

   As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

   0 1 2 3 4 5 6 7 8 9 10

   No

   Fatigue

   As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

   A. General activity

      0 1 2 3 4 5 6 7 8 9 10

      Does not interfere

      Completely interferes

   B. Mood

      0 1 2 3 4 5 6 7 8 9 10

      Does not interfere

      Completely interferes

   C. Walking ability

      0 1 2 3 4 5 6 7 8 9 10

      Does not interfere

      Completely interferes

   D. Normal work (includes both work outside the home and daily chores)

      0 1 2 3 4 5 6 7 8 9 10

      Does not interfere

      Completely interferes

   E. Relations with other people

      0 1 2 3 4 5 6 7 8 9 10

      Does not interfere

      Completely interferes

   F. Enjoyment of life

      0 1 2 3 4 5 6 7 8 9 10

      Does not interfere

      Completely interferes

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APPENDIX E: 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.

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>G91 I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G92 I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G93 Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G94 I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G95 I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G96 I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G97 I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOCIAL/FAMILY WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>G91 I feel close to my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G92 I get emotional support from my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G93 I get support from my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G94 My family has accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G95 I am satisfied with family communication about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G96 I feel close to my partner (or the person who is my main support)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Q6 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.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>G97 I am satisfied with my sex life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
**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

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>QED</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>QES2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>QES3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>QES4</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>QES5</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>QES6</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### FUNCTIONAL WELL-BEING

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GF1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF4</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF5</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF6</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF7</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
**FACT-P (Version 4)**

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

<table>
<thead>
<tr>
<th>ADDITIONAL CONCERNS</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am losing weight</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have a good appetite</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have aches and pains that bother me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have certain parts of my body where I experience pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>My pain keeps me from doing things I want to do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am satisfied with my present comfort level</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to feel like a man</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble moving my bowels</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have difficulty urinating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I urinate more frequently than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>My problems with urinating limit my activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to have and maintain an erection</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
APPENDIX F: European Quality of Life 5-Domain Scale

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about

I have some problems in walking about

I am confined to bed

Self-Care

I have no problems with self-care

I have some problems washing or dressing myself

I am unable to wash or dress myself

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

I have no problems with performing my usual activities

I have some problems with performing my usual activities

I am unable to perform my usual activities

Pain/Discomfort

I have no pain or discomfort

I have moderate pain or discomfort

I have extreme pain or discomfort

Anxiety/Depression

I am not anxious or depressed

I am moderately anxious or depressed

I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
APPENDIX G: Guidance on Reducing the Risks of Pharmacokinetic Drug-Drug Interactions with MDV3100

There is a potential for other medicinal products to affect MDV3100 exposures and for MDV3100 to affect exposures to other medicinal products. Examples of drugs with the potential for drug-drug interactions with MDV3100 are provided below. For the most current list of drugs that may be subject to drug-drug interactions, consult the following sources:

- http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm
- http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Potential for Other Medicinal Products to Affect MDV3100 Exposures

CYP2C8 inhibitors and inducers
Clinical data indicate that CYP2C8 plays an important role in the metabolism of MDV3100; therefore, strong inhibitors (e.g., gemfibrozil) or inducers (e.g., rifampicin) of CYP2C8 should be used with caution during MDV3100 treatment. If concomitant use of strong CYP2C8 inhibitors cannot be avoided, then the dose of study drug should be reduced to 80 mg per day (2 capsules).

Potential for MDV3100 to Affect Exposures to Other Medicinal Products

Enzyme induction
Clinical data indicate that MDV3100 is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. UGT may be induced as well. These results suggest that MDV3100 causes enzyme induction via activation of PXR. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4, CYP2C9, CYP2C19, or UGT should be used with caution when administered concomitantly with MDV3100 and may require dose adjustment to maintain therapeutic plasma concentrations. Such substrates include, but are not limited to:

- Macrolide antibiotics (e.g., clarithromycin);
- Benzodiazepines (e.g., diazepam, midazolam);
- Immune modulators (e.g., cyclosporine, tacrolimus);
- HIV antivirals (e.g., indinavir, ritonavir);
- Anti-epileptics (e.g., phenobarbitone, phenytoin);
- Coumarins (e.g., warfarin);
- Certain anti-cancer agents (e.g., cabazitaxel, irinotecan, sunitinib).

In consideration of the long half-life of MDV3100 (approximately 1 week), effects on enzymes may persist for 1 month or longer after stopping MDV3100.
**P-gp substrates**

In vitro data indicate that MDV3100 may be a P-gp inhibitor. The effects of MDV3100 on P-gp substrates have not been evaluated in vivo; however, under conditions of clinical use, MDV3100 may be an inducer of P-gp via activation of PXR. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with MDV3100 and may require dose adjustment to maintain optimal plasma concentrations.
APPENDIX H: Summary of Changes in Amendment 1

The following administrative changes have been made in Amendment 1:

<table>
<thead>
<tr>
<th>Section</th>
<th>Old Text</th>
<th>New Text</th>
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</thead>
<tbody>
<tr>
<td>Synopsis (Statistical Methods), Efficacy Analyses</td>
<td>N/A</td>
<td>The primary analysis of OS will be performed when at least a total of 888 deaths have been reported</td>
</tr>
<tr>
<td>Synopsis (Statistical Methods), Efficacy Analyses</td>
<td>N/A</td>
<td>An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups for both the interim and final analyses.</td>
</tr>
<tr>
<td>Synopsis (Statistical Methods), Efficacy Analyses</td>
<td>N/A</td>
<td>The trial will be continued until the primary analysis of the overall survival co-primary endpoint has been completed.</td>
</tr>
<tr>
<td>Section 9.5.5, Primary Efficacy Variables</td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by time to first skeletal-related event;</td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by overall survival</td>
</tr>
<tr>
<td></td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by time to initiation of cytotoxic chemotherapy.</td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by progression-free survival (PFS).</td>
</tr>
<tr>
<td>Section 9.7, Statistical Methods Planned in the Protocol and Determination of Sample Size</td>
<td>This section outlines the statistical methods and analyses for the study. Specific details of the methods and analyses will be provided in the Statistical Analysis Plan (SAP).</td>
<td>N/A</td>
</tr>
<tr>
<td>Section 9.7.1, Statistical and Analytical Plans</td>
<td>N/A</td>
<td>Separate statistical analysis plans will be used to describe the statistical methods and analyses used to analyze this study for submission to the United States Food and Drug Administration and to the European Medicines Agency. The analysis populations to be used include:</td>
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<td>Section</td>
<td>Old Text</td>
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</tr>
<tr>
<td>Section 9.7.1.1.1, Overall Survival</td>
<td>N/A</td>
<td>There will be a formal interim analysis and a primary analysis for overall survival. The primary analysis of OS will be performed when at least a total of 888 deaths have been reported.</td>
</tr>
<tr>
<td>Section 9.7.1.1.2, Progression-Free Survival</td>
<td>N/A</td>
<td>The study will not be discontinued based upon the primary analysis of PFS.</td>
</tr>
</tbody>
</table>
### APPENDIX I: Summary of Changes in Amendment 2

The following administrative changes have been made in Amendment 2:

<table>
<thead>
<tr>
<th>Section</th>
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</thead>
<tbody>
<tr>
<td>Synopsis (Study Centers)</td>
<td>Approximately 180</td>
<td>Approximately 225</td>
</tr>
<tr>
<td>Synopsis (Methods, Table 1), Section, 9.5.1.1.2, Progression-Free Survival</td>
<td>Criteria for Confirmation of Progression</td>
<td>Criteria for Confirmation of Progression (requirement and timing)</td>
</tr>
<tr>
<td>Synopsis (Methods, Table 1), Section, 9.5.1.1.2, Progression-Free Survival</td>
<td>N/A, new footnote</td>
<td>Confirmation must occur at the next available scan. For confirmation, at least two of the lesions first identified as new must be present at that next available scan (confirmation scan).</td>
</tr>
<tr>
<td>Synopsis (Methods, Table 1), Section 9.1, Overall Study Design and Plan</td>
<td>N/A, new insertion</td>
<td>Note that determination of radiographic progression should be confirmed by the central independent radiology review prior to stopping radiographic imaging.</td>
</tr>
<tr>
<td>Synopsis (Inclusion Criteria), Section 9.3.1, Inclusion Criteria</td>
<td>1. Willing and able to provide informed consent;</td>
<td>1. Age 18 or older and willing and able to provide informed consent</td>
</tr>
<tr>
<td>Synopsis (Inclusion Criteria), Section 9.3.1, Inclusion Criteria</td>
<td>7. Progressive disease at study entry defined as one or more of the following three criteria that occurred while the patient was on androgen deprivation therapy as defined in eligibility criterion #2</td>
<td>7. Progressive disease at study entry defined as one or more of the following three criteria that occurred while the patient was on androgen deprivation therapy as defined in eligibility criterion #3</td>
</tr>
<tr>
<td>Section 2.1 Study Schedule of Activities</td>
<td>a. Assessment may be completed by telephone.</td>
<td>a. Assessment may be completed by telephone.</td>
</tr>
<tr>
<td></td>
<td>b. Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient’s request or if deemed necessary by the Investigator.</td>
<td>b. Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient’s request or if deemed necessary by the Investigator.</td>
</tr>
<tr>
<td></td>
<td>c. Beginning after Study Drug discontinuation, all patients MUST undergo long-term follow-up to assess for survival, subsequent treatments for prostate cancer, skeletal-related events, and radiographic progression. Visit schedule will follow schedule of events.</td>
<td>c. Beginning after Study Drug discontinuation, all patients MUST undergo long-term follow-up to assess for survival, subsequent treatments for prostate cancer, skeletal-related events, and</td>
</tr>
</tbody>
</table>
Section 2.1 Study Schedule of Activities

<table>
<thead>
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<tbody>
<tr>
<td>a. A brief physical examination is required at each visit, with the exception of the Screening visit during which a complete physical examination will be completed.</td>
<td>a. or prior to initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first.</td>
</tr>
<tr>
<td>b. A single ECG will be taken at specified study visits, with the exception of the Day 1 visit during which three ECGs will be obtained during a 15-minute interval.</td>
<td>b. The informed consent must be signed within 6 weeks of randomization; otherwise the Screening visit must be repeated.</td>
</tr>
<tr>
<td>c. If medically indicated.</td>
<td>c. A brief physical examination is required at each visit, with the exception of the Screening visit during which a complete physical examination will be completed.</td>
</tr>
<tr>
<td>d. Laboratory assessments are to be obtained pre-dose and include serum chemistries, urinalysis, and hematology.</td>
<td>d. A single ECG will be taken at specified study visits, with the exception of the Day 1 visit during which three ECGs will be obtained during a 15-minute interval.</td>
</tr>
<tr>
<td>e. Genotyping samples will only be collected from patients who agree to provide genotyping samples as documented by signing a separate Genotyping informed consent form. In the event of unusual PK patterns or safety findings, genotype analysis of relevant drug metabolism and transporter genes will be conducted. If there is no requirement for analysis, the whole blood sample will be destroyed.</td>
<td>e. If medically indicated.</td>
</tr>
<tr>
<td>f. PK samples will be drawn at Week 5, 13, 25, and adverse event-related unscheduled visits prior to week 25. Plasma PK samples to be obtained pre-dose.</td>
<td>f. Laboratory assessments include serum chemistries, urinalysis, and hematology.</td>
</tr>
<tr>
<td>g. At each study visit with a PK draw, patients will be asked the time that study drug was taken on the preceding 2 days.</td>
<td>g. Genotyping samples will only be collected from patients who agree to provide genotyping samples as documented by signing a separate Genotyping informed consent form. In the event of unusual PK patterns or safety findings, genotype analysis of relevant drug metabolism and transporter genes will be conducted. If there is no requirement for analysis, the whole blood sample will be destroyed.</td>
</tr>
<tr>
<td>h. The window for all radiological (CT/MRI) assessments is ± 7 days. At Weeks 9, 17, and 25 all other procedures must be completed within the ± 3 day window.</td>
<td>h. All protocol-specified PSAs are to be done at local laboratories.</td>
</tr>
<tr>
<td>i. Disease progression observed by CT or MRI for soft tissue disease on Week 17 or later does not require a confirmatory scan.</td>
<td>i. PK samples will be drawn pre-dose at Week 5, 13, 25, and at adverse event-related unscheduled visits prior to Week 25. Patients should hold their dose of study drug on these visit days and should be instructed to take</td>
</tr>
</tbody>
</table>
### Section Old Text New Text

<table>
<thead>
<tr>
<th>Section 2.1 Study Schedule of Activities</th>
<th>1. Chest CT is required if screening chest x-ray demonstrates metastatic chest disease.</th>
<th>their study drug after the PK sample is drawn. At each study visit with a PK draw, patients will be asked the time that study drug was taken on the preceding 2 days.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Serious adverse events will be collected from the time the patient signs the consent form until the Safety Follow-up visit. Non-serious adverse events will be collected from the time of first study drug dosing until the Safety Follow-Up visit.</td>
<td>2m. The abdominopelvic CT scan or MRI, bone scan, chest x-ray or chest CT must occur within 6 weeks of randomization; otherwise the Screening visit must be repeated.</td>
<td>*m. The window for all radiological (CT/MRI) assessments is ± 7 days. At Weeks 9, 17, and 25 all other procedures must be completed within the ± 3 day window.</td>
</tr>
<tr>
<td>3. For study visit days, patients will self-administer study drug in the clinic upon instruction from the staff.</td>
<td>3m. Disease progression observed by CT or MRI for soft tissue disease on Week 17 or later does not require a confirmatory scan.</td>
<td>*m. Chest CT is required at all imaging time points, if screening chest x-ray demonstrates metastatic chest disease.</td>
</tr>
<tr>
<td>4. The Brief Pain Inventory will assess pain related to prostate cancer only.</td>
<td>4m. The Brief Pain Inventory will assess pain related to prostate cancer only.</td>
<td>*m. The Brief Pain Inventory will assess pain related to prostate cancer only.</td>
</tr>
<tr>
<td>5. Serious adverse events will be collected from the time the patient signs the consent form until the Safety Follow-up visit (or until screen fail for screen fail patients). Non-serious adverse events will be collected from the time of first study drug dosing until the Safety Follow-Up visit.</td>
<td>5m. For study visit days, patients will self-administer study drug upon instruction from the staff.</td>
<td>*m. For study visit days, patients will self-administer study drug upon instruction from the staff.</td>
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<tr>
<td>9.3.3 Removal of Patients from Therapy</td>
<td>Patients may withdraw consent to participate in the trial at any time for any reason and discontinue treatment. Investigators or the Medical Monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the Safety Follow-up visit. Patients who discontinue treatment will continue to be followed for radiographic progression (until disease progression has been confirmed), skeletal-related event, additional treatments for prostate cancer, and survival.</td>
<td>Patients may withdraw consent to participate in the trial at any time for any reason and discontinue treatment. Investigators or the Medical Monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the Safety Follow-up visit. Patients who discontinue treatment will continue to be followed for radiographic progression (until disease progression has been confirmed), skeletal-related event, additional treatments for prostate cancer, and survival. Note that determination of radiographic progression should be confirmed by the central independent radiology review prior to stopping radiographic imaging.</td>
</tr>
<tr>
<td>9.4.2.2, Directions for Administration</td>
<td>All study patients will take 4 capsules of study drug once daily. If dosing is missed on one day for any reason, double-dosing should NOT occur the following day. Patients will hold their dose of study drug on clinic visit days; they will be instructed to take their study medication after PK samples are drawn. The study drug can be taken with or without food.</td>
<td>Study patients will take four capsules of study drug once daily. If dosing is missed on one day for any reason, double-dosing should NOT occur the following day. Patients will hold their dose of study drug prior to the visit on clinic visit days; on PK visit days they will be instructed to take their study medication after PK samples are drawn. The study drug can be taken with or without food.</td>
</tr>
<tr>
<td>9.4.2.4, Storage and Labeling</td>
<td>Study drug should be stored in a secure location with limited access within the following temperature range: 59°F to 86°F (15°C to 30°C).</td>
<td>Study drug should be stored in a secure location with limited access at 77°F (25°C), with excursions permitted to 59°F to 86°F (15°C to 30°C).</td>
</tr>
</tbody>
</table>
### Section 9.4.6, Blinding

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<tbody>
<tr>
<td>Unblinding <strong>will</strong> occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. <strong>Treatment unblinding may occur per</strong> Principal Investigator <strong>request and approval</strong> by the Medivation Medical Monitor or designee. Patients whose treatment assignment has been unblinded will be permanently discontinued from treatment.</td>
<td>Unblinding <strong>should</strong> occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. <strong>The Principal Investigator should make every effort to contact</strong> the Medivation Medical Monitor or designee before unblinding a patient in IVRS/IWRS. <strong>To unblind a patient, the Principal Investigator will access the Unblinding Module in IVRS/IWRS.</strong> Patients whose treatment assignment has been unblinded will be permanently discontinued from treatment.</td>
</tr>
</tbody>
</table>

### Section 9.4.7, Prior and Concomitant Therapy

<table>
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<tr>
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<tbody>
<tr>
<td>N/A, new paragraph</td>
<td>Hormonal treatment for treating complications of LHRH treatment (e.g., hot flashes) will be allowed with Medical Monitor approval.</td>
</tr>
</tbody>
</table>

### Section 9.4.7, Prior and Concomitant Therapy

<table>
<thead>
<tr>
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</table>
| N/A, new paragraph | The following additional therapies are allowed during treatment with study medication but only once the patient has confirmed radiographic progression or has a skeletal-related event:  
- Hormonal therapies including other anti-androgens;  
- Biological anti-tumor treatments. |

### Section 9.4.7, Prior and Concomitant Therapy

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Anti-androgen therapy must be continued during the trial. If anti-androgen therapy is discontinued, the patient must be withdrawn from study treatment.</td>
<td><strong>Androgen deprivation therapy (either bilateral orchiectomy or LHRH agonist/antagonist)</strong> must be continued during the trial. If androgen deprivation therapy is discontinued, the patient must be withdrawn from study treatment.</td>
</tr>
</tbody>
</table>

### Section 9.4.8, Treatment Compliance

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Study drug accountability will be performed at <strong>specified study visits</strong> to document compliance with the dosing regimen.</td>
<td>Study drug accountability will be performed to document compliance with the dosing regimen.</td>
</tr>
<tr>
<td>Section</td>
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</tr>
<tr>
<td>Section 9.5.1.2.6, Brief Pain Inventory</td>
<td>The Brief Pain Inventory questionnaire is a validated instrument that is a patient self-rated scale assessing level of pain, effect of the pain on activities of daily living, and analgesic use. The short form of the Brief Pain Inventory is used in this study and contains nine main questions.</td>
</tr>
<tr>
<td>Section 9.5.1.3, Adverse Events</td>
<td>An adverse event or experience is defined as any symptom, sign, illness, or untoward experience (including a clinically significant laboratory finding classified as Grade 3 or higher by the National Cancer Institute’s Common Terminology Criteria for Adverse Events [CTCAE] v4.0) that develops or worsens during the course of the study, whether or not the event is considered related to study drug, and should be recorded only after the first dose of study drug is taken. Serious adverse events are recorded from the time the informed consent form is signed.</td>
</tr>
<tr>
<td>Section 9.5.1.3, Adverse Events</td>
<td>N/A, new paragraph</td>
</tr>
<tr>
<td>Section</td>
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</tr>
<tr>
<td><strong>Section 9.5.1.3.2, Disease Progression as an Adverse Event</strong></td>
<td>It is anticipated that a proportion of patients will experience disease progression.</td>
</tr>
<tr>
<td><strong>Section 9.5.1.4.1 Serious Adverse Events – Reporting</strong></td>
<td><strong>All serious adverse events occurring between the times the patient signs the informed consent and the Safety Follow-up visit must be recorded, reported, and followed up by the site Investigator using the procedure described above.</strong></td>
</tr>
<tr>
<td><strong>Section 9.5.1.4.2 Clarification in Reporting of Deaths</strong></td>
<td><strong>As overall survival is one of the co-primary endpoints of the study, all patients must be followed for survival until death and information relating to a patient’s death (e.g., date of death and primary cause of death) should be 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 the Safety Follow-up Visit will not be reported as serious adverse events, and will be captured on the designated case report form.</strong></td>
</tr>
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<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Section 9.5.15, Clinical Laboratory Tests</td>
<td>The only exception should be for Unscheduled Visits, for which another clinical laboratory may be used, if necessary or for the urgent management of an adverse event.</td>
</tr>
<tr>
<td>Section 9.5.2, Drug Concentration Measurements</td>
<td>On PK sample collection days, it is important to take all reasonable measures to ensure accurate recording of information on dosing and timing of sample collections relative to dosing history. Provision of the actual time of dosing with study drug for the previous two doses must be documented, including dosing times.</td>
</tr>
<tr>
<td>Section 9.5.6.1, Screening (Days -42 to -1) and (Days -28 to -1)</td>
<td>9.5.6.1 Screening (Days -28 to -1)</td>
</tr>
<tr>
<td>Section 9.5.6.1, Screening (Days -42 to -1) and (Days -28 to -1)</td>
<td>During this visit, the patient will be thoroughly informed about all aspects of the study, including all scheduled visits and activities, and will be requested to sign and date the informed consent form prior to any study-specific procedures. The original signed and dated informed consent form must be retained by the Investigator in the patient’s file and a copy must be provided to the patient.</td>
</tr>
<tr>
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</tr>
<tr>
<td>Section 9.5.6.1, Screening (Days -42 to -1) and (Days –28 to –1)</td>
<td>N/A, new paragraph</td>
</tr>
<tr>
<td>Section 9.5.6.1, Screening (Days -42 to -1) and (Days –28 to –1)</td>
<td>All protocol-specified procedures at the Screening visit must occur within 28 days of randomization; otherwise the Screening visit must be repeated.</td>
</tr>
</tbody>
</table>
Section 9.5.6.1, Screening (Days -42 to -1) and (Days −28 to −1)

- Signed informed consent;
- Medical history;
- 12-lead ECG;
- Vital signs (blood pressure, heart rate, temperature);
- Complete physical examination, including weight and height;
- Central laboratory assessments (hematology, chemistry, urinalysis, and PSA);
- Abdominopelvic CT scan or MRI;
- Bone scan;
- Postero-anterior and lateral chest x-ray and chest CT scan also if suspected or documented chest metastatic disease is demonstrated on plain chest x-ray;
- ECOG performance status (see APPENDIX B);
- Record concomitant medications;
- Brief Pain Inventory (Short Form).

- Medical history;
- 12-lead ECG;
- Vital signs (blood pressure, heart rate, temperature);
- Complete physical examination, including weight and height;
- Laboratory assessments (central: hematology, chemistry, and urinalysis; and local: PSA);
- ECOG performance status (see APPENDIX B);
- Record concomitant medications;
- Brief Pain Inventory (Short Form), to assess pain related to prostate cancer only;
- At least two business days prior to Study Day 1, complete and sign the Randomization Authorization Form;
- Fax the Randomization Authorization Form to the study Medical Monitor together with a copy of the screening ECG Analysis Report, screening central laboratory reports, and concomitant medication list (may be completed on the Randomization Authorization Form);
- The patient may undergo his Day 1 visit only after receipt of the signed Randomization Authorization Form, or confirmation email, that has been approved by a study Medical Monitor or designee.
Section 9.5.7.1, Study Day 1 (Week 1)

- Triplicate 12-lead ECGs during a 15-minute interval;
- Vital signs (blood pressure, heart rate, temperature);
- Brief physical examination including weight;
- ECOG performance status;
- Brief Pain Inventory (Short Form);
- Brief Fatigue Inventory (APPENDIX D) and assessment of the severity of the patient’s fatigue;
- FACT-P and EQ-5D quality of life questionnaires;
- Review and record concomitant medications and any interval new medical history since Screening;
- Review and record any serious adverse events that occurred from the time the patient signed the informed consent form (if not already reported) and report as applicable and required by the protocol;
- Review of inclusion and exclusion criteria and confirmation that the patient is eligible for the study;
- Complete and sign the randomization authorization form;
- Fax the Randomization Authorization Form to the study Medical Monitor together with a copy of the screening ECG, screening central laboratory reports, and concomitant medication list (may be completed on the Randomization Authorization Form);
- Once the Randomization Authorization Form has been approved by a study Medical Monitor with a signed copy or approval email received from Medivation or designee, the patient may be randomized into the study;
- Randomize the patient using the IVRS/IWRS.
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</table>
| Section 9.5.7.1, Study Day 1 (Week 1)| • **Central** laboratory assessments (hematology, chemistry, urinalysis, and PSA). Repeat laboratory assessments are not required if within 3 days of screening central laboratory draw date;  
• Whole blood sample for potential genotype analysis. Genotyping samples will only be collected from patients who agree to provide genotyping samples as documented by signing a separate Genotyping informed consent form;  
• Dispense study drug for the first 28 days (1 bottle). | • Laboratory assessments (**central**: hematology, chemistry, and urinalysis; and **local**: PSA). Repeat laboratory assessments are not required if within 3 days of screening central laboratory draw date;  
• Whole blood sample for potential genotype analysis. Genotyping samples will only be collected from patients who agree to provide genotyping samples as documented by signing a separate Genotyping informed consent form;  
• **Instruct patient to self administer study drug** (dosing must occur within 3 days of randomization);  
• Dispense study drug for the first 28 days (**One** bottle). |
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</tr>
</thead>
<tbody>
<tr>
<td>Section 9.5.7.2, Study Day 29 (Week 5)</td>
<td>• 12-lead ECG;</td>
<td>• 12-lead ECG;</td>
</tr>
<tr>
<td>(± 3 days)</td>
<td>• Vital signs (blood pressure, heart rate, temperature);</td>
<td>• Vital signs (blood pressure, heart rate, temperature);</td>
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<td></td>
<td>• Central laboratory assessment (hematology, urinalysis, and chemistry);</td>
<td>• Central laboratory assessment (hematology, urinalysis, and chemistry);</td>
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<td></td>
<td>• Enquire from the patient and record the time that study medication was</td>
<td>• Ask the patient and record the time that study medication was taken on the preceding 2 days. (Patients should hold study drug administration prior to this visit and take study drug after the PK blood draw. PK sample should be taken even if patient did not hold study drug);</td>
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<td></td>
<td>taken on the preceding 2 days;</td>
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<td></td>
<td>• PK sample.</td>
<td>• PK sample;</td>
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<td></td>
<td>• Brief physical examination including weight;</td>
<td>• Brief physical examination including weight;</td>
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<td></td>
<td>• ECOG performance status;</td>
<td>• ECOG performance status;</td>
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<td></td>
<td>• Record concomitant medications;</td>
<td>• Record concomitant medications;</td>
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<td>• Record adverse events;</td>
<td>• Record adverse events;</td>
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<td></td>
<td>• Dispense study drug for next 28 days (1 bottle);</td>
<td>• Dispense study drug for next 28 days (One bottle);</td>
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<td></td>
<td>• FACT-P quality of life questionnaire.</td>
<td>• FACT-P quality of life questionnaire.</td>
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<tr>
<td>Section 9.5.7.3, Study Day 57 (Week 9) (±3 days)</td>
<td>• Vital signs (blood pressure, heart rate, temperature); • Brief physical examination including weight; • ECOG performance status; • Record concomitant medications; • Record adverse events; • Dispense study drug for next 28 days (1 bottle); • Abdominopelvic (chest when applicable) CT scan or MRI (whichever imaging study was conducted at the Screening visit). The window for radiological (CT/MRI) assessments at this visit is ±7 days; • Bone scan. The window for the bone scan at this visit is ±7 days.</td>
<td>• Vital signs (blood pressure, heart rate, temperature); • Brief physical examination including weight; • ECOG performance status; • Record concomitant medications; • Record adverse events; • <strong>Instruct patient to self administer study drug:</strong> • Dispense study drug for next 28 days (<strong>One</strong> bottle); • Abdominopelvic (<strong>and chest if screening demonstrated metastatic chest disease</strong>) CT scan or MRI (whichever imaging study was conducted at the Screening visit). The window for radiological (CT/MRI) assessments at this visit is ±7 days; • Bone scan. The window for the bone scan at this visit is ±7 days.</td>
</tr>
</tbody>
</table>
### Section 9.5.7.4, Study Day 85 (Week 13) (+ 3 days)

- 12-lead ECG;
- Vital signs (blood pressure, heart rate, temperature);
- **Central** laboratory assessment (hematology, chemistry, urinalysis, and PSA);
- **Enquire from** the patient and record the time that study medication was taken on the preceding 2 days;
- PK sample;
- Brief physical examination including weight;
- ECOG performance status;
- Record concomitant medications;
- Record adverse events;
- Dispense study drug for next 28 days (1 bottle);
- Brief Pain Inventory (Short Form);
- FACT-P and EQ-5D quality of life questionnaires.

**Old Text**

- 12-lead ECG;
- Vital signs (blood pressure, heart rate, temperature);
- Laboratory assessment (**central**: hematology, chemistry, and urinalysis; and **local**: PSA);
- Ask the patient and record the time that study medication was taken on the preceding 2 days. (Patients should hold study drug administration prior to this visit and take study drug after the PK blood draw. PK sample should be taken even if patient did not hold study drug);
- PK sample;
- Brief physical examination including weight;
- ECOG performance status;
- Record concomitant medications;
- Record adverse events;
- **Instruct patient to self administer study drug**;
- Dispense study drug for next 28 days (One bottle);
- Brief Pain Inventory (Short Form), to assess pain related to prostate cancer only;
- FACT-P and EQ-5D quality of life questionnaires.
<table>
<thead>
<tr>
<th>Section</th>
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<th>New Text</th>
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</thead>
</table>
| Section 9.5.7.5, Study Day 113 (Week 17) (± 3 days) | - Vital signs (blood pressure, heart rate, temperature);  
- Central laboratory assessment (hematology, chemistry, urinalysis, and PSA);  
- Brief physical examination including weight;  
- ECOG performance status;  
- Record concomitant medications;  
- Record adverse events;  
- Dispense study drug for next 28 days (1 bottle);  
- Abdominopelvic (chest when applicable) CT scan or MRI using the same modality as at the Screening visit. The window for radiological (CT/MRI) assessments at this visit is ± 7 days;  
- Bone scan. The window for the bone scan at this visit is ± 7 days. | - Vital signs (blood pressure, heart rate, temperature);  
- Local laboratory assessment (PSA);  
- Brief physical examination including weight;  
- ECOG performance status;  
- Record concomitant medications;  
- Record adverse events;  
- Instruct patient to self administer study drug;  
- Dispense study drug for next 28 days (One bottle);  
- Abdominopelvic (and chest if screening demonstrated metastatic chest disease) CT scan or MRI using the same modality as at the Screening visit. The window for radiological (CT/MRI) assessments at this visit is ± 7 days;  
- Bone scan. The window for the bone scan at this visit is ± 7 days. |
| Section 9.5.7.6, Study Day 141 (Week 21) (± 3 days) | - Vital signs (blood pressure, heart rate, temperature);  
- Central laboratory assessment (hematology, chemistry, urinalysis, and PSA);  
- Brief physical examination including weight;  
- ECOG performance status;  
- Record concomitant medications;  
- Record adverse events;  
- Dispense study drug for next 28 days (1 bottle). | - Vital signs (blood pressure, heart rate, temperature);  
- Local laboratory assessment (PSA);  
- Brief physical examination including weight;  
- ECOG performance status;  
- Record concomitant medications;  
- Record adverse events;  
- Instruct patient to self administer study drug;  
- Dispense study drug for next 28 days (One bottle). |
<table>
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<th>Section</th>
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</thead>
</table>
| Section 9.5.7.7, Study Day 169 (Week 25) (± 3 days) | • 12-lead ECG;  
• Vital signs (blood pressure, heart rate, temperature);  
• Central laboratory assessment (hematology, chemistry, urinalysis, and PSA);  
• Enquire from the patient and record the time that study medication was taken on the preceding 2 days;  
• PK sample;  
• Brief physical examination including weight;  
• ECOG performance status;  
• Record concomitant medications;  
• Record adverse events;  
• Dispense study drug for next 84 days (three bottles);  
• Brief Pain Inventory (Short Form);  
• FACT-P and EQ-5D quality of life questionnaires;  
• Abdominopelvic (chest when applicable) CT scan or MRI using the same modality as at the Screening visit The window for radiological (CT/MRI) assessments at this visit is ± 7 days;  
• Bone scan. The window for the bone scan at this visit is ± 7 days. | • 12-lead ECG;  
• Vital signs (blood pressure, heart rate, temperature);  
• Laboratory assessment (central: hematology, chemistry, and urinalysis; and local: PSA);  
• Ask the patient and record the time that study medication was taken on the preceding 2 days. (Patients should hold study drug administration prior to this visit and take study drug after the PK blood draw. PK sample should be taken even if patient did not hold study drug);  
• PK sample;  
• Brief physical examination including weight;  
• ECOG performance status;  
• Record concomitant medications;  
• Record adverse events;  
• Instruct patient to self administer study drug;  
• Dispense study drug for next 84 days (three bottles);  
• Brief Pain Inventory (Short Form), to assess pain related to prostate cancer only;  
• FACT-P and EQ-5D quality of life questionnaires;  
• Abdominopelvic (and chest if screening demonstrated metastatic chest disease) CT scan or MRI using the same modality as at the Screening visit The window for radiological (CT/MRI) assessments at this visit is ± 7 days;  
• Bone scan. The window for the bone scan at this visit is ± 7 days. |
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<tr>
<th>Section</th>
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</thead>
<tbody>
<tr>
<td>Section 9.5.7.9, Study Day 253 (Week 37) (± 7 days)</td>
<td></td>
<td>12-lead ECG; Vital signs (blood pressure, heart rate, temperature); Central laboratory assessment (hematology, chemistry, urinalysis, and PSA); Brief physical examination including weight; ECOG performance status; Record concomitant medications; Record adverse events; Dispense study drug for next 84 days (three bottles); FACT-P and EQ-5D quality of life questionnaires; Abdominopelvic (chest when applicable) CT scan or MRI using the same modality as at the Screening visit; Bone scan.</td>
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<td>Section</td>
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</tr>
</tbody>
</table>
| Section 9.5.7.11, Study Day 337 (Week 49) and every subsequent 84 days (± 7 days) | - 12-lead ECG;  
- Vital signs (blood pressure, heart rate, temperature);  
- **Central** laboratory assessment (hematology, chemistry, urinalysis, and PSA);  
- Brief physical examination including weight;  
- ECOG performance status;  
- Record concomitant medications;  
- Record adverse events;  
- Dispense study drug for next 84 days (three bottles);  
- FACT-P and EQ-5D quality of life questionnaires;  
- Abdominopelvic (chest when applicable) CT scan or MRI using the same modality as at the Screening visit;  
- Bone scan. | - 12-lead ECG;  
- Vital signs (blood pressure, heart rate, temperature);  
- Laboratory assessment (**central**: hematology, chemistry, and **local**: PSA);  
- Brief physical examination including weight;  
- ECOG performance status;  
- Record concomitant medications;  
- Record adverse events;  
- Instruct patient to self administer study drug;  
- Dispense study drug for next 84 days (three bottles);  
- FACT-P and EQ-5D quality of life questionnaires;  
- Abdominopelvic (**and chest if screening demonstrated metastatic chest disease**) CT scan or MRI using the same modality as at the Screening visit;  
- Bone scan. |
<p>| Section 9.5.7.12, Safety Follow-Up Visit | All patients terminating study drug treatment will be <strong>followed for 28 days</strong> following the last dose of study drug or the start of cytotoxic chemotherapy or an investigational agent, whichever occurs first. | All patients terminating study drug treatment will be <strong>seen 28 days (± 7 days)</strong> following the last dose of study drug or <strong>prior to</strong> the start of cytotoxic chemotherapy or an investigational agent, whichever occurs first. |
| Section 9.5.7.1.2, Safety Follow-Up Visit | - <strong>Central</strong> laboratory assessment (hematology, chemistry, urinalysis, and PSA); | - Laboratory assessment (<strong>central</strong>: hematology, chemistry, and <strong>and</strong>: urinalysis; and <strong>local</strong>: PSA); |</p>
<table>
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<tr>
<th>Section</th>
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<th>New Text</th>
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<tbody>
<tr>
<td>Section 9.5.7.13, Long-Term Follow-Up (± 7 days)</td>
<td>• Radiographic progression (until confirmed) via CT or MRI, using the same modality as at the Screening visit, and bone scan. Imaging for assessment of radiographic progression is not required if radiographic progression has been previously determined (including the protocol-specified confirmatory scans) and with the confirmation of the central independent radiology review.</td>
<td>• Radiographic progression (until confirmed) via CT or MRI, using the same modality as at the Screening visit, and bone scan. Imaging for assessment of radiographic progression is not required if radiographic progression has been previously determined (including the protocol-specified confirmatory scans). Note that determination of radiographic progression should be confirmed by the central independent radiology review prior to stopping radiographic imaging.</td>
</tr>
<tr>
<td>Section 9.5.7.13, Long-Term Follow-Up (± 7 days)</td>
<td>Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted.</td>
<td>Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Contact via an alternate, pre-approved contact is permissible if the patient is not reachable.</td>
</tr>
<tr>
<td>Section 9.5.7.14, Unscheduled Visits</td>
<td>If the Unscheduled visit occurs prior to Week 25 then the following procedures should also be performed:</td>
<td>If the Unscheduled visit occurs prior to Week 25 and the unscheduled visit is due to an adverse event then the following procedures should also be performed:</td>
</tr>
<tr>
<td>Section 9.5.7.14, Unscheduled Visits</td>
<td>• <strong>Enquire from</strong> the patient and record the time that study medication was taken on the preceding 2 days; • PK sample.</td>
<td>• <strong>Ask</strong> from the patient and record the time that study medication was taken on the preceding 2 days. (Patients should hold study drug administration for this day prior to this visit and take study drug after the PK blood draw. PK sample should be taken even if patient did not hold study drug); • PK sample.</td>
</tr>
<tr>
<td>Section 9.7.12, Safety Analyses</td>
<td>Laboratory data consist of hematology, urinalysis, and chemistry laboratory tests. Only data collected by the central laboratory will be used to do the analyses.</td>
<td>Laboratory data consist of hematology, urinalysis, and chemistry laboratory tests.</td>
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<td>Section</td>
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<td>------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Section 12, Laboratory Requirements</td>
<td>A central laboratory will be used for clinical laboratory sample processing for this study.</td>
<td>A central laboratory will be used for clinical laboratory sample processing for this study except for PSA testing which will be conducted locally.</td>
</tr>
<tr>
<td>Section 15, Retention of Records</td>
<td>Investigators must maintain all study documentation for a period of 2 years following the approval date of the drug, or until two years after the investigational drug program is discontinued. Study documentation includes the Investigator’s Brochure, signed protocol and amendments; signed informed consents; notification of serious adverse events and related reports; any dispensing and accountability logs; shipping records of investigational product and trial related materials; documentation of the financial aspects of the trial, insurance statement, and signed agreement between involved parties; dated and documented IRB approval, and approval of regulatory authority(ies); normal laboratory values; decoding procedures for blinded trials; initiation visit report; curricula vitae and all correspondence pertaining to the conduct of the study. Medivation or designee will notify the Investigator when any records may be discarded.</td>
<td>Investigators must maintain all study documentation for at least a period of 2 years following the approval of the drug, or until 2 years after the investigational drug program is discontinued; or in accordance with local requirements (if longer). Study documentation includes all Essential Documents as defined in ICH E6 Guidelines for Good Clinical Practice. Medivation or designee will notify the Investigator when any records may be discarded.</td>
</tr>
</tbody>
</table>
APPENDIX J: Summary of Changes in Amendment 3

The main purpose of this amendment is to uncouple the interim analysis of progression-free survival from the completion of enrollment, which proceeded more quickly than expected. In addition, information on potential drug-drug interactions is updated based on recently completed clinical trials. Other changes are minor in nature (administrative or clarifications).

The following changes have been made in Amendment 3. Global changes are listed first, and minor corrections (e.g., spelling, formatting) are not shown. Some changes are shown only at their first occurrence.

<table>
<thead>
<tr>
<th>Section</th>
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<tbody>
<tr>
<td>Global</td>
<td>PFS</td>
<td>Radiographic PFS or rPFS</td>
</tr>
<tr>
<td>Title Page, Investigational Product</td>
<td>MDV3100 [3-(4-cyano-3-trifluoromethylphenyl)-1-(3-fluoro-4-(methylcarbamoyl) phenyl)-5,5-dimethyl-2-thioximidazolin-4-one]</td>
<td>Enzalutamide (formerly MDV3100)</td>
</tr>
<tr>
<td>Title Page, Sponsor</td>
<td>Medivation, Inc. 201 Spear Street, Third Floor</td>
<td>Medivation, Inc. 525 Market Street, 36th Floor</td>
</tr>
<tr>
<td>Approval Page, Regulatory Affairs Approver</td>
<td>Gia DePillis, PhD</td>
<td>Cheryl Madsen, RAC</td>
</tr>
<tr>
<td>Synopsis (Methods)</td>
<td>This study is a multinational Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 (160 mg/day) ...</td>
<td>This study is a multinational Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral enzalutamide (formerly MDV3100, as used throughout this protocol) (160 mg/day) ...</td>
</tr>
</tbody>
</table>
### Synopsis (Statistical Methods), Efficacy Analyses, Overall Survival

A formal interim analysis for overall survival will be performed at the time of the primary PFS analysis following the completion of accrual of the trial. Approximately 50% of the required total number of death events for the primary overall survival analysis is projected to occur at this milestone.

### Synopsis (Statistical Methods), Efficacy Analyses, Radiographic Progression-Free Survival

The primary analysis of PFS will be conducted following the completion of trial enrollment. An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups at the significance level of 0.001 (two-sided).

The primary analysis of rPFS will be based upon the first 410 rPFS events observed and will be conducted at the time of the formal interim analysis of overall survival. An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups at the significance level of 0.001 (two-sided).

### 4. List of Abbreviations and Terms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
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<tbody>
<tr>
<td>PFS</td>
<td>Progression-Free Survival</td>
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<tr>
<td>rPFS</td>
<td>Radiographic Progression-Free Survival</td>
</tr>
<tr>
<td>P-gp</td>
<td>P-glycoprotein</td>
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<tr>
<td>PXR</td>
<td>Pregnane X Receptor</td>
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<tr>
<td>UGT</td>
<td>Uridine 5'-diphospho-glucuronosyltransferase</td>
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</table>

### 7.2.2 Nonclinical Pharmacokinetics and Metabolism

In vitro drug metabolism studies suggest that MDV3100 may have the potential to induce cytochrome P450 (CYP) 3A4 and to directly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5, and CYP3A4/5. In consideration of time-dependent inhibition data, a metabolite of MDV3100 may inhibit CYP1A2.

Text deleted.

### 7.2.4 Previous Human Experience

N/A

Refer to the Investigator’s Brochure for additional information about MDV3100.

### 9.1 Overall Study Design and Plan

Study films (CT/MRI and bone scan) should be read on site and also be submitted in digital format to the central imaging contract research organization for an independent central radiology review.

Study films (CT/MRI and bone scan) should be read on site and also be submitted in digital format to the central imaging contract research organization, Perceptive Informatics, Inc., for an independent central radiology review.
<table>
<thead>
<tr>
<th>Section</th>
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<tbody>
<tr>
<td>9.3.3.1 Removal of Patients from Therapy for Adverse Events or Lack of Compliance</td>
<td>Creatinine &gt; 305 µmol/L (4.0 mg/dL);</td>
<td>Creatinine &gt; 354 µmol/L (4.0 mg/dL);</td>
</tr>
<tr>
<td>9.4.7 Prior and Concomitant Therapy</td>
<td>APPENDIX G provides a list of potent CYP enzyme inhibitors and inducers that may have a theoretical concern of potential drug-drug interactions with MDV3100. In vitro drug metabolism studies suggest that MDV3100 may have the potential to induce CYP3A4 and to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5; therefore, concomitant medications that are substrates of any of these enzymes should be used with caution, and relevant monitoring should be considered, especially for substrates known to cause seizure, because the possibility of drug-drug interactions cannot be fully excluded. Since the metabolism of MDV3100 is not known, caution should be taken for the concomitant use of strong inhibitors and inducers of CYP enzymes and alternative products used when available.</td>
<td>APPENDIX G provides a list of medicinal products that have a potential for drug-drug interactions with MDV3100. Cytochrome P450 (CYP) 2C8 plays an important role in the metabolism of MDV3100; therefore, use caution when co-administering MDV3100 with strong inhibitors or inducers of CYP2C8. MDV3100 can induce CYP2C9, CYP2C19, CYP3A4, uridine 5'-diphosphoglucuronosyltransferase (UGT), and the efflux transporter P-glycoprotein (P-gp) via activation of the nuclear pregnane X receptor (PXR). Co-administration of MDV3100 with substrates of these enzymes or transporter may reduce the oral bioavailability and/or increase the clearance of the substrate, resulting in decreased exposures. In consideration of the half-life of MDV3100 (approximately 1 week), effects on enzymes and transporters may persist for one month or longer after stopping MDV3100.</td>
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<tr>
<td>9.6.3 Data Management</td>
<td>N/A</td>
<td>Perceptive Informatics, Inc., will be responsible for managing the blinded independent review of radiographic data as described in the independent review charter. Perceptive Informatics will assist with the collection of images from the investigator sites and will be responsible for reviewing these images and maintaining the database, including entry of the independently read imaging data.</td>
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<tr>
<td>Section</td>
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<tr>
<td>9.7.1.1.1 Overall Survival</td>
<td>A formal interim analysis for overall survival will be performed at the time of the primary PFS analysis when accrual of the study enrollment is complete. According to the enrollment projections and the assumptions for overall survival, approximately 50% of the required total number of death events (444) for the primary overall survival analysis are projected to occur at the time of the primary PFS analysis. A two-stage group sequential design with Lan-DeMets alpha-spending function based upon the O’Brien-Fleming approach will be used. Alpha-spending for the interim overall survival analysis and the primary overall survival analysis will be 0.0029 and 0.048 (both two-sided), respectively. If the actual number of events for the interim analysis is not 444, alpha-spending between those two overall survival analyses will be adjusted accordingly. The overall alpha for overall survival will be preserved at the two-sided 0.049 significance level. The interim analysis of overall survival and the primary analysis of PFS will be conducted by an independent statistician under the charter of the Data Monitoring Committee.</td>
<td>A formal interim analysis for overall survival will be performed at approximately 50% of the required total number of death events (444 of 888) for the primary overall survival analysis. A two-stage group sequential design with Lan-DeMets alpha-spending function based upon the O’Brien-Fleming approach will be used to preserve the associated two-sided type I error rate of 0.049. Alpha-spending for the interim overall survival analysis and the primary overall survival analysis will be 0.0029 and 0.048 (both two-sided), respectively. If the actual number of events for the interim analysis is not 444, alpha-spending between those two overall survival analyses will be adjusted accordingly. The interim analysis of overall survival will be conducted by an independent statistician under the charter of the Data Monitoring Committee.</td>
</tr>
<tr>
<td>9.7.1.1.2 Radiographic Progression-Free Survival</td>
<td>N/A</td>
<td>This analysis will be based upon the first 410 rPFS events observed in the trial. The primary analysis of rPFS will be conducted by an independent statistician and reviewed by the external Data Monitoring Committee. The study will not be discontinued based upon the primary analysis of rPFS.</td>
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<tr>
<td>9.7.2 Determination of Sample Size</td>
<td>• A minimum of 410 PFS events (radiographic progression or death, whichever occurs first) provides ≥ 99% power to detect a target hazard ratio of 0.57 based on a two-sided log-rank test and significance level of 0.001.</td>
<td>• The required 410 rPFS events (radiographic progression or death, whichever occurs first) provides ≥ 99% power to detect a target hazard ratio of 0.57 based on a two-sided log-rank test and significance level of 0.001.</td>
</tr>
<tr>
<td>Appendix G: Guidance on Reducing the Risks</td>
<td></td>
<td></td>
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<tr>
<td>of Pharmacokinetic Drug-Drug Interactions</td>
<td></td>
<td>(Replaced entire Appendix with updated information about potential drug-drug interactions)</td>
</tr>
</tbody>
</table>
APPENDIX K: Summary of Changes in Amendment 4

The following changes have been made in Amendment 4. Some changes appear in multiple sections, but may be shown only in the major section. Minor or inconsequential corrections may not be shown. Key changes between old text and new text are shown in **bold font** to aid review in some places.
<table>
<thead>
<tr>
<th>Section</th>
<th>Rationale</th>
<th>Old Text</th>
<th>New Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title Page, Sponsor’s Medical Monitors</td>
<td>Administrative</td>
<td>Sarah Noonberg, MD, PhD</td>
<td>Sarah Noonberg, MD, PhD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Craig Berman, MD</td>
<td>Teresa Parli, MD</td>
</tr>
<tr>
<td>Synopsis (Study Objectives); Secondary Objectives; 8. Study Objectives</td>
<td>To define protected secondary endpoints for analysis</td>
<td>Key Secondary Objectives</td>
<td>Secondary Objectives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by time to first skeletal-related event;</td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by time to first skeletal-related event;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by time to initiation of cytotoxic chemotherapy.</td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by time to initiation of cytotoxic chemotherapy;</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by time to prostate-specific antigen (PSA) progression;</td>
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<td></td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by PSA response ≥ 50%;</td>
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<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by best overall soft tissue response;</td>
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<td>• To determine the safety of treatment with MDV3100 as compared to placebo.</td>
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<tr>
<td>Synopsis (Study Objectives); Secondary Objectives; 8. Study Objectives (continued)</td>
<td>To define exploratory endpoints for analysis</td>
<td>Other Secondary Objectives</td>
<td>Exploratory Objectives</td>
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<td></td>
<td></td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by time to prostate-specific antigen (PSA) progression;</td>
<td>• To evaluate quality of life …</td>
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<td>• To evaluate quality of life …</td>
<td>• To evaluate emergence of pain relative to baseline at 6 months using the Brief Pain Inventory for MDV3100 versus placebo;</td>
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<td></td>
<td></td>
<td>• To evaluate emergence of pain relative to baseline at 3 and 6 months using the Brief Pain Inventory for MDV3100 versus placebo;</td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by time to first subsequent antineoplastic therapy (cytotoxic or hormonal);</td>
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<td></td>
<td></td>
<td>• To determine the safety of treatment with MDV3100 as compared to placebo;</td>
<td>• To determine the benefit of MDV3100 as compared to placebo as assessed by PSA response ≥ 90%;</td>
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<td></td>
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<td>• To characterize MDV3100 exposure …</td>
<td>• To characterize MDV3100 exposure …</td>
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<td></td>
<td></td>
<td>• To collect pharmacokinetics (PK) …</td>
<td>• To collect pharmacokinetics (PK) …</td>
</tr>
<tr>
<td>Synopsis (Methods), Table 1; Table 9.5.1.1.2-1 Protocol-Specified Documentation for Radiographic Evidence of Disease Progression</td>
<td>To provide clarification and to match the updated imaging review charter definition of radiographic progression</td>
<td>Progression detected at an unscheduled visit either prior to Week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.</td>
<td>Progression detected by bone scan at an unscheduled visit either prior to Week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan. Progression detected by CT/MRI at an unscheduled visit prior to Week 13 will require a confirmatory scan at least 6 weeks later whereas progression on or after Week 13 does not require confirmation.</td>
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<tr>
<td>Synopsis (Methods); 9.1 Overall Study Design and Plan; 9.3.3 Removal of Patients from Therapy 9.5.7.13 Long-Term Follow-Up (± 7 days)</td>
<td>To clarify that central review will be limited to the final analysis of rPFS</td>
<td>Note that determination of radiographic progression should be confirmed by the central independent radiology review prior to stopping radiographic imaging.</td>
<td>Note that determination of radiographic progression should be confirmed by the central independent radiology review prior to stopping radiographic imaging <strong>until the time that at least 410 rPFS events are confirmed as required for the primary PFS analysis.</strong> After this time, radiographic progression should be confirmed by the local radiology review prior to stopping radiographic imaging. However, scans should continue to be sent to the central imaging contract research organization for archiving.</td>
</tr>
<tr>
<td>Synopsis (Methods); 9.1 Overall Study Design and Plan; 9.5.7.13 Long-Term Follow-Up (± 7 days)</td>
<td>To clarify the data to be collected during Long-Term Follow-up</td>
<td>All patients are to be followed for survival or date of death.</td>
<td>All patients are to be followed for survival status, skeletal-related events, and subsequent treatments for prostate cancer.</td>
</tr>
<tr>
<td>Synopsis (Criteria for Evaluation), Secondary Efficacy Outcomes</td>
<td>To provide consistency with the changes in objectives</td>
<td>The key secondary efficacy outcomes include:</td>
<td>Secondary efficacy outcomes include:</td>
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<td></td>
<td></td>
<td>• A comparison of the time to first skeletal-related event …</td>
<td>• A comparison of the time to first skeletal-related event …</td>
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<td></td>
<td>• A comparison of the time to initiation of cytotoxic chemotherapy …</td>
<td>• A comparison of the time to initiation of cytotoxic chemotherapy …</td>
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<td>• A comparison of the time to PSA progression between the MDV3100-treated and the placebo groups;</td>
<td>• A comparison of the time to PSA progression between the MDV3100-treated and the placebo groups;</td>
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<td>• A comparison of PSA response ≥ 50% between the MDV3100-treated and the placebo groups;</td>
<td>• A comparison of PSA response ≥ 50% between the MDV3100-treated and the placebo groups;</td>
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<td></td>
<td></td>
<td>• A comparison of best overall soft tissue response between the MDV3100-treated and the placebo groups.</td>
<td>• A comparison of best overall soft tissue response between the MDV3100-treated and the placebo groups.</td>
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<tr>
<td>Synopsis (Criteria for Evaluation), Secondary Efficacy Outcomes (continued)</td>
<td>Other secondary efficacy outcomes include:</td>
<td>Exploratory efficacy outcomes include:</td>
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<td></td>
<td>• A comparison of the time to PSA progression between the MDV3100-treated and the placebo groups;</td>
<td>• FACT-P and EQ-5D data summarized descriptively;</td>
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<td></td>
<td>• FACT-P and EQ-5D data summarized descriptively;</td>
<td>• A comparison of the rate of pain progression, defined as increase of $\geq 30%$ from baseline in the average of Brief Pain Inventory pain intensity item scores (items 3, 4, 5, and 6) at 6 months between the MDV3100-treated and placebo groups;</td>
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<td></td>
<td>• A summary of pain score at baseline, 3 months, and 6 months for the MDV3100-treated and the placebo groups.</td>
<td>• A comparison of the time to first subsequent antineoplastic therapy (cytotoxic or hormonal) between the MDV3100-treated and the placebo groups;</td>
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<td></td>
<td>• A comparison of PSA response $\geq 90%$ between the MDV3100-treated and the placebo groups.</td>
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<tr>
<td>Synopsis (Statistical Methods), Overall Survival; 9.7.1.1.1 Overall Survival</td>
<td>To update as a result of additional data released on overall survival in a similar Phase 3 clinical study of abiraterone acetate in chemotherapy-naïve patients with castration-resistant prostate cancer (COU-AA-302). The availability of these data allowed re-evaluation of the optimal number of death events for the interim and final analyses</td>
<td>The primary analysis of OS will be performed when at least a total of 888 deaths have been reported. A formal interim analysis for overall survival will be performed at approximately 50% of the required total number of death events for the primary overall survival analysis.</td>
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<td>The primary analysis of overall survival will be performed when at least a total of 765 deaths have been reported. A formal interim analysis for overall survival will be performed at approximately 516 deaths or 67% of the required total number of death events for the primary overall survival analysis.</td>
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<tr>
<td>Synopsis (Statistical Methods), Radiographic Progression-Free Survival</td>
<td>To provide additional clarification to match statistical analysis plan</td>
<td>Time from randomization to the first objective evidence of radiologic progression or death due to any cause (whichever occurs first) will be assessed. Radiographic disease progression is defined by the criteria in Table 1. The primary analysis of rPFS will be based upon the first 410 rPFS events observed and will be conducted at the time of the formal interim analysis of overall survival.</td>
<td>Time from randomization to the first objective evidence of radiologic progression or death due to any cause within 168 days after treatment discontinuation, (whichever occurs first) will be assessed. Radiographic disease progression is defined by the criteria in Table 1. The primary analysis of rPFS will be based upon at least the first 410 rPFS events observed and will be conducted at the time of the formal interim analysis of overall survival.</td>
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<tr>
<td>Synopsis (Statistical Methods), Secondary Efficacy Endpoints; 9.7.1.1.3.3 Time to PSA Progression 9.7.1.1.3.4 PSA Response ≥ 50%; 9.7.1.1.3.5 Best Overall Soft Tissue Response</td>
<td>To provide consistency with the changes in objectives</td>
<td>Key Secondary Efficacy Endpoints 1. Time to First Skeletal-Related Event: … 2. Time to Initiation of Cytotoxic Chemotherapy: … An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups at the significance level of 0.05 (two-sided).</td>
<td>Secondary Efficacy Endpoints 1. Time to First Skeletal-Related Event: … 2. Time to Initiation of Cytotoxic Chemotherapy: … An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups.</td>
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<tr>
<td>Synopsis (Statistical Methods), Secondary Efficacy Endpoints; 9.7.1.1.3.3 Time to PSA Progression 9.7.1.1.3.4 PSA Response ≥ 50%; 9.7.1.1.3.5 Best Overall Soft Tissue Response (continued)</td>
<td></td>
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<td>3. <strong>Time to PSA Progression:</strong> PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 μg/L (2 ng/mL) above the nadir (or baseline value for patients who did not have a decline in PSA value at Week 13). This increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later. Time from randomization to first observation of PSA progression will be assessed. An unstratified log-rank test will be used to compare the MDV3100 treated and the placebo groups; 4. <strong>PSA Response ≥ 50%:</strong> Confirmed PSA responses will be defined as ≥ 50% reductions in PSA from baseline to lowest postbaseline PSA result, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response. PSA response ≥ 50% will be calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment. An unstratified Cochran-Mantel-Haenszel mean score test will be used to compare the response rates between the MDV3100-treated and the placebo groups;</td>
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<tr>
<td>Synopsis (Statistical Methods), Secondary Efficacy Endpoints; 9.7.1.1.3.3 Time to PSA Progression 9.7.1.1.3.4 PSA Response ≥ 50%; 9.7.1.1.3.5 Best Overall Soft Tissue Response (continued)</td>
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<td>5. <strong>Best Overall Soft Tissue Response</strong>: The best overall soft tissue response as assessed by investigators using RECIST 1.1 will be summarized. Only patients with measurable soft tissue disease at screening (i.e., at least 1 target lesion per RECIST 1.1) will be included in this analysis. A Cochran-Mantel-Haenszel mean score test will be used to compare the proportion of patients with an objective response (complete response or partial response) per RECIST 1.1 between the MDV3100-treated and the placebo groups.</td>
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<tr>
<td>Synopsis (Statistical Methods), Exploratory Efficacy Endpoints;</td>
<td>To provide consistency with the changes in objectives</td>
<td>Other Secondary Efficacy Endpoints:</td>
<td>Exploratory Efficacy Endpoints:</td>
</tr>
<tr>
<td>9.7.1.1.4.4 Brief Pain Inventory</td>
<td></td>
<td>1. <strong>Time to PSA Progression</strong>: Time from randomization to first observation of PSA progression will be assessed. For patients with PSA declines at Week 13, 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 3 or more weeks later. For patients with no PSA decline at Week 13, 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 3 or more weeks later. An unstratified log-rank test will be used to compare the MDV3100-treated and the placebo groups. The Brief Pain Inventory pain score will be summarized descriptively at baseline, 3 months, and 6 months.</td>
<td>1. <strong>FACT-P Quality of Life</strong>: …</td>
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<tr>
<td>9.7.1.1.4.5 Time to First Subsequent Antineoplastic Therapy;</td>
<td></td>
<td>2. <strong>EQ-5D Quality of Life</strong>: …</td>
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<td>9.7.1.1.4.6 PSA Response ≥ 90%</td>
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<td>3. <strong>Pain score per Brief Pain Inventory</strong>: …</td>
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<td>4. <strong>Time to First Subsequent Antineoplastic Therapy (Cytotoxic or Hormonal)</strong>: An unstratified log-rank test will be used to compare this endpoint between the MDV3100-treated and the placebo groups at the significance level of 0.05 (two-sided);</td>
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<td>5. <strong>PSA Response ≥ 90%</strong>: Defined similarly to PSA response ≥ 50%, an unstratified Cochran-Mantel-Haenszel mean score test at the significance level of 0.05 (two-sided) will be used to compare this endpoint between the MDV3100-treated and the placebo groups.</td>
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<tr>
<td>2.1 Study Schedule of Activities (footnotes)</td>
<td>For clarification and to match the updated imaging review charter</td>
<td>o Disease progression observed by CT or MRI for soft tissue disease on Week 17 or later does not require a confirmatory scan.</td>
<td>o Disease progression observed by CT or MRI for soft tissue disease on Week 17 or later (or Week 13 or later if done during an unscheduled visit) does not require a confirmatory scan.</td>
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<td></td>
<td>To clarify the safety reporting period</td>
<td>\footnote{Serious adverse events will be collected from the time the patient signs the consent form until the Safety Follow-up visit} (or until screen fail for screen fail patients). Non-serious adverse events will be collected from the time of first study drug dosing until the Safety Follow-Up visit.</td>
<td>\footnote{Serious adverse events will be collected from the time the patient signs the consent form until the end of the safety reporting period} (or until screen failure). Non-serious adverse events will be collected from the time of first study drug dosing until the end of the safety reporting period. The safety reporting period ends at the time of the Safety Follow-up visit, 28 days after last dose of study drug, or initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first.</td>
</tr>
<tr>
<td>7.2 MDV3100</td>
<td>To clarify that MDV3100 is no longer strictly an investigational agent</td>
<td>MDV3100 is an investigational product that is the first triple-acting, oral androgen-receptor antagonist with clinically relevant therapeutic potential in prostate cancer that has progressed despite androgen deprivation therapy.</td>
<td>MDV3100 is an oral androgen-receptor antagonist with clinically relevant therapeutic potential in prostate cancer that has progressed despite androgen deprivation therapy.</td>
</tr>
<tr>
<td>9.1 Overall Study Design and Plan</td>
<td>For clarification and to match the updated imaging review charter</td>
<td>This confirmatory scan should demonstrate persistence of the new bone lesions. Disease progression observed by CT or MRI for soft tissue disease on Week 17 or later does not require a confirmatory scan.</td>
<td>This confirmatory scan should demonstrate persistence of the new bone lesions. Disease progression observed by CT or MRI for soft tissue disease on Week 17 or later (or Week 13 or later if done during an unscheduled visit) does not require a confirmatory scan.</td>
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<tr>
<td>9.3.3.2 Maintenance of Study Drug Therapy in the Setting of Disease Progression and Initiation of Other Non-Investigational Antineoplastic Agents (Also in Synopsis Methods and Section 9.1 Overall Study Design and Plan)</td>
<td>Correction for consistency with Section 9.4.7 Prior and Concomitant Therapy</td>
<td>PSA rise without evidence of confirmed radiographic progression or a skeletal-related event is strongly discouraged as a criterion to start a new systemic antineoplastic therapy during the first 12 weeks of therapy and is discouraged as a criterion to start a new systemic antineoplastic therapy throughout the study. <strong>If another non-cytotoxic antineoplastic agent is initiated, study drug therapy should be continued per the Investigator’s clinical judgment as long as the patient is tolerating the study drug and continues androgen deprivation therapy.</strong></td>
<td>PSA rise without evidence of confirmed radiographic progression or a skeletal-related event is strongly discouraged as a criterion to start a new systemic antineoplastic therapy during the first 12 weeks of therapy and is discouraged as a criterion to start a new systemic antineoplastic therapy throughout the study. Study drug should be handled and stored safely and properly in accordance with the study drug label.</td>
</tr>
<tr>
<td>9.4.2.4 Storage and Labeling</td>
<td>To be consistent with the storage conditions stated on the Xtandi commercial product label</td>
<td>Study drug should be stored in a secure location with limited access at 77°F (25°C), with excursions permitted to 59°F to 86°F (15°C to 30°C).</td>
<td>Study drug should be handled and stored safely and properly in accordance with the study drug label.</td>
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<tr>
<td>9.4.7 Prior and Concomitant Therapy</td>
<td>To clarify potential drug-drug interaction</td>
<td>… Cytochrome P450 (CYP) 2C8 plays an important role in the metabolism of MDV3100; therefore, use caution when co-administering MDV3100 with strong inhibitors or inducers of CYP2C8.</td>
<td>… Cytochrome P450 (CYP) 2C8 plays an important role in the metabolism of MDV3100; therefore, use caution when co-administering MDV3100 with strong inhibitors (e.g., gemfibrozil) or inducers (e.g., rifampicin) of CYP2C8 as they can affect MDV3100 plasma exposure. Concomitant use of strong CYP2C8 inhibitors should be avoided if possible as they may result in higher plasma exposure to MDV3100. If concomitant use of strong CYP2C8 inhibitors cannot be avoided, then the dose of study drug should be reduced to 80 mg per day (2 capsules).</td>
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</table>
| 9.5.1.1.2 Radiographic Progression-Free Survival | To allow for optimal treatment of known complications of advanced prostate cancer | … The following treatments are allowed during the study (and do not require study drug discontinuation) including, but not limited to:  
  • …  
  • Steroids given at a maximum equivalent daily dose of 10 mg of prednisone; | … The following treatments are allowed during the study (and do not require study drug discontinuation) including, but not limited to:  
  • …  
  • Steroid use per standard of care; |
<p>|         |            | Deaths from any cause and radiographic progression comprise the rPFS events. | Deaths due to any cause within 168 days after treatment discontinuation and radiographic progression comprise the rPFS events. |</p>
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<tr>
<td>9.5.1.2.4 PSA Response ≥ 50%</td>
<td>To provide consistency with the changes in objectives</td>
<td>(none)</td>
<td>Confirmed PSA responses will be defined as ≥ 50% reductions in PSA from baseline to lowest postbaseline PSA result as determined by the central laboratory, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response.</td>
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<tr>
<td>9.5.1.2.5 Best Overall Soft Tissue Response</td>
<td>To provide consistency with the changes in objectives</td>
<td>(none)</td>
<td>Patients with measurable soft tissue disease at screening (i.e., at least 1 target lesion per RECIST 1.1) who have an objective response (complete response or partial response) per RECIST 1.1 by independent review during the study will be included in this assessment.</td>
</tr>
<tr>
<td>9.5.1.3 Exploratory Efficacy Assessments</td>
<td>To provide consistency with the changes in objectives</td>
<td>(none)</td>
<td>Exploratory Efficacy Assessments</td>
</tr>
<tr>
<td>9.5.1.3.4 Time to First Subsequent Antineoplastic Therapy</td>
<td>To provide consistency with the changes in objectives</td>
<td>(none)</td>
<td>All antineoplastic therapies, including cytotoxic and hormonal therapies, will be considered for this assessment.</td>
</tr>
<tr>
<td>9.5.1.3.5 PSA Response ≥ 90%</td>
<td>To provide consistency with the changes in objectives</td>
<td>(none)</td>
<td>Confirmed PSA responses will be defined as ≥ 90% reductions in PSA from baseline to lowest postbaseline PSA result as determined by the central laboratory, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response.</td>
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<tr>
<td>9.5.1.5.1 Serious Adverse Events – Reporting</td>
<td>Vendor name change</td>
<td>All serious adverse events should be recorded once the informed consent form is signed and must be reported immediately (within 24 hours of the site’s knowledge of the event) by facsimile to the company listed below. Name: <strong>Verius, Ltd.</strong> SAE Fax: +44 (0) 1223 413689 (GMT) OR regional fax number provided to sites. Email: <a href="mailto:safety@verius.co.uk">safety@verius.co.uk</a> Phone: +44 (0)1223 402660 Cell: +44 (0)7768 665181... A completed serious adverse event report form signed by the Investigator must be faxed to <strong>Verius</strong> within 24 hours of the site’s knowledge of the event.</td>
<td>All serious adverse events should be recorded once the informed consent form is signed and must be reported immediately (within 24 hours of the site’s knowledge of the event) by facsimile to the company listed below. Name: <strong>ProductLife, Ltd.</strong> SAE Fax: +44 (0) 1223 413689 (GMT) OR regional fax number provided to sites. Email: <a href="mailto:safety@verius.co.uk">safety@verius.co.uk</a> Phone: +44 (0)1223 402660 Cell: +44 (0)7768 665181... A completed serious adverse event report form signed by the Investigator must be faxed to <strong>ProductLife</strong> within 24 hours of the site’s knowledge of the event.</td>
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| 9.7.1 Statistical and Analytical Plans | To clarify that patients receiving partial doses will be included | The safety population is defined as all randomized patients who received **at least one dose** of study drug. | The safety population is defined as all randomized patients who received at least 1 dose or **partial dose** of study drug. |

<p>| 9.7.1.1 Overall Survival | To update values for alpha spend for the interim and final overall survival analysis based on the revised number of required death events | Alpha-spending for the interim overall survival analysis and the primary overall survival analysis will be <strong>0.0029</strong> and <strong>0.048</strong> (both two-sided), respectively. If the actual number of events for the interim analysis is not <strong>444</strong>, alpha-spending between those two overall survival analyses will be adjusted accordingly. | Alpha-spending for the interim overall survival analysis and the primary overall survival analysis will be <strong>0.012</strong> and <strong>0.045</strong> (both two-sided), respectively. If the actual number of events for the interim analysis is not <strong>516</strong>, alpha-spending between the two overall survival analyses will be adjusted accordingly. |</p>
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<tr>
<td>9.7.1.1.2 Radiographic Progression-Free Survival</td>
<td>To provide additional clarification to match statistical analysis plan</td>
<td>The duration of rPFS will be calculated for all randomized patients from the date of randomization to the date of first objective evidence of radiographic progression (soft tissue or bone lesion) or date of death due to any cause, whichever occurs first. Conventions for censoring will be described in the statistical analysis plan. This analysis will be based upon the first 410 rPFS events observed in the trial.</td>
<td>The duration of rPFS will be calculated for all randomized patients from the date of randomization to the date of first objective evidence of radiographic progression (soft tissue or bone lesion) as assessed by independent review or date of death on study due to any cause, whichever occurs first. Death on study is defined as death due to any cause within 168 days after treatment discontinuation. This 168-day interval represents 2 consecutive tumor assessments, 12 weeks apart. Conventions for censoring will be described in the statistical analysis plan. This analysis will be based upon at least the first 410 rPFS events observed in the trial.</td>
</tr>
<tr>
<td>9.7.1.1.3 Secondary Efficacy Endpoints</td>
<td>To provide additional clarity on protected secondary endpoints</td>
<td>(none)</td>
<td>All secondary efficacy endpoint analyses will be performed by adjusting for multiple comparisons. All planned secondary endpoint analyses will maintain a study-wide type I error of 5%. The detailed methodology will be presented in the statistical analysis plan.</td>
</tr>
<tr>
<td>9.7.1.1.3.3 Time to PSA Progression</td>
<td>Formerly other secondary efficacy endpoint (text moved and did not change)</td>
<td>9.7.1.1.4.1</td>
<td>9.7.1.1.3.3</td>
</tr>
<tr>
<td>Section</td>
<td>Rationale</td>
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<tr>
<td>9.7.1.3.4 PSA Response ≥ 50%</td>
<td>To provide consistency with the changes in objectives</td>
<td>(none)</td>
<td>Confirmed PSA responses will be defined as ≥ 50% reductions in PSA from baseline to lowest postbaseline PSA result as determined by the local laboratory, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response. PSA response ≥ 50% will be calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment. An unstratified Cochran-Mantel-Haenszel mean score test will be used to compare the response rates between the MDV3100-treated and the placebo groups.</td>
</tr>
<tr>
<td>9.7.1.3.5 Best Overall Soft Tissue Response</td>
<td>To provide consistency with the changes in objectives</td>
<td>(none)</td>
<td>The best overall soft tissue response as assessed by investigators using RECIST 1.1 will be summarized. Only patients with measurable soft tissue disease at screening (i.e., at least 1 target lesion per RECIST 1.1) will be included in this analysis. A Cochran-Mantel-Haenszel mean score test will be used to compare the proportion of patients with an objective response (complete response or partial response) per RECIST 1.1 between the MDV3100-treated and the placebo groups.</td>
</tr>
<tr>
<td>Section</td>
<td>Rationale</td>
<td>Old Text</td>
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<td>----------------------------------------------</td>
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<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>9.7.1.1.4 Exploratory Efficacy Endpoints</td>
<td>To provide consistency with the changes in objectives</td>
<td>Other Secondary Efficacy Endpoints</td>
<td>Other exploratory efficacy endpoints include assessments of FACT-P, EQ-5D, Brief Pain Inventory, time to first subsequent antineoplastic therapy (cytotoxic or hormonal), and PSA response ≥ 90%. No adjustment will be made for multiple comparisons.</td>
</tr>
<tr>
<td>9.7.1.1.4.5 Time to First Subsequent Antineoplastic Therapy</td>
<td>To provide consistency with the changes in objectives</td>
<td>(none)</td>
<td>All antineoplastic therapies, including cytotoxic and hormonal therapies, will be considered for this endpoint. Time to first subsequent antineoplastic therapy will be compared between the MDV3100-treated and the placebo groups using an unstratified log-rank test at the significance level of 0.05 (two-sided).</td>
</tr>
<tr>
<td>9.7.1.1.4.6 PSA Response ≥ 90%</td>
<td>To provide consistency with the changes in objectives</td>
<td>(none)</td>
<td>Confirmed PSA responses will be defined as ≥ 90% reductions in PSA from baseline to lowest postbaseline PSA result as determined by the local laboratory, with a consecutive assessment conducted at least 3 weeks later required to confirm the PSA response. PSA response ≥ 90% will be calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment. An unstratified Cochran-Mantel-Haenszel mean score test at the significance level of 0.05 (two-sided) will be used to compare the response rates between the MDV3100-treated and the placebo groups.</td>
</tr>
<tr>
<td>Section</td>
<td>Rationale</td>
<td>Old Text</td>
<td>New Text</td>
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</tr>
<tr>
<td>9.7.1.2 Safety Analyses</td>
<td>To correct an error</td>
<td>The treatment emergent period will be defined as the period of time from the first dose date of study drug up to 30 days after last dose date of study drug or the date of initiation of investigational agent, whichever occurs first.</td>
<td>The treatment emergent period will be defined as the period of time from the first dose date of study drug up to 28 days after last dose date of study drug or the date of initiation of investigational agent, whichever occurs first.</td>
</tr>
</tbody>
</table>
| 9.7.2 Determination of Sample Size | To update values based on the revised statistical analysis plan | The study is planned to randomize approximately 1,680 patients (840 patients per treatment arm) in order to observe at least 888 deaths due to any cause.  
...  
  • ...  
  • A target hazard ratio of 0.83. The expected median overall survival for the placebo arm is 24 months as measured from the date of randomization. A target hazard ratio of 0.83 corresponds to a 21% increase in median overall survival for the MDV3100 arm relative to the placebo arm (29 versus 24 months);  
  • A minimum of 888 death events provides 80% power to detect the target hazard ratio of 0.83 based on a two-sided log-rank test and significance level of 0.049. | The study is planned to randomize approximately 1,680 patients (840 patients per treatment arm) in order to observe at least 765 deaths due to any cause.  
...  
  • ...  
  • A target hazard ratio of 0.815. The expected median overall survival for the placebo arm is 28 months as measured from the date of randomization. A target hazard ratio of 0.815 corresponds to a 22.7% increase in median overall survival for the MDV3100 arm relative to the placebo arm (approximately 34.4 versus 28 months);  
  • A minimum of 765 death events provides 80% power to detect the target hazard ratio of 0.815 based on a two-sided log-rank test and significance level of 0.049. |
<table>
<thead>
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<th>Section</th>
<th>Rationale</th>
<th>Old Text</th>
<th>New Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.7.2 Determination of Sample Size (continued)</td>
<td>The co-primary analysis of rPFS was determined from the following considerations:</td>
<td>• A target hazard ratio of 0.57. The expected median rPFS for the placebo arm is 4 months as measured from the date of randomization. A target hazard ratio of 0.57 corresponds to a 75% increase in median rPFS for the MDV3100 arm relative to the placebo arm (7 versus 4 months); • The required 410 rPFS events (radiographic progression or death, whichever occurs first) provides ≥ 99% power to detect a target hazard ratio of 0.57 based on a two-sided log-rank test and significance level of 0.001.</td>
<td>The co-primary analysis of rPFS was determined from the following considerations: • A target hazard ratio of 0.57. The expected median rPFS for the placebo arm is 8 months as measured from the date of randomization. A target hazard ratio of 0.57 corresponds to a 75% increase in median rPFS for the MDV3100 arm relative to the placebo arm (approximately 14 versus 8 months); • The required minimum of 410 rPFS events (radiographic progression or death on study, defined as death from any cause within 168 days after treatment discontinuation, whichever occurs first) provides ≥ 99% power to detect a target hazard ratio of 0.57 based on a two-sided log-rank test and significance level of 0.001.</td>
</tr>
</tbody>
</table>

<p>| 13. Case Report Forms | To provide additional clarification of the roles and responsibilities pertaining to central imaging | (none) | Perceptive Informatics, Inc. is responsible for designing and managing the case report forms for the blinded independent review of radiographic tumor scans as described in the independent review charter. Treatment assignment blinding will be maintained until the study is unblinded after database lock. |</p>
<table>
<thead>
<tr>
<th>Section</th>
<th>Rationale</th>
<th>Old Text</th>
<th>New Text</th>
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</thead>
<tbody>
<tr>
<td>APPENDIX G</td>
<td>To clarify potential drug-drug interaction</td>
<td>Potential for Other Medicinal Products to Affect MDV3100 Exposures&lt;br&gt;&lt;br&gt;CYP2C8 inhibitors and inducers&lt;br&gt;&lt;br&gt;Clinical data indicate that CYP2C8 plays an important role in the metabolism of MDV3100; therefore, strong inhibitors (e.g., gemfibrozil) or inducers (e.g., rifampicin) of CYP2C8 should be used with caution during MDV3100 treatment.</td>
<td>Potential for Other Medicinal Products to Affect MDV3100 Exposures&lt;br&gt;&lt;br&gt;CYP2C8 inhibitors and inducers&lt;br&gt;&lt;br&gt;Clinical data indicate that CYP2C8 plays an important role in the metabolism of MDV3100; therefore, strong inhibitors (e.g., gemfibrozil) or inducers (e.g., rifampicin) of CYP2C8 should be used with caution during MDV3100 treatment. If concomitant use of strong CYP2C8 inhibitors cannot be avoided, then the dose of study drug should be reduced to 80 mg per day (2 capsules).</td>
</tr>
</tbody>
</table>
APPENDIX L: Summary of Changes in Amendment 5

The main purpose of Amendment 5 is to allow access to MDV3100 (enzalutamide) to patients in PREVAIL who may derive clinical benefit. Patients receiving enzalutamide or placebo as randomized double-blind treatment may receive enzalutamide during the open-label period. Patients who do not participate in the open-label period or withdraw consent for further treatment will continue long-term follow-up assessments per protocol. Long-term data will be collected to monitor safety, enable time-to-event analyses of skeletal-related events and new prostate cancer treatments, and perform a 5-year landmark analysis of survival rate. Additionally, the vendor contact information is updated in this amendment for reporting of serious adverse events.

The independent Data Monitoring Committee recommendation to halt the study due to compelling efficacy of enzalutamide over placebo was based on the committee’s review of the results of the prespecified analyses of the coprimary endpoints: the interim analysis of overall survival and the primary (final) analysis of radiographic progression-free survival:

- Patients treated with enzalutamide demonstrated a statistically significant overall survival advantage compared with patients receiving placebo ($p < 0.0001$). Enzalutamide provided a 30% reduction in risk of death compared with placebo (hazard ratio = 0.70; 95% confidence interval, 0.59-0.83).

- Patients treated with enzalutamide demonstrated a statistically significant radiographic progression-free survival advantage compared with patients receiving placebo ($p < 0.0001$). Enzalutamide provided an 81% reduction in risk of radiographic progression or death compared with placebo (hazard ratio = 0.19; 95% confidence interval, 0.15-0.23).

- The percentage of patients alive in the enzalutamide arm was 72% compared with 65% in the placebo arm at the time of the interim analysis data cutoff date. Treatment with enzalutamide resulted in a calculated point estimate for median overall survival of 32.4 months (95% confidence interval, 31.5 months-upper limit not yet reached) versus 30.2 months (95% confidence interval, 28.0 months-upper limit not yet reached) for patients receiving placebo.

- The median radiographic progression-free survival was not yet reached (95% confidence interval, 13.8 months-upper limit not yet reached) in the enzalutamide arm versus 3.9 months (95% confidence interval, 3.7-5.4) in the placebo arm.

The following changes have been made in Amendment 5.
<table>
<thead>
<tr>
<th>Section</th>
<th>Rationale</th>
<th>Old Text</th>
<th>New Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synopsis</td>
<td>Introduces rationale for adding open-label period</td>
<td>None</td>
<td>Following the independent Data Monitoring Committee recommendation to halt the double-blind period of the study due to compelling clinical benefit of MDV3100 (enzalutamide) over placebo for the coprimary endpoints of overall survival (hazard ratio 0.70, ( p &lt; 0.0001 )) and radiographic progression-free survival (hazard ratio 0.19, ( p &lt; 0.0001 )), all ongoing enzalutamide-treated patients and ongoing and previous placebo-treated patients will be offered the opportunity to receive open-label study drug and continue in this protocol. The data collected during the open-label period will be limited to safety assessments, survival status, skeletal-related events, and new prostate cancer therapies. Long-term follow-up data (survival status, skeletal-related events, and new prostate cancer therapies) will be collected every 12 weeks up to at least 5 years after the last patient randomized or until the study average survival follow-up time from randomization is 5 years, whichever is first. These data will be used to perform a 5-year landmark analysis of survival rate. The complete details for the conduct of the open-label period are provided in Supplement 1: Open-Label Period. Patients who do not participate in the open-label period or withdraw consent for further treatment will continue</td>
</tr>
<tr>
<td>Section</td>
<td>Rationale</td>
<td>Old Text</td>
<td>New Text</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Synopsis</strong></td>
<td></td>
<td>None</td>
<td>The completed double-blind protocol remains unchanged. The double-blind period will conclude at the time of database lock and the open-label period will commence at the time of data unblinding.</td>
</tr>
<tr>
<td>(New section)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-Blind Period</td>
<td>Explains why changes are not made throughout the main protocol</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
| 9.5.1.5.1 Serious Adverse Events – Reporting | Updates vendor contact information for reporting serious adverse events | Name: ProductLife, Ltd.  
SAE Fax: +44 (0) 1223 413689 (GMT)  
OR regional fax number provided to sites  
Email: safety@verius.co.uk  
Phone: +44 (0)1223 402660  
Cell: +44 (0)7768 665181 | Name: ProductLife, Ltd.  
SAE Fax: +44 (0) 1223 413689 (GMT)  
OR regional fax number provided to sites  
Email: safety@verius.co.uk  
Phone: +44 (0)1223 402660 |
| Supplement 1: Open-Label Period (New element) | Describes procedures for the new open-label period | None                                  | (See Supplement)                                                          |
Supplement 1: Open-Label Period

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

**Rationale:** Following the independent Data Monitoring Committee recommendation to halt the double-blind period of the study due to compelling clinical benefit of MDV3100 (enzalutamide) over placebo, all ongoing enzalutamide-treated patients and ongoing and previous placebo-treated patients will be offered the opportunity to receive open-label study drug and continue in this protocol. The data collected during the open-label period will be limited to safety assessments, survival status, skeletal-related events, and new prostate cancer therapies. Long-term follow-up data (survival status, skeletal-related events, and new prostate cancer therapies) will be collected every 12 weeks up to at least 5 years after the last patient randomized or until the study average survival follow-up time from randomization is 5 years, whichever is first. These data will be used to perform a 5-year landmark analysis of survival rate.

Patients who do not participate in the open-label period or withdraw consent for further treatment will continue long-term follow-up assessments per protocol.

**Schedule and Assessments:**

Patients previously receiving enzalutamide will sign informed consent on open-label day 1 (their next regular scheduled visit following approval and activation of this protocol at the study site) and have clinic visits every 12 weeks thereafter. Patients previously receiving placebo will sign informed consent at screening and have clinic visits on open-label day 1, week 5, week 13, and every 12 weeks thereafter. Eligible patients previously receiving placebo must have their open-label day 1 visit within 6 months after the approval and activation of this protocol at the study site and no later than 6 weeks after screening. The enrollment period will end after this time.

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

Study assessments will include survival status, skeletal-related events, new prostate cancer therapies, and safety evaluations including adverse events, concomitant medications, clinical laboratory tests, physical examinations, electrocardiograms (ECGs), and vital signs. Local laboratories will perform the clinical laboratory tests, and ECGs will be reviewed locally.

Patients are to have safety follow-up 28 days after the last dose of open-label enzalutamide. If a new cytotoxic or investigational anticancer treatment is initiated before 28 days after the last dose, then safety follow-up should occur immediately before starting the new treatment.

Long-term follow-up data will be collected every 12 weeks up to at least 5 years after the last patient randomized or until the study average survival follow-up time from randomization is 5 years, whichever is first. The information collected will include survival status, skeletal-related events, and new prostate cancer therapies.

**Schematic:**

[Diagram showing the flow of patients from randomized double-blind treatment through open-label treatment and long-term follow-up.]
**Inclusion Criteria:**
The inclusion criteria apply to patients receiving enzalutamide or placebo during double-blind treatment. Eligible patients must meet all inclusion criteria.

1. Received randomized double-blind treatment in PREVAIL;
2. Open-label day 1 visit is within 6 months after this amendment is approved and becomes effective at the study site;
3. Is willing to maintain androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) agonist/antagonist or has had a bilateral orchiectomy;
4. Is able to swallow enzalutamide capsules whole and to comply with study requirements throughout the study;
5. Throughout the study, a male patient and his female partner of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) starting at screening and continuing through 3 months after the final study drug administration or per local guidelines where these require additional description of contraceptive methods. Two acceptable methods of birth control thus include the following:
   - Condom (barrier method);
   - One of the following is required:
     - Established and ongoing use of oral, injected, or implanted hormonal method by the female partner
     - Placement of an intrauterine device or intrauterine system by the female partner
     - Additional barrier method: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner
     - Tubal ligation in the female partner
     - Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy), for > 6 months
6. Agrees to use a condom if having sex with a pregnant woman throughout the study;
7. Agrees to avoid sperm donation while taking enzalutamide.

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

1. Is taking commercially available enzalutamide (Xtandi);
2. Has any clinically significant cardiovascular, dermatologic, endocrine, gastrointestinal, hematologic, hepatic, infectious, metabolic, neurologic, psychological, pulmonary, or renal disorder or any other condition, including excessive alcohol or drug abuse, or secondary malignancy, that may interfere with study participation in the opinion of the investigator or medical monitor;
3. Has current or previously treated brain metastasis or active leptomeningeal disease;
4. Has a history of seizure or a condition that may increase the risk of seizure;
5. Has 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. For patients with documented liver metastases, ALT and AST exclusion is > 5-times ULN;
6. Has creatinine > 2 mg/dL (177 μmol/L) at screening.

**Enzalutamide Administration, Storage, and Accountability:**
All patients will self-administer four 40-mg soft gelatin enzalutamide capsules (160 mg/day) by mouth once daily with or without food, unless they were receiving a reduced dose during double-blind treatment (treatment will continue at the reduced dose). Patients should return all study drug bottles to the site at each visit. Enzalutamide should be handled and stored safely and properly in accordance with the study drug label. Study site personnel must make reasonable efforts to obtain all bottles and unused study drug from patients who do not routinely return the bottles at study site visits.
Duration of Treatment and Criteria for Discontinuation:
Open-label enzalutamide administration may continue as long as the investigator considers treatment to be beneficial or until any intolerable adverse event develops.

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

If enzalutamide is coadministered with a strong CYP2C8 inhibitor (ie, gemfibrozil), the dose of enzalutamide should be reduced to 80 mg once daily. If coadministration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Patients whose treatment is interrupted due to an adverse event and restarted will continue to have regularly scheduled study visits based on their enrollment date in the open-label period. Patients will permanently discontinue treatment with enzalutamide for the following reasons:

- **Adverse event**: If intolerable and cannot be ameliorated by adequate medical intervention; or that in the opinion of the investigator or medical monitor will lead to undue risk if enzalutamide continues;
- **Seizure** or any condition that significantly predisposes the patient to seizure such as brain metastasis or clinically evident stroke;
- **Initiation of cytotoxic chemotherapy or investigational therapy**;
- **Persistent laboratory abnormality** as follows:
  - Creatinine > 354 μmol/L (4.0 mg/dL)
  - Bilirubin, AST, or ALT > 5-times the ULN
  - Absolute neutrophil count ≤ 750/μL

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

- **Withdrawal of consent** (patient decision anytime for any reason). Patients may withdraw consent for further treatment, but may still consent to participate in the long-term follow-up assessments of survival status, skeletal-related events, and new prostate cancer therapies. Patients may also consent to have follow-up for survival status only (via family, physician contacts, and public records). Study site personnel should document in the patient’s source records the specific details of the procedures the patient allows (eg, long-term follow-up) or declines (eg, further treatment);
- **Gross noncompliance** with protocol procedures and study drug management;
- **Sponsor discontinuation of study**: The sponsor has the right to terminate the study anytime. However, the sponsor will ensure that enzalutamide will be available to all patients who participate in the open-label period for as long as they are deriving clinical benefit.

Patients who discontinue treatment with enzalutamide for any reason will have safety follow-up 28 days after the last dose or before initiating treatment with a cytotoxic chemotherapy or investigational agent. If a new cytotoxic or investigational anticancer treatment is initiated before 28 days after the last dose of enzalutamide, then safety follow-up should occur immediately before starting the new treatment. Long-term follow-up will commence after completion of safety follow-up.

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

Prior and Concomitant Medications:
Medications taken within 4 weeks before open-label day 1 and any medications prescribed for chronic or intermittent use, or dose adjustments of these medications, must be recorded on the case report forms and source documents.
Concomitant medications include all vitamins, herbal remedies, and over-the-counter and prescription medications. Concomitant medications will be assessed at screening and all clinic visits. If the use of any medication during the study is due to an adverse event, the adverse event must be recorded on the adverse event case report form and in the patient’s clinical record.

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

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

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

### Statistical Methods:

All safety analyses will be conducted using the safety population, defined as all patients who receive any amount of enzalutamide. The detailed methods for statistical analyses, including the 5-year landmark analysis of survival rate, will be presented in the statistical analysis plan.

Kaplan-Meier methods will be used to describe time-to-event analyses (survival, skeletal-related events, and new prostate cancer therapies).

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, vital signs, and ECGs. 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.
## Supplement Table 1: Schedule of Activities (Open-Label Period)

<table>
<thead>
<tr>
<th>Study Period or Visit</th>
<th>OL Screen&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Treatment</th>
<th>Unscheduled&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Safety Follow-Up</th>
<th>L-T Follow-Up&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
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<tr>
<td></td>
<td>na</td>
<td>OL&lt;sup&gt;d&lt;/sup&gt;</td>
<td>OL5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>OL13+q12</td>
<td>Varies</td>
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<td>Study Week Window (Days)&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>-42</td>
<td>±7</td>
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<td>Informed consent&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>Eligibility criteria</td>
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<tr>
<td>Enrollment Authorization Form&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
<td>12-Lead electrocardiogram&lt;sup&gt;k&lt;/sup&gt;</td>
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<td>Brief physical examination&lt;sup&gt;j&lt;/sup&gt;</td>
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<td>X</td>
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<td>Adverse events review&lt;sup&gt;l&lt;/sup&gt;</td>
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<td>Concomitant medications review</td>
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<td>Skeletal-related events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Survival, new PC therapies</td>
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</tbody>
</table>

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<sup>a</sup> Only for patients starting new treatment with enzalutamide (previously received placebo). Qualifying patients continuing treatment with enzalutamide may proceed to open-label day 1 procedures. The investigator will assess and confirm patient eligibility. All screening procedure results and relevant medical history must be available to determine eligibility. All inclusion criteria must be met and no exclusion criteria may apply. No eligibility waivers will be granted.

<sup>b</sup> Anytime necessary to assess or follow up adverse events, or at the patient’s or investigator’s request.

<sup>c</sup> Every 12 weeks up to at least 5 years after the last patient randomized or until the study average survival follow-up time from randomization is 5 years, whichever is first.

<sup>d</sup> For patients previously receiving placebo, open-label day 1, week 1, must be within 6 months after the approval and activation of this protocol at the study site and no later than 6 weeks after screening. For patients continuing treatment with enzalutamide, open-label day 1 will be their next regular scheduled visit following approval and activation of this protocol at the study site.

<sup>e</sup> Only for patients starting new treatment with enzalutamide (previously received placebo).

<sup>f</sup> 28 days after the last dose of open-label enzalutamide. If a new cytotoxic or investigational anticancer treatment is initiated before 28 days after the last dose, then safety follow-up should occur immediately before starting the new treatment.

<sup>g</sup> Drug supply must be taken into account if a window is used to schedule the next visit.
h Must obtain before performing any study-specific procedures at screening for patients starting new treatment with enzalutamide and on day 1 for all others.

i Only for patients continuing enzalutamide treatment.

j When the investigator determines a patient is eligible, study site personnel will complete and fax or email this form to the number provided on the form. The sponsor medical monitor will approve the enrollment in writing or contact the study site. No form is required for patients continuing enzalutamide treatment.

k Read locally and report any clinically significant abnormalities as adverse events per CTCAE v4 criteria.

l Symptom-directed. Includes investigating any new abnormalities. Includes assessment of vital signs (blood pressure, heart rate), weight.

m Collection and reporting of adverse event information follow the same procedures as those during double-blind treatment (Sections 9.5.1.4 and 9.5.1.5).

n 3 bottles (124-count each) assigned via interactive web response system (IWRS).

o Hematology, serum chemistry. Report any clinically significant abnormalities as adverse events per CTCAE v4 criteria.

CTCAE v4, Common Terminology Criteria for Adverse Events, version 4; L-T, long-term; na, not applicable; OL, open label; PC, prostate cancer; q12, every 12 (weeks); X opt, optional assessment.