A Randomized, Double-Blind, Placebo-Controlled, Phase IIIb Study of the Efficacy and Safety of Continuing Enzalutamide in Chemotherapy Naïve Metastatic Castration Resistant Prostate Cancer Patients Treated with Docetaxel plus Prednisolone Who Have Progressed on Enzalutamide Alone

Protocol for Phase IIIb Study of Enzalutamide (ASP9785)

A study to assess the benefit of treatment beyond progression with enzalutamide in men who are starting treatment with docetaxel after worsening of their prostate cancer when taking enzalutamide alone

ISN/Protocol: 9785-MA-1001

Version: Final v4.3 (1 Mar 2022)

Incorporating Non-Substantial Amendment 6, 1 Mar 2022

EudraCT 2013-004711-50

Sponsor:

Astellas Pharma Europe Ltd. (APEL)
300 Dashwood Lang Road, Bourne Business Park

Addlestone KT15 2NX

United Kingdom

Investigator information is on file at Astellas

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I. SIGNATURES

1. SPONSOR'S SIGNATURE

A Randomized, Double-Blind, Placebo-Controlled, Phase IIIb Study of the Efficacy and Safety of Continuing Enzalutamide in Chemotherapy Naïve Metastatic Castration Resistant Prostate Cancer Patients Treated with Docetaxel plus Prednisolone Who Have Progressed on Enzalutamide Alone

ISN/Protocol: 9785-MA-1001 Version: 4.3

Required signatures (e.g. Protocol authors, Sponsor's reviewers and contributors, etc.) are located in **Section 13, Signatures**; e-signatures (when applicable) are located at the end of this document.

2. COORDINATING INVESTIGATORS' SIGNATURES

A Randomized, Double-Blind, Placebo-Controlled, Phase IIIb Study of the Efficacy and Safety of Continuing Enzalutamide in Chemotherapy Naïve Metastatic Castration Resistant Prostate Cancer Patients Treated with Docetaxel plus Prednisolone Who Have Progressed on Enzalutamide Alone

ISN/Protocol: 9785-MA-1001 Version: 4.3

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigators:

PPD

3. INVESTIGATOR'S SIGNATURE

A Randomized, Double-Blind, Placebo-Controlled, Phase IIIb Study of the Efficacy and Safety of Continuing Enzalutamide in Chemotherapy Naïve Metastatic Castration Resistant Prostate Cancer Patients Treated with Docetaxel plus Prednisolone Who Have Progressed on Enzalutamide Alone

ISN/Protocol: 9785-MA-1001 Version: 4.3

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that Sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: _____

<Insert name and qualifications of the Investigator> Date (DD Mmm YYYY)

Printed Name: _____

Address: _____

_____

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	Astellas Pharma Global Development, Inc. Global Pharmacovigilance Fax number: +44 800 471 5263 Email: safety-us@astellas.com
Medical Expert	PPD PPD Medical Affairs EMEA Astellas Pharma Europe Ltd, Telephone PPD Email: PPD
Medical Monitor	PPD PPD Parexel FSP Tel: PPD Email: PPD
Clinical Research Contact:	PPD PPD Medical Affairs EMEA Astellas Pharma Europe Ltd., Telephone PPD Email: PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ADT	Androgen Deprivation Therapy
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
AST	Aspartate Aminotransferase (GOT)
ANC	Absolute Neutrophil Count
APEB	Astellas Pharma Europe BV
APEL	Astellas Pharma Europe Ltd.
AR	Androgen Receptor
AUC	Area under the curve
BPI-SF	Brief Pain Inventory – Short Form
CA	Competent Authority
C_{max}	Maximum concentration
CR	Complete Response
CRPC	Castration-resistant Prostate Cancer
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CYP	Cytochrome P450
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol 5 dimension, 5 level health state utility index
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FAS	Full Analysis Set
FDA	Food and Drugs Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
ISN	International Study Number
IRT	Interactive Response Technology
LA-CRF	Liver Abnormality Case Report Form
LFT	Liver Function Tests

Abbreviations	Description of abbreviations
LHRH	Luteinizing hormone-releasing hormone
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OS	Overall Survival
PCWG2	Prostate Cancer Working Group 2
PK	Pharmacokinetics
PFS	Progression-Free Survival
PPS	Per Protocol Set
PR	Partial Response
PSA	Prostate-specific Antigen
PSA-DT	Prostate-specific Antigen Doubling Time
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Stable Disease
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRE	Skeletal-related Event
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total Bilirubin
ULN	Upper Limit of Normal
WBC	White Blood Cell

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
Chronic opiate analgesia	Parenteral opiate use for ≥7 days or use of WHO Analgesic Ladder Level 3 oral opiates for ≥3 weeks.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.

Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet one or more criteria required for participation in a trial.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	1 Mar 2022 v4.3 (Final)
Sponsor: Astellas Pharma Europe Ltd. (APEL)	**Protocol Number:** 9785-MA-1001
Name of Investigational Product: Enzalutamide	**Phase of Development:** IIIb

Title of Study:
A Randomized, Double-Blind, Placebo-Controlled, Phase IIIb Study of the Efficacy and Safety of Continuing Enzalutamide in Chemotherapy Naïve Metastatic Castration Resistant Prostate Cancer Patients Treated with Docetaxel Plus Prednisolone Who Have Progressed on Enzalutamide Alone

Planned Study Period:

Q3 2014 – Q4 2022

Study Objective(s):

Primary:

To compare the efficacy of continuing treatment with enzalutamide after adding docetaxel and prednisolone versus placebo plus docetaxel and prednisolone, as measured by progression-free survival (PFS) in subjects with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) with progression during treatment with enzalutamide alone.

Secondary:

To evaluate the effect of continuing treatment with enzalutamide after adding docetaxel and prednisolone versus placebo plus docetaxel and prednisolone, as measured by the following endpoints in subjects with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) with progression during treatment with enzalutamide alone:

- Time to prostate-specific antigen (PSA) progression;
- PSA response;
- Objective response rate;
- Time to pain progression;
- Time to opiate use for cancer-related pain;
- Time to first skeletal-related event;
- Quality of life.

Safety profile including cumulative dose of docetaxel and Health Resource Use will be described for these subjects.

Planned Total Number of Study Centers and Location(s): Approximately 80-90 centers in Europe

Study Population: Patients with progressive metastatic prostate cancer who have failed androgen-deprivation therapy (ADT) but who are naïve to chemotherapy will be recruited to Period 1 of the study.

Subjects from Period 1 who subsequently progress on enzalutamide alone and continue to meet entry criteria will be randomized to treatment in Period 2.

Number of Subjects to be Enrolled / Randomized: Approx 650 enrolled (Period 1) / 274 randomized (Period 2)

Study Design Overview: This double-blind, randomized, placebo-controlled trial of patients with chemotherapy- naïve mCRPC will evaluate the efficacy and safety of continuing treatment with enzalutamide plus docetaxel and prednisolone compared with treatment with placebo in combination with docetaxel and prednisolone.

The study will be conducted in consecutive periods; period 1 of open label treatment with enzalutamide followed by period 2, randomized double-blind treatment with continued enzalutamide or placebo in combination with docetaxel and prednisolone.

Open Label (Period 1):
Subjects will attend a Screening Visit to determine eligibility for open label treatment in Period 1.

Following Screening, enrolled subjects will receive open label treatment with enzalutamide (160 mg/day). At Week 13, all subjects will be assessed by PSA and imaging. The initial PSA response (stable or declining) must be confirmed by a second consecutive value at least 3 weeks later. As PSA may not remain stable or decline in all subjects who subsequently benefit from enzalutamide, this study design is based on the hypothesis that subsequent addition of docetaxel will be of greater benefit in those subjects who have a confirmed initial PSA response. Therefore, subjects with no confirmed PSA response or evidence of radiographic progression (assessed at Week 13) will be ineligible for participation in Period 2 and will typically have safety follow-up; however, Period 1treatment may continue for some subjects as long as the investigator considers it to be of clinical benefit (stopping on initiation of any new antineoplastic therapy). Subjects with confirmed PSA response will continue Period 1 until disease progression as supported by evidence of at least one of the following criteria (see Assessments):

- PSA progression with rapid PSA doubling time (PSA-DT);
- Radiographic progression defined as:
    - Bone disease progression, or;
    - Soft tissue disease progression.

Administration of open label enzalutamide will continue until randomization to Period 2 treatment, confirmation of ineligibility for Period 2 treatment (subjects will be discontinued from the study), intolerable toxicity, subject withdrawal, or death, whichever occurs first. Enrolment to Period 2 will cease after approximately 274 subjects have been enrolled or 182

primary endpoint events have been reached, whichever occurs first. Subjects who are not randomized into period 2 at this time may continue receiving open label treatment in an extension period in another Astellas-sponsored study. Subjects who decides not to enter the extension period, will discontinue from the study and be treated as per standard of care. Subjects will have a 30 day safety follow-up visit as per protocol following discontinuation.

After enrolment to Period 2 has ceased, subjects will be followed per the site's standard of care in relation to efficacy assessments (e.g., PSA testing, radiographic scans), which will enable the investigator to confirm if the subject is still deriving clinical benefit. There are no protocol-specific efficacy assessments that are to be completed for this study after end of enrolment. Subjects will be required to return to the site to review AEs, record concomitant medications, confirm that no discontinuation criteria are met, the return of unused enzalutamide and to receive more study drug if applicable.

Randomization (Period 2):
Subjects with confirmed disease progression on enzalutamide alone who continue to meet all eligibility criteria may proceed to randomization. Randomization must occur within 4 weeks of progression observed in Period 1.

Treatment allocation will be in a 1:1 ratio, stratified by disease progression (evidence of radiographic progression or not) in Period 1 to the following treatments:

- Enzalutamide (160 mg daily) in combination with docetaxel (75 mg/m^2 every 3 weeks) and prednisolone (10 mg daily);
- Enzalutamide placebo (daily) in combination with docetaxel (75 mg/m^2 every 3 weeks) and prednisolone (10 mg daily).

Administration of docetaxel will continue for up to 10 cycles, however, subjects assessed by the Investigator to be benefiting from treatment may continue on docetaxel for additional cycles.

Administration of blinded enzalutamide/placebo will continue until disease progression, intolerable toxicity, subject withdrawal or death, whichever occurs first.

When the required number of evaluable endpoint-events for primary analysis have been reached, subjects ongoing in period 2 will be able to continue receiving double blind treatment until the database is unblinded after database lock for the primary analysis.

Any ongoing subjects in Period 2 at the point of unblinding in the enzalutamide+docetaxel arm that are still receiving and benefitting from enzalutamide treatment, will have the option to continue treatment via an extension period in another Astellas-sponsored study. Subjects in the docetaxel plus placebo arm will leave the study and be treated as per local standard of care. Those subjects that decide not to enroll into the extension study will then leave the study and be treated as per local standard of care. Subjects will have a 30 day safety follow-up visit as per protocol.

Follow-up:
All subjects will have a safety follow-up visit 30 days after the last dose of Investigational Medicinal Product (IMP) or prior to the initiation of a subsequent antineoplastic therapy for prostate cancer, whichever occurs first.

In Period 2, subjects who discontinue IMP for a reason other than disease progression will continue to attend study visits (at 12 weekly intervals) for assessments until withdrawal of consent, disease progression or death.

Follow-up will be performed for a maximum of 112 days or until radiographic progression, or initiation of a new anti-neoplastic therapy is documented. Follow-up will cease after database lock for the primary analysis.

Assessments:
PSA testing will be performed at every scheduled visit excepting Period 1, Week 5 visit and Period 2, Weeks 4, 7 and 10 visits.

PSA progression with rapid PSA-DT will be defined as:

- PSA rise of ≥ 25% and an absolute increase of ≥ 2 ng/mL above nadir (in the event of a decline from baseline, the increase must be confirmed by a second PSA value 3 or more weeks later), and
- PSA-DT of ≤ 12 weeks determined in at least 3 PSA measurements collected at intervals of 4 or more weeks apart during a period of 3 or more months.

Radiographic assessment of disease will be determined in bone by whole-body radionuclide bone scan and in soft tissue by computed tomography (CT) or magnetic resonance imaging (MRI). Each study site should have a designated radiologist or Investigator as the primary imaging reviewer and designate the same reader to evaluate the images for any one subject for the duration of the trial.

- Radiographic images will be assessed every 12 weeks, but images may be obtained sooner if progression is clinically suspected. Scans may be performed up to 7 days prior to the scheduled visit.

Radiographic disease progression will be defined as one (or both) of the following:

- Bone disease progression defined by the appearance of 2 or more new bone lesions on whole body radionuclide bone scan per the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria.
  Progression at Week 13 in either Period requires a confirmatory scan performed six or more weeks later (or the next scheduled scan). Confirmation scans, if taken, must show 2 additional lesions compared with the first (Week 13) scan;
- Soft tissue disease progression per the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 with a consistent methodology applied to assess any given subject.

Functional status will be assessed by the Eastern Cooperative Oncology Group (ECOG) score, cancer-related pain will be assessed by the Brief Pain Inventory Short Form (BPI-SF), Quality of Life will be assessed by the Functional Assessment of Cancer Therapy-Prostate (FACT-P), and EuroQol 5 dimension, 5 level health state utility index (EQ-5D-5L). Health Resource Use information will be collected.

Assessments of safety will include adverse events (AEs), clinical laboratory tests, physical examinations, vital signs, and 12-lead electrocardiograms (ECGs). An Independent Data Monitoring Committee (IDMC) will monitor safety data on an ongoing basis.

Biomarker Sub-study:

Subjects in a subset of countries and sites will be invited to participate in a voluntary, exploratory, biomarker sub-study. For subjects who have consented to provide samples for this sub-study, blood samples for circulating biomarker analysis will be taken at the following timepoints:

Period 1:

Week 1/Day1 (pre dosing with enzalutamide), Week 5, Week 13, and when subjects progress clinically (4 samples).

Period 2: Week 1/Day 1 (pre study drug in Period 2), Cycle 2 (Week 4), Cycle 5 (Week 13), Cycle 9 (Week 25), when subjects progress clinically or reach another endpoint in the study and at Follow-Up (30 days after last dose of IMP) (6 samples)

Any subject who consents to participate in the biomarker sub-study but fails to provide a valid baseline sample for Period 1, may still participate in Period 2 of the biomarker sub-study. In this case, the last sample of Period 1 (the sample taken when they progress clinically) should be taken as part of the baseline for Period 2. Informed Consent for the biomarker samples must be taken before any samples are collected. Samples are to be handled according to the laboratory manual and shipped to a central laboratory for processing. The analysis of the exploratory biomarkers will be described in a separate biomarker plan.

Extension Period:

When sufficient numbers of subjects have been randomized into Period 2 (around 274) or when 182 evaluable events for the primary endpoint are reached, whichever occurs first, enrollment to Period 2 will close. Subjects who are still on enzalutamidein Period 1 at this timepoint and who are still benefitting from treatment will have the opportunity to continue with open label enzalutamide via an Extension Period in another Astellas-sponsored study, until the investigator or subject decides it is no longer in the subject's best interests to continue; a decision to initiate alternative antineoplastic therapy is made; or there is disease progression, intolerable toxicity, subject withdrawal or death, whichever occurs first. Assessments will be limited to collection of efficacy and laboratory assessments that are performed as part of standard of care for the subject, Serious Adverse Events (SAEs) and Adverse Events (AEs). Protocol-specified efficacy and laboratory assessments will cease.

Similarly, when at least 182 endpoint-events have occurred in Period 2 of the study, the data will be cleaned and analyzed. Allowing for attrition, there may be some subjects still active in Period 2 when this data analysis cut-off is reached. These subjects will be able to continue to receive blinded study drug until the study is unblinded after database lock, at which time, subjects in the enzalutamide+docetaxel arm, who are still on enzalutamide will be able to continue receiving enzalutamide) until the investigator or subject decides it is no longer in the subject's best interests to continue study drug; a decision to initiate alternative antineoplastic therapy is made; or there is

disease progression, intolerable toxicity, subject withdrawal or death, whichever occurs first. Assessments will be limited as described above.

Subjects in the docetaxel plus placebo arm will leave the study and be treated as per standard of care. Subjects who decide not to continue treatment via the extension periods, will leave the study and be treated as per standard of care.

Inclusion/Exclusion Criteria:

Inclusion:

Inclusion Criteria - Period 1 (assessed at the Screening Visit)

Subjects must meet the following criteria prior to initiation of IMP:

1. Age 18 or older;
2. Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable);
3. Histologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features;
4. Ongoing ADT with a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist at a stable dose and schedule within 4 weeks of initiation of IMP, or bilateral orchiectomy (i.e., surgical or medical castration);
5. Serum testosterone level ≤ 1.73 nmol/L (≤ 50 ng/dL);
6. Metastatic (M1) disease documented by at least 2 bone lesions on bone scan, or soft tissue disease documented by CT/MRI;
7. Progressive disease at study entry defined as the following occurring in the setting of castrate levels of testosterone:
    - PSA progression defined by a minimum of three rising PSA levels with an interval of ≥ 1 week between each determination.
    - The PSA value at Screening should be ≥ 2 µg/L (≥ 2 ng/mL). In the event of prior androgen receptor inhibitor use, the most recent local PSA and the Screening PSA assessed by the central laboratory (central PSA) must be obtained at least 4 weeks after the last dose of androgen receptor inhibitor;
8. Asymptomatic or minimally symptomatic prostate cancer (BPI-SF question 3 score of < 4) at Screening;
9. ECOG performance score of 0-1 at Screening;
10. Estimated life expectancy of ≥ 12 months from Screening;
11. Be suitable and willing to receive chemotherapy as part of the trial;

12. Able to swallow the IMP and comply with study requirements;
13. Subjects and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control* (one of which must be a condom) starting at Screening and continue throughout the study period and for 3 months after the final IMP administration;
14. Subjects must not donate sperm starting at Screening and throughout the study period and for 3 months after the final IMP administration. A condom is required throughout the study period and for 3 months after the final IMP administration if the subject is engaged in sexual activity with a pregnant woman;
15. Subject agrees not to participate in another interventional study while on treatment. Subjects who are participating in a control arm of an interventional study which includes only standard of care, or in an observational phase following an interventional study, may be eligible for this study, providing they meet all the other entry criteria.

Inclusion Criteria – Period 2 (assessed at the Period 2 Eligibility Assessment)

Subjects must meet the following criteria prior to randomization:

1. Have confirmed progressive disease on open label enzalutamide treatment, defined as one or more of:
    - PSA progression with rapid PSA-DT defined as a PSA rise of ≥ 25% and an absolute increase of ≥ 2 ng/mL above nadir, confirmed by a second PSA value at least 3 weeks later and a PSA-DT of ≤ 12 weeks determined in at least 3 PSA measurements collected at intervals of 4 or more weeks apart during a period of 3 or more months;
    - Bone disease progression defined by the appearance of 2 or more new bone lesions on whole-body radionuclide bone scan per the PCWG2 criteria;
    - Soft tissue disease progression per the RECIST 1.1, with a consistent methodology applied to assess any given subject;
2. Ongoing ADT with a LHRH agonist or antagonist at a stable dose and schedule for at least 4 weeks, or bilateral orchiectomy (i.e., surgical or medical castration);
3. Serum testosterone level ≤ 1.73 nmol/L (≤ 50 ng/dL);
4. ECOG performance score of 0-2;
5. Subjects receiving bisphosphonates or denosumab for bone health must have been on a stable dose for at least 4 weeks;
6. Able to swallow the IMP and comply with study requirements;
7. Subjects and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control* (one of which must be a condom) starting at Screening and continue throughout the study period and for the later of 3 months after the final IMP administration or 6 months after the final docetaxel administration;

8. Subjects must not donate sperm starting at Screening and throughout the study period and for the later of 3 months after the final IMP administration or 6 months after the final docetaxel administration. A condom is required throughout the study period and for 3 months after the final IMP administration if the subject is engaged in sexual activity with a pregnant woman;
9. Be suitable and willing to receive chemotherapy as part of the trial.

*Acceptable forms of birth control include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

Exclusion Criteria

Exclusion Criteria - Period 1 (assessed at the Screening Visit)

Subject will be excluded from participation if any of the following apply:

1. Absolute neutrophil count (ANC) < 1,500/μL, platelet count < 100,000/μL, or hemoglobin < 6.2 mmol/L (< 10 g/dL)
   (NOTE: subjects must not have received any growth factors or blood transfusions within seven days prior to the hematologic laboratory values obtained at Screening);
2. Total bilirubin > upper limit of normal (ULN); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times ULN; Child-Pugh B and C hepatic impairment;
3. Creatinine > 177 μmol/L (> 2 mg/dL);
4. Albumin ≤ 30 g/L (≤ 3.0 g/dL;
5. Prior treatment with the following agents for the treatment of prostate cancer:
   - Aminoglutethimide;
   - Ketoconazole;
   - Abiraterone;
   - Enzalutamide or participation in a clinical trial of enzalutamide;
   - ^{223}Ra, ^{89}Sr, ^{153}Sm, ^{186}Re/^{188}Re;
   - Immunomodulatory therapies (e.g. Sipuleucel-T, DCVAC);
   - Cytotoxic chemotherapy (e.g. docetaxel, cabazitaxel, mitoxantrone, estramustine);
   - Participation in a clinical trial of an investigational agent that inhibits the androgen receptor or androgen synthesis (e.g. ARN-509, ODM-201, VT-464; unless the treatment was placebo);
6. Current or prior treatment within 4 weeks prior to initiation of IMP with the following agents for the treatment of prostate cancer:

- Antiandrogens (e.g., bicalutamide, nilutamide, flutamide);
- 5-α reductase inhibitors (e.g., finasteride, dutasteride);
- Estrogens;
- Anabolic steroids;
- Drugs with antiandrogenic properties such as spironolactone > 50 mg/kg;
- Progestational agents;

7. Subject has received investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to initiation of IMP;
8. Use of opiate analgesia for pain from prostate cancer within 4 weeks prior to initiation of IMP;
9. Radiation therapy to bone lesions or prostatic bed within 4 weeks prior to initiation of IMP;
10. Major surgery within 4 weeks prior to initiation of IMP;
11. History of seizure or any condition that may predispose to seizures at any time in the past (e.g., prior cortical stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization). History of loss of consciousness or transient ischemic attack within 12 months prior to Screening;
12. Known or suspected brain metastasis or active leptomeningeal disease;
13. History of another malignancy within the previous 5 years other than non-melanoma skin cancer;
14. Clinically significant cardiovascular disease including:
    - Myocardial infarction within six months prior to Screening;
    - Uncontrolled angina within three months prior to Screening;
    - Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram or multi-gated acquisition scan (MUGA) 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;
    - Bradycardia as indicated by a heart rate < 45 beats per minute on the screening ECG or physical examination;
    - Uncontrolled hypertension as indicated by a resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at Screening;

15. Gastrointestinal disorders affecting absorption (e.g., extensive small bowel resection, active inflammatory bowel disease);
16. Medical contraindications to the use of prednisolone or docetaxel;
17. Allergies to any of the active ingredients or excipients in the study drugs;
18. Any condition which, in the Investigator's opinion, makes the subject unsuitable for study participation.

Exclusion Criteria - Period 2 (assessed at the Period 2 Eligibility Assessment)

Subject will be excluded from participation if any of the following apply:

1. Cancer pain requiring chronic administration of opiate analgesia (parenteral opiate use for ≥7 days or use of WHO Analgesic Ladder Level 3 oral opiates for ≥3 weeks;
2. ANC < 1,500/μL, platelet count < 100,000/μL, or hemoglobin < 6.2 mmol/L (< 10 g/dL) (NOTE: subjects must not have received any growth factors or blood transfusions within seven days prior to the hematologic laboratory values obtained at the Period 2 Eligibility Assessment);
3. Total bilirubin > ULN; ALT or AST ≥ 2.5 times ULN; Child-Pugh B and C hepatic impairment;
4. Creatinine > 177 μmol/L (> 2 mg/dL);
5. Albumin ≤ 30 g/L (≤ 3.0 g/dL).

Investigational Products:

Period 1 and 2: Enzalutamide soft gelatin capsules

Dose: 160mg once daily (4 x 40 mg capsules)

Mode of Administration: Oral, with or without food

Period 2 only: Placebo capsules, identical in appearance to enzalutamide capsules

Dose: 4 capsules once daily

Mode of Administration: Oral, with or without food

Comparative Drug(s):

n/a

Background Therapy (*Non-Investigational Medicinal Products)*:

Period 2 only: Docetaxel and prednisolone (or prednisone as a substitute)

Dose(s): Docetaxel: 75 mg/m^2/3 weeks; Prednisolone/Prednisone: 10 mg/day

Mode of Administration: Docetaxel: intravenous infusion, administered every 3 weeks over 1 hour; Prednisolone/Prednisone: 5 mg, will be administered as 1 tablet by mouth twice daily with food.

Concomitant Medication Restrictions or Requirements:

Required: All subjects who have not had a bilateral orchiectomy are required to maintain castration therapy with an LHRH agonist/antagonist for the duration of the study.

Prohibited: The following medications are prohibited while the subject is on IMP:

- Aminoglutethimide;
- Ketoconazole (for the treatment of prostate cancer);
- Abiraterone;
- ^{223}Ra, ^{89}Sr, ^{153}Sm ^{186}Re/^{188}Re;
- Immunomodulatory therapies (e.g. Sipuleucel-T, DCVAC);
- Cytotoxic chemotherapy not required by protocol (e.g. cabazitaxel, mitoxantrone, estramustine);
- Investigational agents;
- Antiandrogens (e.g. bicalutamide, nilutamide, flutamide);
- 5-α reductase inhibitors (e.g. finasteride, dutasteride);
- Estrogens;
- Anabolic steroids;
- Drugs with antiandrogenic properties such as spironolactone > 50 mg/kg;
- Progestational agents.

Restricted: The dosage and regimen of bisphosphonates or denosumab for bone health and any chronic permitted concomitant medications should be stabilized during Period 1 (> 4 weeks prior to randomization) and held constant throughout Period 2.

Duration of Treatment: Subjects will continue IMP until disease progression, intolerable toxicity or withdrawal.

Endpoints for Evaluation:

Primary:

The primary efficacy endpoint is PFS with progression defined as radiographic progression, unequivocal clinical progression, or death on study.

PFS is defined as the time from randomization to the earliest objective evidence of radiographic progression, unequivocal clinical progression, or death on study, whichever occurs first.

- Radiographic disease progression is defined for bone disease by the appearance of 2 or more new lesions on whole-body radionuclide bone scan per PCWG2 criteria or for soft tissue disease by RECIST 1.1;

- Unequivocal clinical progression is defined as any of the following:
    - new onset cancer pain requiring chronic administration of opiate analgesia;
    - deterioration from prostate cancer of ECOG performance status score to 3 or higher;
    - initiation of subsequent lines of cytotoxic chemotherapy or radiation therapy or surgical intervention due to complications of tumor progression. Radiotherapy for palliative management of symptoms due to prostate cancer will not be considered unequivocal clinical progression;
- Death on study is defined as death within 112 days of treatment discontinuation without objective evidence of radiographic progression.

Secondary:

Secondary endpoints include:

- Time to PSA progression, defined as the time from randomization to the date of the first PSA value in Period 2 demonstrating progression (Period 2). The PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir recorded in Period 2 is documented, which must be confirmed by a second consecutive value obtained at least 3 weeks later;
- PSA response, defined as the percentage change in PSA from randomization to Week 13 (or earlier for those that discontinue therapy), as well as the maximum decline in PSA that occurs at any point after treatment;
- Objective response rate, defined as the best overall radiographic response after randomization as per Investigator assessments of response for soft tissue disease per RECIST 1.1, in subjects who have a measurable tumor;
- Time to pain progression, defined as the time to an increase of ≥ 30% from randomization in the mean of BPI-SF pain intensity item scores (items 3, 4, 5, and 6);
- Time to opiate use for cancer-related pain, defined as the time to initiation of chronic administration of opiate analgesia;
- Time to first SRE, defined as the time from randomization to radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain;
- Quality of life, as assessed using FACT-P and EQ-5D-5L.

Other Endpoints:

- Cumulative dose of docetaxel.
- Health resource use (hospitalization and duration thereof; number and types of visits to a health professional) in Period 1 and Period 2

Exploratory Endpoints:

- To analyze candidate biomarkers in circulation for association with response or progression and for identifying mechanisms of resistance.

Safety Endpoints:

- Safety in both Periods will be assessed by AEs, clinically significant changes in physical examination, vital signs, laboratory values, and ECGs.
- Deaths, defined as deaths due to any cause, will be summarized descriptively.

Statistical Methods: All efficacy analyses will be based on the full analysis set (FAS) population, defined as all subjects who are randomized and receive at least one dose of IMP.

Randomization will be central and treatment allocation will be 1:1 stratified by disease progression in Period 1 (evidence of radiographic progression or not).

Sample Size Justification: The following assumptions were used to determine the sample size calculation for the primary endpoint of PFS:

- The estimated median PFS is 6 months for the control group (placebo plus docetaxel and prednisolone);
- Assuming the true treatment effect has a Hazard Ratio (HR) of 0.66, with 2-sided type 1 error rate of 0.05 and 80% power, at least 182 progression events are needed. This will allow statistical significance be claimed at the conclusion of the study if the observed HR is <=0.75, approximately;
- If the recruitment period is up to 18 months, the follow-up of subjects in Period 2 is approximately 6 months, and the recruitment rate is non-uniform, at least 274 subjects will need to be randomized.

Allowing for attrition prior to randomization, approximately 650 subjects will be enrolled.

Efficacy:

Primary Efficacy Endpoint:

The treatment effect of enzalutamide compared to placebo based on PFS disease progression will be tested using a stratified log-rank test, stratified by the randomization stratification factor, at the 0.05 2-sided significance level (based on 182 events).

Secondary Endpoints:

- Time to PSA Progression: The median time to PSA progression and the corresponding confidence intervals will be calculated. A stratified log-rank test will be used to compare the time to PSA progression between the 2 treatment groups. Kaplan-Meier curves will be used to estimate the distribution of time to PSA progression;
- PSA response will be reported using a waterfall plot for each treatment group;
- Objective Response Rate: Rates of complete response (CR), partial response (PR), stable disease (SD), CR+PR, and CR+PR+SD will be tabulated along with exact binomial confidence intervals (Clopper-Pearson);

- Time to pain progression: The statistical analyses for evaluating treatment effect of enzalutamide compared to placebo on time to pain progression will be the same as that described for time to PSA progression;
- Time to opiate use for cancer-related pain: The statistical analyses for evaluating treatment effect of enzalutamide compared to placebo on time to opiate use for cancer-related pain will be the same as that described for time to PSA progression;
- Time to first SRE: The statistical analyses for evaluating treatment effect of enzalutamide compared to placebo on time to first SRE will be the same as that described for time to PSA progression;
- Quality of Life: The FACT-P and EQ-5D-5L data will be summarized descriptively by treatment group and study visit.

Analysis of Other Endpoints:

- Health Resource Use: Will be summarized descriptively for both Periods (by treatment group in Period 2);
- Cumulative dose of docetaxel: Will be summarized descriptively by treatment group.

Exploratory Endpoints:

- Whole blood will be collected for the purpose of obtaining and analyzing Circulating Tumor Cells (CTCs) as well as evaluation of biomarkers in serum or plasma that may be temporally associated with disease progression and the development of resistance to enzalutamide treatment. These biomarkers include circulating tumor DNA and RNA, to identify mutations, genomic aberrations and expression levels of the androgen receptor and other candidate genes and inflammatory cytokines, growth factors and metabolites. Changes of CTC genetic, transcriptome or protein levels and/or cancer-specific circulating plasma nucleic acids as well as other plasma factors following androgen receptor targeting may be associated with clinical outcomes in CRPC. Standard descriptive statistics (mean, median, standard deviation, range, minimum, maximum, etc) will be used to summarize these correlative endpoints by treatment group and study visit as appropriate. The analysis of the exploratory biomarkers will be described in a separate biomarker plan.

Pharmacokinetics: Not applicable

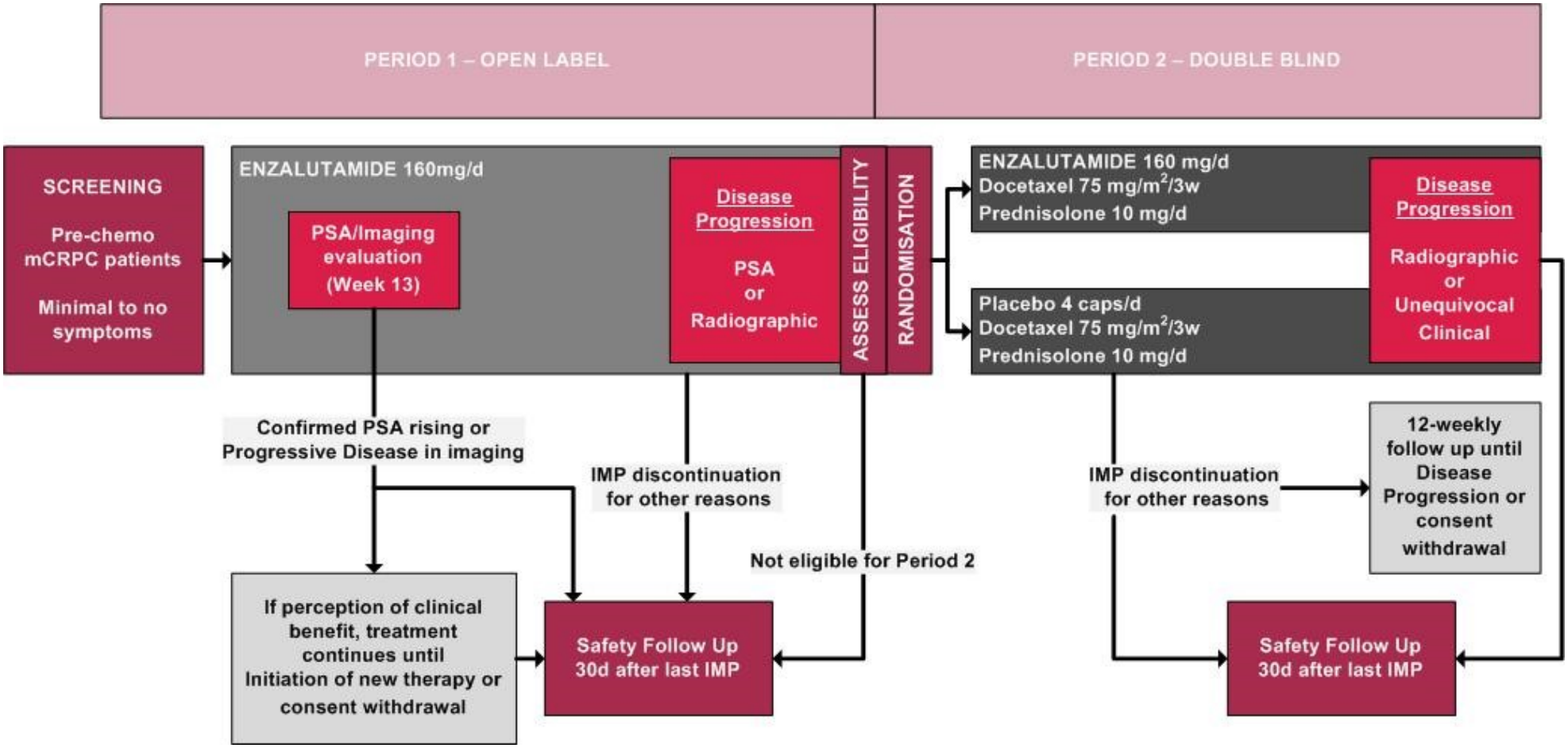
Safety: All safety analyses will include the safety population, defined as all subjects who receive 1 dose or partial dose of IMP in each Period. A safety population will be defined for each Period (1 or 2).

Safety will be summarized in Period 1 and Period 2 by the frequency of serious AEs, frequency and severity of AEs, frequency of IMP discontinuation due to adverse events, and frequency of new clinically significant changes in clinical laboratory values, vital signs, and ECGs.

Laboratory values will be classified and summarized for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. All data will be listed by period in the study.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



Schedule of Assessments - Period 1

Visit	Screening	Open label Enzalutamide				Unsched[i]	Extension Period 1[n]	FU After last drug[j or q]
Week	-4 to -1	1	5	13	25 then q12wk	n/a	q12wk	30d after last drug
Day	-28 to -1	1	29	85	169 + q84d	n/a	n/a	n/a
Window (days)	n/a	n/a	±7	±7	±7	n/a	±7	±3
Informed Consent	X							
Demographics/Medical History[a]	X							
Inclusion/Exclusion	X	X						
Vital Signs	X	X	X	X	X	X	X[p]	X
Physical Examination[b]	X	X	X	X	X	X	X[p]	X
12-lead ECG	X							
Hematology/Clinical Chemistry[c]	X	X	X	X	X	X	X[o]	X
PSA	X	X		X[g]	X	X	X[o]	
Informed Consent for Biomarker samples[k]	X					X[k]		
Biomarker sample		X[l]	X	X		X[m]		
Testosterone	X							
ECOG	X	X	X	X	X	X	X[p]	X
BPI-SF	X							
FACT-P, EQ-5D-5L	X							
Health Resource Use	X			X	X			
Radiographic assessments[d]	X[f]			X[h]	X	X	X[p]	
Enzalutamide dispensing		X		X	X		X	
Enzalutamide accountability			X	X	X		X	X
Adverse Events[e]	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X

a. Includes age, initial diagnosis of prostate cancer, Gleason score at time of diagnosis along with details and dates of all treatments for prostate cancer;
b. All physical examinations will include weight.
Screening physical examination will be a full examination including height, subsequent examinations will be brief only and symptom-focused;
c. Clinical labs (also PSA and testosterone) will be collected for central laboratory assessment;
d. Whole body radionuclide bone scan and abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) for soft tissue may be performed up to 7 days prior to the scheduled visit to permit review of results at the visit;
e. All Adverse Events (AEs) and Serious adverse events (SAEs) including death will be collected from the time the subject signs the consent form until 30 days after last dose of IMP.
f. Screening imaging assessments should include a Chest X-ray (CXR) or chest CT as well as whole body radionuclide bone scan and abdominopelvic CT/MRI.
Radiographic assessments collected within 42 days prior to Day 1 may be used to establish the presence of metastatic disease;
g. Subjects will be assessed for PSA response at Week 13 which should be confirmed by a subsequent test at least 3 weeks later. Subjects without a confirmed PSA response at Week 13 will be ineligible for participation in Period 2;
h. Radiographic progression by bone scan at the first assessment at Week 13 requires a confirmatory scan 6 or more weeks later. Subjects with confirmed radiographic progression at Week 13 will be ineligible for participation in Period 2 and will typically have safety follow up; however, Period 1treatment may continue for some subjects as long as the investigator considers it to be of clinical benefit (stopping on initiation of any new antineoplastic therapy);
i. Unscheduled visit assessments are optional and should be dictated by the clinical reason for visit attendance (e.g. if progression is suspected, radiographic assessments may be performed);
j. Safety follow-up in subjects not progressing to Period 2 before the data cut off will be 30 days after the last dose of IMP or prior to initiation of new antineoplastic therapy, whichever is earliest.
k. Participation in the Biomarker sub-study is optional, and a separate Informed Consent is to be signed prior to collecting any samples for it. If a subject is already enrolled in Period 1 of the study, but agrees to provide biomarker samples, consent for the biomarker collection for Period 2 can be taken at any time prior to the biomarker sample collection;
l. To be taken pre-enzalutamide administration;
m. Sample to be taken when subject progresses clinically, as part of the baseline samples for Period 2 of the study. If a subject misses week 1/day 1 samples in Period 1, and consents to the sub-study, this should be the first sample taken.
n. Open-label enzalutamide treatment may be continued for subjects still in treatment in Period 1 when enrollment to Period 2 closes or when the 182 primary endpoints events are reached, whichever occurs first (approximately 274 subjects randomized into Period 2)
o. Laboratory tests to be performed locally as required for the subject's standard of care. Relevant results will only be collected in the event of SAEs and AEs.
p. Results to be collected in the eCRF if the assessments are performed as part of the standard of care of the subject.
q. Safety follow up in subjects after the data cut off will be 30 days after the last dose of IMP or prior to initiation of new antineoplastic therapy, whichever is earliest. Laboratory tests to be performed locally as required for the subject's standard of care. Relevant results will only be collected in the event of SAEs and AEs.

ECG – Electrocardiogram; PSA - Prostate-specific Antigen; ECOG - Eastern Cooperative Oncology Group; BPI-SF - Brief Pain Inventory – Short Form; FACT-P - Functional Assessment of Cancer Therapy - Prostate, EQ-5D-5L - EuroQol 5 dimension, 5 level health state utility index; FU – Follow up

Schedule of Assessments - Period 2

Visit	Eligibility Assessment for Period 2[e]	Randomized (Double-Blind) Treatment on background of Docetaxel + Prednisolone[g]							Ongoing (Double-Blind) Treatment[p]	Unsched[k]	Extension Period 2		FU After last IMP[l] or s
Cycle	n/a	1	2-4	5	6-8	9	10	Additional	n/a	n/a	Additional	n/a	n/a
Week	-4 to -1	1	4/7/10	13	16/19/22	25	28	Varies q3wk cycles[j]	37 then q12wk	n/a	Varies q3wk cycles	37 then q12wk	30d after last drug
Day	-28 to -1	1	22/43/64	85	106/127/148	169	190	n/a	253 then q84d	n/a	n/a	q84d	n/a
Window (days)		n/a	±3	±3	±3	±3	±3	±3	±7	n/a	±7	±7	±7
Inclusion/Exclusion[a]	X	X											
Randomization		X											
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X[r]	X
Physical Examination[b]	X	X	X	X	X	X	X	X	X	X	X	X[r]	X
12-lead ECG	X			X		X			X				X
Hematology/Clinical Chemistry[c]	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X	X[q]	X[q]	X
PSA	X	X		X	X	X	X	X	X	X	X[q]	X[q]	X
Biomarker sample		X[m]	X[n]	X		X				X[o]			X
Testosterone	X												
ECOG	X	X	X	X	X	X	X	X	X	X	X	X[r]	X
BPI-SF	X	X	X	X	X	X	X	X	X	X			X
FACT-P, EQ-5D-5L		X		X		X			X				
Health Resource Use		X		X		X			X				
Radiographic Assessments[d]	X[f]			X[i]		X			X	X	X[r]	X[r]	
IMP dispensing		X		X		X			X			X	
Docetaxel administration		X	X	X	X	X	X	X			X		
IMP accountability		X		X		X			X			X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Eligibility will be checked against criteria for Period 2;

b. All physical examinations will include weight;

c. Clinical labs (also PSA and testosterone) will be collected for central laboratory assessment during scheduled clinic visits;

d. Whole body radionuclide bone scan and abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) for soft tissue may be performed up to 7 days prior to the scheduled visit to permit review of results at the visit;

e. The window for assessment of suitability to continue into Period 2 will commence from the point that progression is determined in Period 1 (i.e. confirmation of PSA or radiographic progression). Assessments collected at the last visit in Period 1 may be used to determine eligibility for Period 2 if collected within 4 weeks prior to randomization;

f. Period 2 baseline scans may utilize the most recent scans collected in Period 1 if collected within 4 weeks prior to randomization.
Scans should include a Chest X-ray (CXR) or chest CT;

g. Subjects who discontinue docetaxel before completion of 10 cycles (e.g. for toxicity) may continue with double-blind treatment and continue to attend study visits (at 12 weekly intervals) for assessments until IMP discontinuation criteria or endpoint criteria are met.

h. Local laboratory hematology samples for nadir count assessment will be collected approximately 1 week after docetaxel administration in all cycles; during the first 3 cycles additional hematology samples will be collected approximately 2 weeks after docetaxel administration.
Local laboratory hematology should also be collected to support dosing decisions prior to administration of docetaxel.
Patients with elevated liver function tests (LFTs) should have LFTs assessed prior to administration of docetaxel;

i. Radiographic progression by bone scan at the first assessment at Week 13 requires a confirmatory scan 6 or more weeks later;

j. If docetaxel treatment continues such that there is overlap with the subsequent 12-weekly visit cycle (e.g. Week 37, Week 49) then all assessments of those visits should be performed in addition to those required for docetaxel treatment;

k. Unscheduled visit assessments are optional and should be dictated by the clinical reason for visit attendance (e.g., if progression is suspected radiographic assessments may be performed);

l. Safety follow-up will be 30 days after the last dose of IMP or prior to initiation of new antineoplastic therapy, whichever is earliest
Subjects who discontinue IMP for a reason other than disease progression will continue to attend study visits (at 12 weekly intervals) for assessments until withdrawal of consent, disease progression or death.

m. Biomarker sample to be taken prior to first dose of double-blind study medication in Period 2;

n. Biomarker sample to be taken at Cycle 2 (Week 4);

o. Biomarker sample to be taken when the subject progresses clinically or reaches one of the endpoints of the study.

p. Double blind treatment may be continued for any subjects still in treatment in Period 2 between data cut-off and unblinding

q. Laboratory tests to be performed locally as required for the subject's standard of care. The results will only be collected in the event of SAEs and AEs.

r. Results to be collected in the eCRF if the assessments are performed as part of the standard of care of the subject.

s. Safety follow up in subjects after unblinding will be 30 days after the last dose of IMP or prior to initiation of new antineoplastic therapy, whichever is earliest. Laboratory tests to be performed locally as required for the subject's standard of care. Biomarker sampling will cease. Relevant results will only be collected in the event of SAEs and AEs.

ECG – Electrocardiogram; PSA - Prostate-specific Antigen; ECOG - Eastern Cooperative Oncology Group; BPI-SF - Brief Pain Inventory – Short Form; FACT-P - Functional Assessment of Cancer Therapy - Prostate, EQ-5D-5L - EuroQol 5 dimension, 5 level health state utility index; FU – Follow up

1 INTRODUCTION

1.1 Background

Prostate cancer represents the most common non-skin cancer neoplasm amongst men in Europe and is ranked the third most common cause of cancer death in men, after lung and colorectal cancer based on 2008 estimates (Ferlay et al 2010).

A variety of strategies (surgery, radiotherapy, androgen-deprivation therapy [ADT]) are employed in the management of early disease (Horwich et al 2013, Heidenreich et al 2014). As the disease advances, treatment strategies focus on continuing deprivation of androgens, which are well established as drivers of tumor growth in prostate cancer (Huggins and Hodges 1941; Ryan and Tindall 2011). Inevitably, tumors acquire characteristics enabling survival and growth despite androgen deprivation, resulting in a clinical state of castration-resistant prostate cancer (CRPC), defined as progression despite castrate hormone levels (testosterone <50ng/dL). Second-line hormonal therapies aim to delay time to progression, metastasis and limit symptoms. Metastatic castration-resistant prostate cancer (mCRPC), where tumors have spread beyond the primary site, is associated with symptoms related to bony or soft-tissue metastases, such as bone pain, pathologic fractures, or spinal cord compression, which worsen quality of life and ultimately accelerate progression to death within 24-48 months after onset of castration resistance.

Standard first-line therapy in mCRPC after failure of classic hormonal therapies is with docetaxel. Docetaxel is a β-actin binding taxane that triggers apoptosis through effects on the microtubule and cell mitosis (Fitzpatrick and de Wit 2014). Recent studies have reported that docetaxel also has antitumor activity associated with disruption of androgen receptor (AR) signaling (Thadani-Mulero et al 2012). The duration of response to docetaxel remains limited, however, and novel therapies for second-line treatment have recently been approved for use in Europe, including enzalutamide, abiraterone, cabazitaxel and Radium-223 chloride (Merseburger et al 2013).

Enzalutamide is an AR inhibitor that targets several steps in the AR-signaling pathway. It competitively inhibits binding of androgens to the AR, impedes movement of the AR to the nucleus of prostate cancer cells (nuclear translocation), and inhibits the association of the AR with DNA, even in the setting of AR overexpression and in prostate cancer cells resistant to antiandrogens (Tran et al 2009). Enzalutamide demonstrated a survival benefit in men with mCRPC who had received prior docetaxel (Scher et al 2012). In addition to treatment in the post-chemotherapy setting, enzalutamide and abiraterone have been investigated for treatment of patients who have not yet received chemotherapy and appear to show additional benefit (Ryan et al 2013, Beer et al 2014).

An important area of investigation is to determine the appropriate therapeutic strategies for patients who have progressed on these treatments. Continuing an agent beyond disease progression is one such strategy which has been demonstrated to improve outcomes in a range of cancers (Kuczynski et al 2013) and indeed current treatment guidelines for mCRPC recommend continuation of ADT despite progression on treatment (Heidenrich et al 2014).

In the PREVAIL study of enzalutamide vs placebo in chemotherapy naïve mCRPC (Beer et al 2014) the majority of patients treated with enzalutamide derived a clinical response (78.0% PSA response [>50% decline from baseline], 58.8% Objective Response). Acquired

resistance, the emergence of progressive disease following a period of response to enzalutamide as a single agent, thus represents the most common clinical resistance scenario. Resistance may emerge over time under the pressure of enzalutamide therapy therefore upfront drug combinations may not represent an optimal strategy to circumvent resistance. As castration-resistance is known to be mediated through both AR-dependent and AR-independent pathways, there is potential for metastatic lesions to be composed of different clones possessing these different characteristics (Ahmed and Li 2013). The hypothesis for the proposed study is that sub-populations of the CRPC lesions will continue to be controlled under ongoing enzalutamide treatment (AR signaling is a driver of prostate cancer growth and survival throughout the disease course; Ryan and Tindall, 2011), while addition of docetaxel to the therapeutic regimen will target those clones that have adopted accessory pathways to enhance survival and proliferation.

A series of ongoing studies are targeting mechanisms of resistance using a two-step trial design to follow treatment beyond progression. PLATO (NCT01995513) treats patients with enzalutamide in the chemotherapy-naïve setting with standard follow up; at the time of emergence of PSA progression, patients will be randomized to receive continued enzalutamide plus abiraterone or abiraterone alone. ABIDO (NCT02036060) treats patients with abiraterone before randomization to continued abiraterone plus docetaxel or docetaxel alone upon emergence of progression (radiographic or clinical). This study will evaluate continued treatment with enzalutamide after progression in chemotherapy-naïve patients with mCRPC. The purpose of the study is to evaluate whether continued treatment with enzalutamide in combination with docetaxel chemotherapy offers clinical benefit over switching to treatment with docetaxel chemotherapy alone.

1.2 Non-clinical and Clinical Data

1.2.1 Non-clinical data

Nonclinical pharmacology data demonstrate that enzalutamide is an AR signaling inhibitor that blocks multiple steps in the AR signaling pathway. Enzalutamide competitively inhibits androgen-induced receptor activation, inhibits nuclear translocation of activated AR and inhibits the association of the activated AR with chromatin. These inhibitory effects occur even in the setting of AR overexpression and in prostate cancer cells that are resistant to anti-androgens. By inhibiting AR signaling, enzalutamide elicits several downstream effects, which include reduced expression of AR dependent genes, decreased growth of prostate cancer cells, induction of cancer cell death and tumor regression. Enzalutamide lacks agonist activities such as those that may limit the sustained efficacy of current anti-androgens (Tran et al 2009).

Embryo-fetal development studies showed that enzalutamide treatment of dams in mice, but not in rabbits, resulted in an increased incidence of embryo-fetal deaths and external and skeletal changes. Studies on male and female fertility were not conducted with enzalutamide, but in studies in rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), atrophy, aspermia/hypospermia, and hypertrophy/hyperplasia in the reproductive system were noted, consistent with the pharmacological activity of enzalutamide. In studies in mice (4 weeks), in rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), changes in the reproductive organs associated with enzalutamide were decreases in organ weight with atrophy of the prostate and epididymis. Leydig cell hypertrophy and/or hyperplasia were observed in mice (4 weeks),

rats (2 weeks) and dogs (39 weeks). Additional changes to reproductive tissues included hypertrophy/hyperplasia of the pituitary gland and atrophy in seminal vesicles in rats and testicular hypospermia and seminiferous tubule degeneration in dogs. Gender differences were noted in rat mammary glands (male atrophy and female lobular hyperplasia). Changes in the reproductive organs in both species were consistent with the pharmacological activity of enzalutamide and reversed or partially resolved after an 8-week recovery period. There were no other important changes in clinical pathology or histopathology in any other organ system, including the liver, in either species.

Enzalutamide did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in either the in vitro cytogenetic assay with mouse lymphoma cells or the in vivo mouse micronucleus assay. N-desmethyl enzalutamide and the major inactive carboxylic acid metabolite did not induce mutations in the bacterial reverse mutation (Ames) assay. Long-term animal studies to evaluate the carcinogenic potential of enzalutamide have not been conducted. Enzalutamide was not phototoxic in vitro.

Additional information on the nonclinical experience with enzalutamide is provided in the Enzalutamide Investigator's Brochure (IB).

1.2.2 Clinical Data

As of 01 January 2014, the cumulative exposure to enzalutamide is estimated to be over 2500 male prostate cancer patients and over 200 subjects with no known cancer including healthy male subjects and subjects with hepatic impairment who received at least 1 dose in any clinical study (i.e., not including the expanded access or compassionate use programs).

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

1.2.2.1 S-3100-1-01

The pharmacokinetics (PK), tolerability, and antitumor activity of enzalutamide were first studied in a multicenter, open label, first-in-human, dose-escalation study in 140 patients with CRPC (Scher et al 2010). Patients who were chemotherapy-naïve or who had previous docetaxel-based chemotherapy failure were treated with enzalutamide at doses of 30 to 600 mg/day until disease progression or intolerable side effects developed. The maximum tolerated dose was determined to be 240 mg daily. After review of all data available from S-3100-1-01, the optimal dose of enzalutamide for evaluation in Phase 3 clinical trials was determined to be 160 mg/day.

1.2.2.2 CRPC2 (AFFIRM)

A multinational Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide (160 mg daily) in patients with progressive CRPC previously treated with docetaxel-based chemotherapy was conducted in 1199 men, 800 of whom received treatment with enzalutamide (Scher et al 2012). The primary endpoint was overall survival (OS). European Medicines Agency (EMA) and Food and Drug Administration (FDA) approval of enzalutamide was based on the results of this study.

1.2.2.3 MDV3100-03 (PREVAIL)

A multinational, Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide (160 mg daily) in chemotherapy-naïve patients with progressive

metastatic prostate cancer who have failed ADT was conducted in 1717 men, 871 of whom received treatment with enzalutamide and 845 received treatment with placebo. The co-primary endpoints were OS and radiographic progression-free survival (PFS). The prespecified interim analysis at the time of 540 death events demonstrated statistically significant improvements in overall survival and radiographic progression free survival in patients treated with enzalutamide versus placebo. Enzalutamide treatment resulted in prolongation of overall survival (HR 0.71, $p < 0.0001$) and radiographic progression free survival (HR 0.19, $p < 0.0001$; Beer et al 2014).

1.2.2.4 MDV3100-06

A phase I study was conducted to explore the safety profile of the combination of docetaxel (75 mg/m^2 by 1h infusion every 3 weeks) and enzalutamide given at 160 mg daily in men with mCRPC on ADT. Twenty-two patients were enrolled of whom 21 received the docetaxel-enzalutamide combination and 18 were evaluable for the PK analysis. Exploratory analyses of PSA response rates showed treatment with enzalutamide and docetaxel resulted in rapid, substantial, and sustained PSA responses in almost all patients in the study; 95% of patients had a ≥ 50% reduction in PSA with a median duration of approximately 7.4 months. The combination was generally well tolerated, with no clinically meaningful PK drug-drug interaction.

1.2.2.5 Pharmacokinetics and Drug Metabolism

In PK investigations in men with CRPC, enzalutamide was absorbed rapidly after oral administration, with the time to maximum plasma concentration (t_{max}) after a single dose typically occurring at 1 hour post dose. No major deviations from dose proportionality were observed over the dose range 30 mg to 600 mg.

Terminal half-life was approximately 5.8 days. The average difference between peak (C_{max})and trough (predose plasma concentration, C_{trough}) concentrations was ≤ 25%. Therefore, plasma profiles at steady state resembled a constant infusion. Time-liner PK was observed beyond steady state at Day 28. Plasma concentrations of enzalutamide and the active metabolite, N-desmethyl enzalutamide, were approximately the same.

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

Docetaxel is cleared by CYP3A4/5-dependent pathways therefore the potential for a drug-drug interaction with enzalutamide was studied (see **Section 1.2.2.4 MDV3100-06**). Docetaxel AUC decreased by 11.8% and peak concentration (C_{max}) decreased by 3.7% when

docetaxel was administered concomitantly with enzalutamide relative to when docetaxel was administered without enzalutamide. These small changes in exposure to docetaxel were not clinically relevant.

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

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

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

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Enzalutamide

The most common adverse reactions (≥ 5%) in patients treated with enzalutamide (N = 1671) in the phase 3 studies CRPC2 (AFFIRM) and MDV3100-03 (PREVAIL) were anemia, nausea, constipation, diarrhea, vomiting, abdominal pain, fatigue, asthenia, peripheral edema, urinary tract infection, nasopharyngitis, fall, weight decreased, decreased appetite, back pain, arthralgia, pain in extremity, musculoskeletal pain, bone pain, musculoskeletal chest pain, muscular weakness, myalgia, headache, dizziness, dysgeusia, spinal cord compression, paraesthesia, insomnia, anxiety, haematuria, pollakiuria, dyspnoea, cough, hot flush, and hypertension. Events leading to discontinuation of study drug with a higher incidence in the enzalutamide group were nausea, back pain, cerebrovascular accident, convulsion, and syncope; however, the differences between treatment groups were small.

The safety and tolerability of enzalutamide were evaluated in an integrated safety analysis and continues to be evaluated on an ongoing basis for all enzalutamide program studies. No study has been terminated early for safety reasons.

The reference safety information for enzalutamide is contained in section 5.2.3 of the enzalutamide investigator brochure

1.3.2 Docetaxel with Prednisolone

Safety information for docetaxel is available in the current SPC (Docetaxel SPC). The most frequent adverse reactions observed with docetaxel include neutropenia, anaemia, anorexia, nausea, vomiting, diarrhea, hypersensitivity reactions (flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills, hypotension and/or bronchospasm or generalized rash/erythema); peripheral neurotoxicity (paresthesia, dysesthesia or pain including burning, weakness); reversible cutaneous reactions (rash including localised eruptions, stomatitis, pruritus); nail disorders (hypo- or hyperpigmentation and sometimes pain and onycholysis); infusion site reactions and fluid retention (peripheral oedema and less frequently pleural effusion, pericardial effusion, ascites and weight gain).

1.3.3 Enzalutamide in combination with Docetaxel and Prednisolone

During the combination therapy window, the most common adverse events reported in 5 or more patients (≥ 22.7%) were neutropenia, fatigue, peripheral neuropathy, nausea, constipation, diarrhea, peripheral sensory neuropathy, alopecia, arthralgia, back pain, decreased appetite, dyspnea, dysgeusia, and increased lacrimation. The most common grade 3 or higher adverse events reported in 2 or more patients (≥ 9.1%) were neutropenia (86.4%), febrile neutropenia (18.2%), white blood cell (WBC) count decreased (18.2%), and blood phosphorus decreased (9.1%).

1.4 Risk-Benefit Assessment

The results from Phase III studies (see **Sections 1.2.2.2 CRPC2 (AFFIRM), 1.2.2.3 MDV3100-03 (PREVAIL)**) indicate the benefit of enzalutamide in men with mCRPC following and prior to initiation of chemotherapy. Docetaxel with prednisolone is well-established for the treatment of mCRPC. The results from a Phase I study examining the combination of enzalutamide with docetaxel (see **Section 1.2.2.4 MDV3100-06**) indicated that enzalutamide does not have a clinically meaningful impact on docetaxel PK and the PSA response rate observed in combination was more favorable than the PSA response rate reported in previous studies of enzalutamide or docetaxel alone. These insights justify a larger, randomized study to characterize the potential efficacy benefit and confirm whether the safety profile of enzalutamide plus docetaxel differs from that of docetaxel alone.

Available data then suggest a positive benefit-risk assessment for the investigation of enzalutamide in combination with docetaxel plus prednisolone in men with mCRPC following progression on enzalutamide treatment. As an increase in the occurrence of docetaxel-induced neutropenia during co-administration of enzalutamide cannot be excluded, the Independent Data Monitoring Committee (IDMC; see **Section 10.1 Independent Data-Monitoring Committee)** will be requested to give specific attention to any emerging differences in prevalence of known adverse events, especially hematological toxicities, between the two treatment groups.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

The primary objective of the study is to compare the efficacy of continuing treatment with enzalutamide after adding docetaxel and prednisolone versus placebo plus docetaxel and prednisolone, as measured by PFS in subjects with chemotherapy-naïve mCRPC with progression during treatment with enzalutamide alone.

The secondary objectives of the study are to evaluate the effect of continuing treatment with enzalutamide and adding docetaxel and prednisolone versus placebo plus docetaxel and prednisolone, as measured by the following in subjects with chemotherapy-naïve mCRPC with progression during treatment with enzalutamide alone:

- Time to Prostate-specific antigen (PSA progression
- PSA response
- Objective response rate
- Time to pain progression
- Time to opiate use for cancer-related pain
- Time to first SRE
- Quality of life

Safety profile, including cumulative dose of docetaxel, and Health Resource Use will be described for these subjects. The safety profile as well as Health Resource Use of enzalutamide alone when administered to chemotherapy naïve subjects will also be described.

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This double-blind, randomized, placebo controlled trial of subjects with chemotherapy naïve mCRPC will evaluate the efficacy and safety of continued treatment with enzalutamide after adding docetaxel and prednisolone compared with treatment with placebo in combination with docetaxel and prednisolone.

The study will be conducted in consecutive periods; period 1 of open label treatment with enzalutamide followed by period 2, randomized double-blind treatment with continued enzalutamide or placebo, adding with docetaxel and prednisolone.

2.2.1.1 Open Label (Period 1):

Subjects will attend a screening visit to determine eligibility for open label treatment in Period 1.

Following screening, enrolled subjects will receive open label treatment with enzalutamide (160 mg/day). At Week 13, all subjects will be assessed by PSA and imaging. The initial PSA response (stable or declining) must be confirmed by a second consecutive value at least 3 weeks later. As PSA may not remain stable or decline in all subjects who subsequently benefit from enzalutamide, this study design is based on the hypothesis that subsequent addition of docetaxel will be of greater benefit in those subjects who have a confirmed initial PSA response. Therefore, subjects with no confirmed PSA response or evidence of radiographic progression (assessed at Week 13) will be ineligible for participation in Period 2

and will typically have safety follow up; however, Period 1treatment may continue for some subjects as long as the investigator considers it to be of clinical benefit (stopping on initiation of any new antineoplastic therapy). Subjects with confirmed PSA response will continue Period 1 until disease progression as supported by evidence of at least one of the following criteria (see **Sections 5.2 Demographics and Baseline Characteristics; 5.3 Efficacy Assessment; 5.4 Safety Assessment**):

- PSA progression with rapid PSA doubling time (PSA-DT) defined as:
  - PSA rise of ≥ 25% and an absolute increase of ≥ 2 ng/mL above nadir, confirmed by a second PSA value at least 3 weeks later, and
  - PSA-DT of ≤ 12 weeks determined in at least 3 PSA measurements collected at intervals of 4 or more weeks apart during a period of 3 or more months (Arlen et al 2008);
- Radiographic progression defined as:
  - Bone disease progression, or;
  - Soft tissue disease progression.

Administration of open label enzalutamide will continue until randomization to Period 2 treatment, confirmation of ineligibility for Period 2 treatment (subjects will be discontinued from the study), intolerable toxicity, subject withdrawal, or death, whichever occurs first.

When sufficient numbers of subjects have been randomized into Period 2 (around 274) or the number of evaluable events for the primary endpoint have been reached (182), enrollment to Period 2 will close. Investigators will be notified, and subjects who are still in Period 1 and are benefiting from treatment will have the opportunity to continue with open label enzalutamide via an Extension Period in another Astellas-sponsored study.

2.2.1.2 Randomization (Period 2):

Subjects with confirmed disease progression on enzalutamide alone who continue to meet all eligibility criteria may proceed to randomization. Randomization must occur within 4 weeks of progression observed in Period 1.

Treatment allocation will be in a 1:1 ratio, stratified by disease progression (evidence of radiographic progression or not) in Period 1 to the following treatments:

- Enzalutamide (160 mg daily) in combination with docetaxel (75 mg/m^2 every 3 weeks) and prednisolone (10 mg daily);
- Enzalutamide placebo (daily) in combination with docetaxel (75 mg/m^2 every 3 weeks) and prednisolone (10 mg daily).

Administration of docetaxel will continue for up to 10 cycles, however subjects assessed by the Investigator to be benefiting from treatment may continue on docetaxel for additional cycles. Subjects who discontinue docetaxel before completion of 10 cycles (e.g. for toxicity) may continue treatment with IMP and will continue to attend study visits (at 12 weekly intervals) for assessments until IMP discontinuation criteria or endpoint criteria are met.

Administration of blinded enzalutamide/placebo will continue until disease progression, intolerable toxicity, subject withdrawal or death, whichever occurs first. When the required number of evaluable events for primary endpoint have been reached, subjects ongoing in

period 2 will be able to continue receiving double blind treatment until the database is unblinded after database lock for the primary analysis.

2.2.1.3 Biomarker Sub-study

Subjects in a subset of countries and sites will be invited to participate in a voluntary, exploratory, biomarker sub-study. For subjects who have consented to provide samples for this sub-study, blood samples for circulating biomarker analysis will be taken at the following timepoints:
Period 1:
Week 1/Day1 (pre dosing with enzalutamide), Week 5, Week 13, and when subjects progress clinically (4 samples).
Period 2: Week 1/Day 1 (pre study drug in Period 2), Cycle 2 (Week 4), Cycle 5 (Week 13), Cycle 9 (Week 25), when subjects progress clinically or reach another endpoint in the study and at Follow-Up (30 days after last dose of IMP) (6 samples). Any subject who consents to participate in the biomarker sub-study but fails to provide a valid baseline sample for Period 1, may still participate in Period 2 of the biomarker sub-study. In this case, the last sample of Period 1 (the sample taken when they progress clinically) should be taken as part of the baseline for Period 2. Informed Consent for the biomarker samples must be taken before any samples are collected. Samples are to be handled according to the laboratory manual and shipped to a central laboratory for processing. The analysis of the exploratory biomarkers will be described in a separate biomarker plan.

2.2.1.4 Follow-up:

All subjects will have a safety follow-up visit 30 days after the last dose of Investigational Medicinal Product (IMP) or prior to the initiation of a subsequent antineoplastic therapy for prostate cancer, whichever occurs first.

In Period 2, subjects who discontinue IMP for a reason other than disease progression will continue to attend study visits (at 12 weekly intervals) for assessments until withdrawal of consent, disease progression or death.

Follow-up will be performed for a maximum of 112 days or until radiographic progression, or initiation of a new anti-neoplastic therapy is documented. Follow-up will cease after database lock for the primary analysis.

2.2.1.5 Extension Period:

For those subjects who are still receiving study drug in Period 1 when enrollment to Period 2 closes (approximately 274 subjects randomized, or when the data cut-off for analysis is reached in Period 2, whichever occurs first), there will be the opportunity to continue receiving enzalutamide treatment via an Extension Period in another Astellas-sponsored study. (see section 4.5.3).

2.2.2 Dose Rationale

Enzalutamide 160 mg/day will be evaluated in this study. This is the approved dose in mCRPC patients who have progressed after treatment with docetaxel (Enzalutamide SPC),

and is the dose studied in the chemotherapy-naïve mCRPC patient MDV3100-03 study (PREVAIL).

In Period 2, docetaxel will be administered at 75mg/m^2 as a 1h infusion every 3 weeks in accordance with the approved dose for mCRPC patients. The combination of enzalutamide and docetaxel has been evaluated previously (see **Section 1.2.2.4 MDV3100-06**).

2.3 Endpoints

2.3.1 Primary Endpoints

The primary efficacy endpoint is PFS with progression defined as radiographic progression, unequivocal clinical progression, or death on study.

PFS is defined as the time from randomization to the earliest objective evidence of radiographic progression, unequivocal clinical progression, or death on study, whichever occurs first:

- Radiographic disease progression is defined for bone disease by the appearance of 2 or more new lesions on whole-body radionuclide bone scan per Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria or for soft tissue disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.
- Unequivocal clinical progression is defined as any of the following:
  - new onset cancer pain requiring chronic administration of opiate analgesia,
  - deterioration from prostate cancer of Eastern Cooperative Oncology Group (ECOG) performance status score to 3 or higher,
  - initiation of subsequent lines of cytotoxic chemotherapy or radiation therapy or surgical intervention due to complications of tumor progression.
- Death on study is defined as death within 112 days of treatment discontinuation without objective evidence of radiographic progression.

2.3.2 Secondary Endpoints

Secondary efficacy endpoints include:

- Time to PSA progression, defined as the time from randomization to the date of the first PSA value in Period 2 demonstrating progression (Period 2). The PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir recorded in Period 2 is documented, which must be confirmed by a second consecutive value obtained at least 3 weeks later.
- PSA response, defined as the percentage change in PSA from randomization to Week 13 (or earlier for those that discontinue therapy), as well as the maximum decline in PSA that occurs at any point after treatment.
- Objective response rate, defined as the best overall radiographic response after randomization as per Investigator assessments of response for soft tissue disease per RECIST 1.1, in subjects who have a measurable tumor.
- Time to pain progression, defined as the time to an increase of ≥ 30% from randomization in the mean of Brief Pain Inventory Short Form (BPI-SF) pain intensity item scores (items 3, 4, 5, and 6).

- Time to opiate use for cancer-related pain, defined as the time to initiation of chronic administration of opiate analgesia (parenteral opiate use for ≥7 days or use of WHO Analgesic Ladder Level 3 oral opiates for ≥3 weeks).
- Time to first SRE, defined as the time from randomization to radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.
- Quality of life, as assessed using Functional Assessment of Cancer Therapy - Prostate (FACT-P) and EuroQol 5 dimension, 5 level health state utility index (EQ-5D-5L).

2.3.3 Other Endpoints

- Cumulative dose of docetaxel.
- Health resource use (hospitalization and duration thereof; number and types of visits to a health professional) in Period 1 and Period 2.

2.3.4 Exploratory Endpoints

To analyze candidate biomarkers in circulation for association with response or progression and for identifying mechanisms of resistance.

2.3.5 Safety Endpoints

Safety in both Periods will be assessed by AEs, clinically significant changes in physical examination, vital signs, laboratory values, and electrocardiograms (ECGs) as described in **Section 5.4 Safety Assessment.**

Deaths, defined as deaths due to any cause, will be summarized descriptively.

3 STUDY POPULATION

3.1 Selection of Study Population

The study population for Period 1 will include approximately 650 men with mCRPC who have progressed while on luteinizing hormone-releasing hormone (LHRH) agonist/antagonist or after receiving a bilateral orchiectomy and have not yet received chemotherapy. Approximately 274 subjects from Period 1 who subsequently progress on enzalutamide alone and continue to meet entry criteria will be randomized to treatment in Period 2.

Waivers to the inclusion or exclusion criteria will **NOT** be allowed.

3.1.1 Subject re-screening

Re-screening is allowed only in situations in which a subject underwent the screening procedures (i.e., scans and laboratory work) and due to logistical circumstances, the allocated time window for these tests has expired. Re-screening is not permitted in cases in which the initial test results do not support eligibility. No more than one re-screening attempt will be allowed for each subject in the study.

3.2 Inclusion Criteria

3.2.1 Inclusion Criteria - Period 1 (assessed at the Screening Visit)

Subjects must meet the following criteria prior to initiation of IMP:

1. Age 18 or older;

2. Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable);
3. Histologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features;
4. Ongoing ADT with a LHRH agonist or antagonist at a stable dose and schedule within 4 weeks of initiation of IMP, or bilateral orchiectomy (i.e., surgical or medical castration);
5. Serum testosterone level ≤ 1.73 nmol/L (≤ 50 ng/dL);
6. Metastatic (M1) disease documented by at least 2 bone lesions on bone scan, or soft tissue disease documented by computed tomography (CT)/magnetic resonance imaging (MRI);
7. Progressive disease at study entry defined as the following occurring in the setting of castrate levels of testosterone:
   - PSA progression defined by a minimum of three rising PSA levels with an interval of ≥ 1 week between each determination.
   - The PSA value at Screening should be ≥ 2 µg/L (≥ 2 ng/mL).
     In the event of prior AR inhibitor use, the most recent local PSA and the Screening PSA assessed by the central laboratory (central PSA) must be obtained at least 4 weeks after the last dose of AR inhibitor;
8. Asymptomatic or minimally symptomatic prostate cancer (BPI-SF question 3 score of < 4) at Screening;
9. ECOG performance score of 0-1 at Screening;
10. Estimated life expectancy of ≥ 12 months from Screening;
11. Be suitable and willing to receive chemotherapy as part of the trial;
12. Able to swallow the IMP and comply with study requirements;
13. Subjects and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control* (one of which must be a condom) starting at Screening and continue throughout the study period and for 3 months after the final IMP administration;
14. Subjects must not donate sperm starting at Screening and throughout the study period and for 3 months after the final IMP administration. A condom is required throughout the study period and for 3 months after the final IMP administration if the subject is engaged in sexual activity with a pregnant woman; Subject agrees not to participate in another interventional study while on treatment.
15. Subject agrees not to participate in another interventional study while on treatment. Subjects who are participating in a control arm of an interventional study which includes only standard of care, or in an observational phase following an interventional study, may be eligible for this study, providing they meet all the other entry criteria.

3.2.2 Inclusion Criteria – Period 2 (assessed at the Period 2 Eligibility Assessment)

Subjects must meet the following criteria prior to randomization:

1. Have confirmed progressive disease on open label enzalutamide treatment, defined as one or more of:

- PSA progression with rapid PSA-DT defined as:
  PSA rise of ≥ 25% and an absolute increase of ≥ 2 ng/mL above nadir, confirmed by a second PSA value at least 3 weeks later, and
  PSA-DT of ≤ 12 weeks determined in at least 3 PSA measurements collected at intervals of 4 or more weeks apart during a period of 3 or more months;
- Bone disease progression defined by the appearance of 2 or more new bone lesions on whole-body radionuclide bone scan per the PCWG2 criteria;
- Soft tissue disease progression per RECIST 1.1 with a consistent methodology applied to assess any given subject;

2. Ongoing ADT with a LHRH agonist or antagonist at a stable dose and schedule for at least 4 weeks, or bilateral orchiectomy (i.e., surgical or medical castration);
3. Serum testosterone level ≤ 1.73 nmol/L (≤ 50 ng/dL);
4. ECOG performance score of 0-2;
5. Subjects receiving bisphosphonates or denosumab for bone health must have been on a stable dose for at least 4 weeks;
6. Able to swallow the IMP and comply with study requirements;
7. Subjects and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control* (one of which must be a condom) starting at Screening and continue throughout the study period and for the later of 3 months after the final IMP administration or 6 months after the final docetaxel administration;
8. Subjects must not donate sperm starting at Screening and throughout the study period and for the later of 3 months after the final IMP administration or 6 months after the final docetaxel administration. A condom is required throughout the study period and for 3 months after the final IMP administration if the subject is engaged in sexual activity with a pregnant woman;
9. Be suitable and willing to receive chemotherapy as part of the trial.

*Acceptable forms of birth control include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

3.3 Exclusion Criteria

3.3.1 Exclusion Criteria - Period 1 (assessed at the Screening Visit)

Subjects will be excluded from participation if any of the following apply:

1. Absolute neutrophil count (ANC) < 1,500/μL, platelet count < 100,000/μL, or hemoglobin < 6.2 mmol/L (< 10 g/dL)
   (NOTE: subjects must not have received any growth factors or blood transfusions within seven days of the hematologic laboratory values obtained at Screening);
1. Total bilirubin > upper limit of normal (ULN); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times ULN; Child-Pugh B and C hepatic impairment.
2. Creatinine > 177 μmol/L (> 2 mg/dL);

3. Albumin ≤ 30 g/L (≤ 3.0 g/dL);
4. Prior treatment with the following agents for the treatment of prostate cancer:
   - Aminoglutethimide;
   - Ketoconazole;
   - Abiraterone;
   - Enzalutamide or participation in a clinical trial of enzalutamide;
   - ^{223}Ra, ^{89}Sr, ^{153}Sm, ^{186}Re/^{188}Re;
   - Immunomodulatory therapies (e.g. Sipuleucel-T, DCVAC);
   - Cytotoxic chemotherapy (e.g. docetaxel, cabazitaxel, mitoxantrone, estramustine);
   - Participation in a clinical trial of an investigational agent that inhibits the AR or androgen synthesis (e.g. ARN-509, ODM-201, VT-464; unless the treatment was placebo);
5. Current or prior treatment within 4 weeks prior to initiation of IMP with the following agents for the treatment of prostate cancer:
   - Antiandrogens (e.g. bicalutamide, nilutamide, flutamide);
   - 5-α reductase inhibitors (e.g. finasteride, dutasteride);
   - Estrogens;
   - Anabolic steroids;
   - Drugs with antiandrogenic properties such as spironolactone > 50 mg/kg;
   - Progestational agents;
6. Subject has received investigational therapy within 28 days or 5 half-lives whichever is longer, prior to initiation of IMP;
7. Use of opiate analgesia for pain from prostate cancer within 4 weeks prior to initiation of IMP;
8. Radiation therapy to bone lesions or prostatic bed within 4 weeks prior to initiation of IMP;
9. Major surgery within 4 weeks prior to initiation of IMP;
10. History of seizure or any condition that may predispose to seizures at any time in the past (e.g., prior cortical stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization). History of loss of consciousness or transient ischemic attack within 12 months prior to Screening;
11. Known or suspected brain metastasis or active leptomeningeal disease;
12. History of another malignancy within the previous 5 years other than non-melanoma skin cancer;
13. Clinically significant cardiovascular disease including:
    - Myocardial infarction within six months prior to Screening;
    - Uncontrolled angina within three months prior to Screening;
    - Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram or multi-gated acquisition scan (MUGA) 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;
- Bradycardia as indicated by a heart rate < 45 beats per minute on the screening ECG or physical examination;
- Uncontrolled hypertension as indicated by a resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at Screening;

14. Gastrointestinal disorders affecting absorption (e.g. extensive small bowel resection, active inflammatory bowel disease);
15. Medical contraindications to the use of prednisolone or docetaxel;
16. Allergies to any of the active ingredients or excipients in the study drugs;
17. Any condition which, in the Investigator's opinion, makes the subject unsuitable for study participation.

3.3.2 Exclusion Criteria - Period 2 (assessed at the Period 2 Eligibility Assessment)

Subjects will be excluded from participation if any of the following apply:

1. Cancer pain requiring chronic administration of opiate analgesia (parenteral opiate use for ≥7 days or use of WHO Analgesic Ladder Level 3 oral opiates for ≥3 weeks;
2. Absolute neutrophil count (ANC) < 1,500/μL, platelet count < 100,000/μL, or hemoglobin < 6.2 mmol/L (10 g/dL)
   (NOTE: subjects must not have received any growth factors or blood transfusions within seven days prior to the hematologic laboratory values obtained at the Period 2 Eligibility Assessment);
3. Total bilirubin > ULN; ALT or AST ≥ 2.5 times ULN; Child-Pugh B and C hepatic impairment;
4. Creatinine > 177 μmol/L (2 mg/dL);
5. Albumin ≤ 30 g/L (3.0 g/dL).

4 TREATMENT(S)

4.1 Identification of Study Drugs

4.1.1 Investigational Medicinal Product - Enzalutamide

The IMP, enzalutamide, has the chemical name 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide. It is a white to off-white solid that is insoluble in water and no salt forms are available at approximately pH 2 to 10.

The drug substance is formulated in the surfactant Labrasol® to create a solution. Enzalutamide will be provided as 40 mg liquid-filled soft gelatin capsules. The capsules are white to off-white oblong capsules.

4.1.2 Comparative Drug - Placebo

The corresponding placebo for enzalutamide consists of identical capsules filled with the same excipients but no active product.

4.1.3 Non-Investigational Medicinal Products

Docetaxel will be provided by the Sponsor or may be provided locally. Handling and administration of docetaxel should be in accordance with the SPC (Docetaxel SPC) and local practice for administration of cytotoxic agents. Infusion materials (diluents, pumps, catheters) will be provided locally.

Prednisolone 5 mg will be provided by the Site, along with any other pre-treatments given as standard of care.

4.2 Packaging and Labeling

The IMP used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person at Astellas Pharma Europe B.V. (APEB) or Sponsor's designee in accordance with APEB or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP) guidelines, and applicable local laws/regulations.

The IMP will be labeled according to the requirements as published in Annex 13 of the GMP guidelines and local laws and regulations.

A qualified person of APEB or Sponsor's designee will perform the final release of the IMP according to Directive 2003/94/EC annex 13.

4.2.1 Docetaxel

Docetaxel should be stored and handled in accordance with the SPC (Docetaxel SPC) and local practice for storage of cytotoxic agents. Docetaxel provided for the study is not intended for use outside of the study site.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the Investigator to ensure that study drug deliveries from the Sponsor are received by the Investigator/or designee and;

- that such deliveries are recorded,
- that study drug is handled and stored according to labeled storage conditions,
- that study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- that any unused study drug is returned to the Sponsor.

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

- The Investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The Investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the Investigator to dispense these test drugs.

- A study drug inventory will be maintained by the Investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the Investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return study drug to the Sponsor or designee at the end of the study or upon expiration.

4.4 Blinding

Period 2 of the study will be conducted in a double-blind manner. Subjects will be randomized to receive enzalutamide or placebo in a double-blind fashion such that the Investigator, Sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. Docetaxel will be administered open label.

4.4.1 Blinding Method

The study medication blind will be maintained by the Interactive Response Technology (IRT), which will be accessed by the study sites for subject number and study medication assignments.

4.4.2 Confirmation of the Indistinguishability of the IMP

The control for this blinded study will be placebo capsules that appear identical to the enzalutamide capsules. IMP will be dispensed in the same manner regardless of assigned treatment arm. Subjects will ingest the same number of capsules throughout the study.

4.4.3 Breaking the Treatment Code for Emergency

Treatment unblinding may only occur if the knowledge of the treatment assignment will materially change the planned management of a medical emergency.

For unblinding a subject, the assigned study medication information is accessible through the IRT. The sponsor must be notified immediately if the blind is broken. The date, time, and reason the blind was broken must be recorded in the source documents and on the appropriate Electronic Case Report Form (eCRF) if applicable.

If the Investigator is unblinded, study medication must be stopped immediately and the subject must be discontinued from the study. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure.

4.4.4 Breaking the Treatment Code by the Sponsor

The Sponsor may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR) in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will be provided to the limited staff who are responsible to break the codes for all SUSAR cases for reporting purposes.

The IDMC will be provided access to the dosing assignment for periodic review of the unblinded data as documented in the IDMC Charter.

4.5 Assignment and Allocation

4.5.1 Period 1 – Open Label IMP

The Investigator or designee will contact the IRT to register the subject into the study prior to the commencement of screening activities in Period 1. Subjects who meet the inclusion/exclusion criteria will be assigned to receive active treatment with enzalutamide. The identification number of the medication to be dispensed will be provided by the IRT. At subsequent drug dispensing visits, the Investigator or designee will again contact the IRT to request additional study medication for a subject. The medication number provided by the IRT should be included in the source documentation.

4.5.2 Period 2 – Randomized IMP

Subjects who meet the inclusion/exclusion criteria will be randomly assigned to receive enzalutamide or placebo using a 1:1 randomization schedule. Subjects will be stratified by disease progression (evidence of radiographic progression or not). The sponsor or designee will generate the randomization schedule.

The Investigator or designee will contact the IRT to randomize the subject into the study prior to the initiation of IMP in Period 2. IMP dispensing will be performed as described in **Section 4.5.1 Period 1 – Open Label IMP.**

4.5.3 Continuation of Treatment after Completion of Randomization and before and after Unblinding.

When sufficient numbers of subjects have been randomized into Period 2 (around 274), or the number of evaluable events for the primary endpoint have been reached (182), whichever occurs first, enrollment to Period 2 will close. Subjects who are still in Period 1 will have the opportunity to continue with open label enzalutamide via an Extension Period in another Astellas-sponsored study, until the investigator or subject decides it is no longer in the subject's best interests to continue; a decision to initiate alternative antineoplastic therapy is made; or there is disease progression, intolerable toxicity, subject withdrawal or death, whichever occurs first. Assessments will be limited to collection of efficacy and laboratory assessments that are performed as part of standard of care for the subject, Serious Adverse Events (SAEs) and Adverse Events (AEs). Protocol-specified efficacy and laboratory assessments will cease.

Similarly, when at least 182 endpoint-events have occurred in Period 2 of the study, the data will be cleaned and analyzed. Allowing for attrition, there may be some subjects still active in Period 2 when this data analysis cut-off is reached. These subjects will be able to continue to receive blinded study drug until the study is unblinded after database lock, at which time, subjects in the enzalutamide+docetaxel arm, who are still on enzalutamide will be able to continue receiving enzalutamide until the investigator or subject decides it is no longer in the subject's best interests to continue study drug; a decision to initiate alternative antineoplastic therapy is made; or there is disease progression, intolerable toxicity, subject withdrawal or death, whichever occurs first. Assessments will be limited as described above.

Subjects that are in the docetaxel plus placebo arm will leave the study and be treated as per standard of care. Subjects who decide not to continue receiving treatment via the extension periods will leave the study and be treated as per local standard of care.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

5.1.1.1 Period 1 Open label IMP

All subjects will receive open label enzalutamide 160 mg (4 x 40 mg capsules), orally once daily.

IMP should be taken as close to the same time each day as possible. IMP can be taken with or without food.

5.1.1.2 Period 2 Randomized IMP

Subjects will be randomized to receive blinded oral doses of IMP:

- Enzalutamide treatment arm - 160 mg (4 x 40 mg capsules) of active enzalutamide orally once daily.
- Placebo treatment arm - matching placebo (4 capsules) orally once daily.

IMP should be taken as close to the same time each day as possible. IMP can be taken with or without food.

5.1.1.3 Period 2 Non-IMP

Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer (Docetaxel SPC). In accordance with the SPC, docetaxel 75 mg/m^2 will be administered as a one-hour infusion every 3 weeks.

Prednisolone 5 mg orally twice daily will be administered continuously during docetaxel dosing cycles.

5.1.2 Interruption and Reduction in Dose of the Study Drugs

5.1.2.1 Enzalutamide/Placebo

If a subject misses taking a dose at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a subject misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose.

If a subject experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for 1 week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (3 capsules or 2 capsules) if warranted.

If a subject must be dosed with a strong CYP2C8 inhibitor (e.g. gemfibrozil) then treatment should be administered at a reduced dose (2 capsules) during concomitant treatment (see **Section 5.1.4.2 Drugs That May Affect Exposure to Enzalutamide**).

5.1.2.2 Docetaxel

In accordance with the SPC (Docetaxel SPC), docetaxel should be administered when the neutrophil count is ≥1,500 cells/mm^3. Dosing may be delayed until the neutrophil count has recovered.

In subjects who experience either febrile neutropenia, neutrophil count <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 75 mg/m^2 to 60 mg/m^2. If the subject continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

A 50% docetaxel dose reduction should be considered if subjects require co-administration of a strong CYP3A4 inhibitor such as azole antifungals, ritonavir and some macrolides (clarithromycin, telithromycin; see **Section 5.1.4.4 Drugs That May Affect Exposure to Docetaxel**).

For subjects with total bilirubin > ULN and/or ALT and AST > 3.5 times the ULN concurrent with ALP > 6 times the ULN, docetaxel should not be used. Subjects with elevated LFTs should have LFTs assessed prior to each cycle of docetaxel; see **Schedule of Assessments - Period 2**.

5.1.3 Previous and Concomitant Medication (Drugs and Therapies)

5.1.3.1 Previous Medication (Drugs and Therapies)

Medication taken within four weeks prior to the Period 1 Screening Visit must be captured in the eCRF.

5.1.3.2 Concomitant Medication (Drugs and Therapies)

Concomitant medications will be assessed at Screening (Period 1) and all subsequent clinic visits. All concomitant medications must be recorded in the eCRF. If the use of any medication during the study is due to an AE, the AE must be recorded on the AE case report form (CRF) and in the subject's clinical record.

Throughout the study, ongoing ADT with a LHRH agonist/antagonist is required if the subject has not undergone prior bilateral orchiectomy.

Initiation of bisphosphonates or denosumab for bone health is prohibited following randomization. The dosage and regimen of bisphosphonates or denosumab for bone health and any chronic permitted concomitant medication should be stabilized during Period 1 (> 4 weeks prior to randomization) and held constant throughout Period 2. Standard of care supplementation with calcium and vitamin D is encouraged.

Radiotherapy for palliative management of symptoms due to prostate cancer will not be considered unequivocal clinical progression and will not mandate study drug discontinuation during Period 2. Palliative radiotherapy is discouraged during period 1.

Initiation of excluded concomitant medications (see **Appendix 12.1 List of Excluded Concomitant Medications**) during Periods 1 or 2 will result in permanent treatment discontinuation.

For the purpose of this study, chronic opiate analgesia is defined as parenteral opiate use for ≥7 days or use of WHO Analgesic Ladder Level 3 oral opiates for ≥3 weeks.

Level	WHO Analgesic Ladder
0	No analgesia
1	Non-opioids (e.g. paracetamol, NSAIDs)
2	Weak opioids (e.g. codeine, dihydrocodeine, meptazinol)
3	Strong opioids (e.g. buprenorphine, diamorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone,pethidine, tramadol)

5.1.4 Potential Interactions Between the Test Products and Concomitant Medications

5.1.4.1 Effects of Enzalutamide on Exposure to Other Drugs

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

5.1.4.2 Drugs That May Affect Exposure to Enzalutamide

Coadministration of a strong CYP2C8 inhibitor (eg, gemfibrozil) increases the exposure of enzalutamide plus its active metabolite; therefore, coadministration of enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If coadministration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, the enzalutamide dose should be reduced to 80 mg once daily. If coadministration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

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

5.1.4.3 Effects of Docetaxel on Exposure to Other Drugs

In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolized by (and thus may inhibit the enzyme competitively) CYP3A4 such as ciclosporine, terfenadine, ketoconazole, erythromycin and troleandomycin. As a result, caution should be exercised when treating subjects with these medicinal products as concomitant therapy since there is a potential for a significant interaction.

5.1.4.4 Drugs That May Affect Exposure to Docetaxel

Clinical data indicate that docetaxel exposure and hence toxicity is increased when co-administered with a strong CYP3A4 inhibitor. A 50% docetaxel dose reduction should be considered if subjects require co-administration of a strong CYP3A4 inhibitor such as azole antifungals, ritonavir and some macrolides (clarithromycin, telithromycin).

Docetaxel PK in the presence of prednisone was studied in patients with metastatic prostate cancer. Docetaxel is metabolized by CYP3A4 and prednisone is known to induce CYP3A4. No statistically significant effect of prednisone on the PK of docetaxel was observed (Docetaxel SPC).

5.1.4.5 Potential Pharmacokinetic Interactions Between Enzalutamide and Docetaxel

As a strong CYP3A4 inducer, enzalutamide has theoretical potential to decrease plasma exposure to docetaxel which is cleared by pathways including CYP3A4.

Results from a phase I study indicated that enzalutamide did not have a clinically meaningful impact on docetaxel PK in patients with mCRPC.

5.1.5 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with IMP.

Study drug accountability will be performed to document compliance with the dosing regimen. Subjects will be asked to bring back all remaining IMP and all IMP packaging at each study visit for drug accountability.

Treatment compliance should be monitored closely and deviation in compliance should be reported to the Sponsor.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information will be obtained at the Period 1 Screening visit and will include date of birth (or age, if local regulations do not allow recording of subject's date of birth), race as described by the subject (unless local regulations do not allow recording of subject's race), height and weight.

5.2.2 Diagnosis, Severity, and Duration of Prostate Cancer

A complete medical history of the target disease will be recorded at the Period 1 Screening Visit. This includes documenting the subject's initial diagnosis of prostate cancer, Gleason score at time of diagnosis, dates and types of therapy and other disease specific information as designated in the eCRF.

5.2.3 Chest X-Ray or Chest CT

At the Period 1 Screening visit and Period 2 Eligibility Assessment 2 visit, a Chest x-ray or Chest CT will be performed. A Chest CT is required if the screening Chest x-ray demonstrates metastatic chest disease. Other required scans at Screening are described in **Section 5.3.1 CT/MRI and Bone Scans.**

5.2.4 Medical History

Medical history will include any significant conditions or diseases other than prostate cancer that occurred prior to informed consent.

5.2.5 Performance Status

The ECOG scale (Oken et al, 1982) will be used to assess performance status.

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	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
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

ECOG score will be collected at all visits.

5.3 Efficacy Assessment

5.3.1 CT/MRI and Bone Scans

Radiographic evaluation of metastatic disease is determined separately for soft -tissue and bone disease. Positron emission tomography (PET) scans should not be used to determine disease progression.

Radiographic disease assessment for soft tissue disease is based on an abdominopelvic CT or MRI scan and is defined by RECIST 1.1 (Eisenhauer et al 2009). Chest CT or MRI scans are also required if the Period 1 Screening visit/Period 2 Eligibility Assessment 2 visit Chest x-ray/CT demonstrates lung metastasis, or if clinically indicated. Assessment will include tumor measurements for target lesions, non-target lesions, and assessment for any new lesions. An overall assessment will be characterized for that time point evaluation. At the end of study for that subject, the overall best response to the study regimen will be characterized.

Radiographic disease assessment for bone lesions is based on whole body radionuclide bone scan and is considered progression when a minimum of 2 new metastatic lesions are observed following randomization in accordance with PCWG2 criteria (Scher et al 2008). Progression on bone scan within 12 weeks of baseline scans in either Period requires a confirmation scan (showing 2 additional lesions compared with the first scan) performed 6 or more weeks later.

Study imaging should be read on site. Each site should ideally designate the same reader who will evaluate the images for any one subject for the duration of the study. The imaging method utilized for baseline scans must be utilized throughout the entire study.

Period 1 imaging will be performed during the Period 1 Screening Visit window then assessed at 12 week intervals after Day 1. Period 2 imaging will be performed during the Period 2 Eligibility Assessment window (or use the most recent Period 1 imaging if within

4 weeks prior to randomization) then assessed at 12 week intervals after Day 1. Additionally, imaging may be performed at any time to confirm suspected progression of disease. Scans may be performed up to 7 days prior to the scheduled visit to facilitate availability of results.

5.3.2 Prostate Specific Antigen

Samples for PSA will be collected and analyzed at a central laboratory, see **Appendix 12.2 Central Laboratory Tests**.

PSA testing will be performed at every scheduled visit excepting Period 1, Week 5 visit and Period 2, Weeks 4, 7 and 10 visits.

5.3.3 Brief Pain Inventory (BPI)

The BPI pain questionnaire is a validated instrument that is a subject self rating scale assessing level of pain, effect of the pain on activities of daily living, and analgesic use (http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html). The BPI used in this study is modified from the short form (BPI-SF) and contains 7 questions (questions 2 and 7 from the standard BPI-SF will not be collected). The BPI uses simple numeric rating scales from 0 to 10.

Subjects will be asked to complete a BPI-SF questionnaire to record their cancer-related pain at Screening in Period 1 and then at every scheduled visit during Period 2.

5.4 Safety Assessment

5.4.1 Vital Signs

Vital signs including blood pressure, pulse rate and temperature will be assessed at screening, at every clinic visit while on IMP and at the safety follow-up visit.

5.4.2 Adverse Events

All Adverse Events (AEs) will be collected from the time the subject signs the consent form until 30 days after last dose of IMP. See **Section 5.5 Adverse Events and Other Safety Aspects** for information regarding adverse event collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See **Appendix 12.3 Liver Safety Monitoring and Assessment** for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function testing (LFT, e.g.: AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

Central laboratory tests that will be performed during the conduct of the study are defined in **Appendix 12.2 Central Laboratory Tests**. Central safety laboratory tests will be collected at all scheduled visits. Additional local safety laboratory tests will be collected in accordance with the Docetaxel SPC prior to each treatment cycle; see **Schedule of Assessments - Period 2**.

Clinical significance of out-of-range laboratory findings is to be determined and documented by the Investigator/Sub-investigator who is a qualified physician.

5.4.4 Physical Examination, Height and Weight

A standard, full physical examination will be performed at the Period 1 Screening Visit to assess weight, general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status, lymphatic, genitourinary, and rectal systems. Any abnormalities will be collected as medical history or AEs. Subsequent physical examinations will be brief (i.e. symptom-directed only).

Physical examinations will be performed at all scheduled visits. Weight will be recorded at each visit. Height will be recorded at the Period 1 screening visit only.

5.4.5 Electrocardiogram

A standard 12-lead ECG will be performed on all subjects. Parameters that include heart rate, PR interval, RR interval, QRS interval, QT interval will be collected on the eCRF. Abnormalities and clinical significance as judged by the Investigator will be reported as well. It is recommended that ECG reports are printed in duplicate and photocopied to prevent fading.

An ECG will be performed at Screening in Period 1, at the Eligibility Assessment for Period 2 and then every 12 weeks during Period 2 after Day 1.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the Investigator.

5.5.1.1 Disease Progression

It is anticipated that a proportion of subjects will experience disease progression. Disease progression should not be reported as an AE. Clinical signs and symptoms due to disease progression will be collected as AEs. Individual signs and symptoms will be listed rather than the term “disease progression” with the following exception: if disease progression is the cause of death, this event may be recorded as an AE with “disease progression” as the reported term.

5.5.2 Definition of Serious Adverse Events (SAEs)

An adverse event is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an AE is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety events of interest on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)
- Suspect drug-drug interaction

All of the events of interest noted above should be recorded on the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked ‘serious’ and the SAE worksheet.

The Sponsor has a list of events that they classify as “always serious” events. If an AE is reported that is considered to be an event per this classification as “always serious”, additional information on the event may be requested.

5.5.3 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out".

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

5.5.4 Criteria for Defining the Severity of an Adverse Event

Severity of AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) guidelines (Version 4.03). The items that are not stipulated in the NCI-CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF:

Grade	Assessment Standard
1-Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2-Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3-Severe or medically significant but not immediately life-threatening	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to AE

5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of an SAE, the Investigator must contact the Sponsor by telephone or fax immediately (within 24 hours of awareness).

The Investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor by fax immediately (within 24-hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

For contact details, see Section II Contact Details of Key Sponsor's Personnel.

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee (see Section II Contact Details of Key Sponsor's Personnel).

Follow-up information for the event should be sent promptly (within 7-days of the initial notification.

Full details of the SAE should be recorded on the medical records and on the (e)CRF.

The following minimum information is required:

- International Study Number (ISN)/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the study drug.

The Sponsor or Sponsor's designee will submit expedited safety reports to the regulatory agencies (e.g. EMA, national authorities) as necessary, and will inform the Investigators of such regulatory reports. Investigators must submit safety reports as required by their IEC within timelines set by regional regulations (i.e. European Union [EU], Electronic Common Technical Document [eCTD], FDA). Documentation of the submission to and receipt by the IEC of expedited safety reports should be retained by the site.

The Sponsor will notify all Investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements to the IEC.

The Investigators should provide written documentation of IEC notification for each report to the Sponsor.

You may contact the Sponsor's Medical Monitor/Expert for any other problem related to the safety, welfare, or rights of the subject.

For SUSARs from a blinded trial, unblinded Council for International Organizations of Medical Sciences [CIOMS]-I report will be submitted to the authorities and IEC where required.

New SAEs occurring until 30 days after the last study drug treatment must be reported.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the AE progresses to an ″SAE″, or if a subject experiences a new SAE, the Investigator must immediately report the information to the Sponsor.

Please refer to **Appendix 12.3 Liver Safety Monitoring and Assessment** for detailed instructions on Drug Induced Liver Injury (DILI).

5.5.7 Monitoring of Common Serious Adverse Events

Common serious AEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in **Appendix 12.4**

Common Serious Adverse Events for your reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events" as specified in **Appendix 12.4 Common Serious Adverse Events**. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in **Section 5.5.5 Reporting of Serious Adverse Events (SAEs).**

5.5.8 Procedure in Case of Pregnancy

If during the conduct of the clinical trial, a male subject impregnates his partner the subject should report the pregnancy to the Investigator. The Investigator will report the pregnancy to the Sponsor as an SAE within 30 days from discontinuation of dosing. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The Investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs (spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus]), the Investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- ″Spontaneous abortion″ includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the Investigator
- In the case of a delivery of a living newborn, the ″normality″ of the infant is evaluated at the birth
- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

5.5.9 Emergency Procedures and Management of Overdose

<u>Enzalutamide</u>
An overdose is defined as 2 days of IMP taken over the course of a 24 hour period. Neither the effects of overdose of enzalutamide nor an antidote to overdose are known. In the event of an overdose of enzalutamide, general supportive measures should be initiated, taking into consideration the half-life is 5.8 days for enzalutamide. Subjects may be at increased risk of seizures following an overdose of enzalutamide.

<u>Docetaxel</u>
There is no known antidote for docetaxel overdose. In case of overdose, the subject should be kept in a specialized unit and vital functions closely monitored. In cases of overdose,

exacerbation of AEs may be expected. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Subjects should receive therapeutic granulocyte-colony stimulation factor (G-CSF) as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the Sponsor will inform all Investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IEC of such information when needed.

5.6 Other Measurements, Assessments or Methods

5.6.1 FACT-P

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 (http://www.facit.org/FACITOrg). 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.

Subjects will be asked to complete a FACT-P survey at Screening in Period 1 and then every 12 weeks during Period 2 from Day 1.

5.6.2 EQ-5D-5L

EQ-5D-5L is a standardized instrument for use as a measure of health outcome (http://www.euroqol.org/home.html). It provides a simple descriptive profile and a single index value for health status. EQ-5D-5L is designed for self-completion by respondents. It consists of 2 pages comprising the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels and the subject is asked to indicate his health state by ticking the box with the most appropriate statement.

Subjects will be asked to complete a EQ-5D-5L instrument at Screening in Period 1 and then every 12 weeks during Period 2 from Day 1.

5.6.3 Health Resource Use

Health Resource Use will be assessed by a member of the study team by subject interview and review of the medical record to ascertain responses to the following questions, which will be recorded and transcribed into the eCRF.

Subjects will be questioned for health resource use information at the Period 1 Screening Visit and then every 12 weeks, and every 12 weeks during Period 2 from Day 1.

How many time have you seen the following healthcare professionals in the last 12 weeks? (If more than one health care professional was seen please count them separately) • General Practitioner/family doctor • Hospital Doctor • Practice/district nurse • Hospital nurse
Have you been you been hospitalized in the last 12 weeks? If yes: • Provide length of stay (days) • Was this a: o Routine admission, or o Unscheduled/Emergency room admission? If this was an Unscheduled/Emergency room admission, what was the reason? o Treatment side effect, or o Other (*reason to be recorded*)

5.7 Total Amount of Blood

The total amount of blood for each subject will vary depending on how long they stay on treatment.

The expected blood draw for hematology assessment is approximately 3 mL and biochemistry (including any testosterone or PSA assessment) approximately 10.5 mL. The maximum amount of blood collected for a subject within 24 hours during the treatment Period is approximately 15 mL (including >10% overage).

For a subject in Period 1, the total expected maximum blood draw over 1 year would be approximately 105 mL (assuming 7 study visits). For a subject in Period 2, the total expected blood draw over 1 year would be approximately 266 mL (assuming 14 study visits and allowing for local hematology collection nadir counts [4 mL assumed] during docetaxel treatment).

The maximum amount of blood during the follow-up period is approximately 15 mL.

Furthermore, if any laboratory abnormalities are found for a subject, additional blood may be drawn for monitoring.

For subjects who consent to provide samples for biomarker analysis, a maximum of 30ml of whole blood will be collected according to the laboratory manual to be provided, at specified time points (described in Section V, Schedule of Assessments). Subjects will have a maximum of 4 samples in Period 1, and 6 samples in Period 2 (an addition of no more than approximately 300ml of blood during the study for subjects enrolled in the biomarker sub-study, in addition to the amounts specified above for the main study).

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom IMP is permanently discontinued prematurely for any reason.

The subject is free to withdraw from the IMP and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the Investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Subjects will be discontinued from IMP if any of the following occur:

- Initiation of excluded concomitant medications defined in **Appendix 12.1 List of Excluded Concomitant Medications.**
- Period 1 subjects who do not meet the disease response criteria at Week 13 and continuation of treatment is not warranted.
- Period 1 subjects meeting the criteria for disease progression but who do not meet the criteria for randomization into Period 2.
- Subject develops an AE or toxicity, where continued administration of study drug is deemed not in the subject’s best interest by the Investigator and/or the Sponsor. Refer to **Appendix 12.3 Liver Safety Monitoring and Assessment**.
- Subject withdraws consent for further treatment.

Unless the subject withdraws consent, all subjects discontinuing IMP for any reason will have a safety follow-up visit 30 days after their last dose of IMP or prior to initiation of subsequent antineoplastic therapy for prostate cancer, whichever occurs first.

Subject in Period 1 who do not meet the disease response criteria at Week 13 but who continue treatment will continue to attend study visits until initiation of any new antineoplastic therapy.

Subjects that discontinue IMP in Period 2 for a reason other than disease progression will continue to attend study visits (at 12 weekly intervals) until withdrawal of consent, disease progression or death. Reasonable effort should be made to contact any subject lost to follow-up during the course of the study in order to complete study related assessments and retrieve any outstanding data and IMP. Following unsuccessful telephone contact, an effort to contact the subject by mail using a method that provides proof of receipt should be attempted. Such efforts should be documented in the source documents.

After discontinuation from IMP further treatment is at the discretion of the subject and the treating physician.

Subjects who discontinue docetaxel before completion of 10 cycles (e.g. for toxicity) may continue treatment with IMP and will continue to attend study visits (at 12 weekly intervals) for assessments until IMP discontinuation criteria or endpoint criteria are met.

6.2 Discontinuation of the Site

If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the Investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the Sponsor's responsible biostatistician. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

Prior to Database Lock, a Final Review of Data and Tables, Listings and Figures Meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

7.1 Sample Size

The following assumptions were used to determine the sample size calculation for the primary endpoint of PFS:

- The estimated median PFS is 6 months for the control group (placebo plus docetaxel and prednisolone).
- Assuming the true treatment effect has a hazard ratio (HR) of 0.66, with 2-sided type 1 error rate of 0.05 and 80% power, at least 182 progression events are needed. This will allow statistical significance be claimed at the conclusion of the study if the observed HR is <=0.75, approximately.
- If the recruitment period is up to 18 months, the follow-up of subjects in Period 2 is approximately 6 months, and the recruitment rate is non-uniform, at least 274 subjects will need to be randomized.

Allowing for attrition prior to randomization, it is estimated that approximately 650 subjects will be enrolled. During the study, discontinuation rate, PSA response and disease progression rates will be monitored and if necessary, the total number of subjects enrolled may be adjusted to reach the required number of events at the end of Period 2 (at least 182 events).

7.2 Analysis Set

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set (FAS)

The full analysis set will consist of all subjects who are randomized and receive at least one dose of IMP. This will be the primary analysis set for efficacy analyses. All subjects will be analyzed as randomized when FAS population is used.

7.2.2 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the SAF will be used. The SAF consists of all subjects who took at least one dose of IMP, and will be used for safety analyses, separated for Period 1 and Period 2. All subjects will be analyzed as treated when SAF population is used.

If the subject, at any moment during Period 2, accidently received the wrong treatment, then the subject will be analyzed as if they received enzalutamide as at least one of the actual treatments given was enzalutamide.

7.3 Demographics and Other Baseline Characteristics

7.3.1 Demographics

Demographic information will be summarized using descriptive statistics by treatment arm and stratum.

7.3.2 Medical History

A detailed medical history for each subject will be obtained during Screening and will be summarized by treatment arm and stratum.

7.3.3 Diagnosis of the Target Disease, Severity and Duration of Disease

Each subject's complete cancer history will be collected during the Screening Visit prior to Period 1 treatment. The number and percentage of subjects will be used to summarize the type of cancer, disease status, incidence of metastases and previous therapies. Descriptive statistics will be used to summarize the duration of disease.

7.4 Analysis of Efficacy

Efficacy will be assessed, for the primary and the secondary endpoints, in period 2 only. In addition, exploratory analyses for biomarkers will be conducted, which will be described in a separate Statistical Analysis Plan (SAP)

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

The primary efficacy endpoint of PFS is defined as the time from randomization to the earliest objective evidence of radiographic progression, unequivocal clinical progression or death on study, whichever occurs first.

The treatment effect of enzalutamide compared to placebo based on PFS disease progression will be tested using a stratified log-rank test, stratified by the randomization stratification factor, at the 0.05 2-sided significance level (based on 182 events).

Additionally, the benefit of enzalutamide compared to placebo will be evaluated by a single hazard ratio (enzalutamide /placebo) with its 95% confidence interval based on a Cox regression model stratified by the randomization stratification factor. Kaplan-Meier curves will be used to estimate the distribution of duration of PFS time to disease progression. The 50th percentile of Kaplan-Meier estimates will be used to estimate the median duration of PFS until disease progression. A 2-sided 95% confidence interval will be provided for this estimate. The 25th percentile and its 2-sided 95% confidence interval will also be provided.

A sensitivity analysis for PFS will be conducted using an unstratified log-rank test. A single hazard ratio (enzalutamide /placebo) with its 95% confidence interval based on an unstratified Cox regression model will also be provided.

The duration of PFS will be calculated for all randomized subjects as the duration of time from the date of randomization to the earliest date of disease progression.

The duration of PFS until earliest disease progression date will be right-censored based on one of the following conditions:

- Lost to follow-up since randomization;
- Not known to have disease progression at the data analysis cutoff.

7.4.1.2 Subgroup Analysis

There is one stratification at the start of Period 2 by disease progression. For the primary variable, a Kaplan Meier curve will be created and will be descriptively tabulated by strata. No formal analysis will be performed by strata.

Additionally for randomized patients, the analysis of the primary endpoint will be repeated using Period 1 data analysed by subgroup (type of progression (PSA or radiographic) observed in that period.

7.4.2 Analysis of Secondary Endpoints (Period 2)

7.4.2.1.1 Time to PSA Progression:

PSA progression is defined according to PCWG2 criteria. Time to PSA progression is defined as the time from randomization to the date of the first PSA value demonstrating progression, which must be subsequently confirmed. The median time to PSA progression and the corresponding confidence intervals will be calculated.

The treatment effect of enzalutamide compared to placebo based on time to PSA progression will be tested with a stratified log-rank test at the 2-sided 0.05 significance level.

Additionally, the benefit of enzalutamide compared to placebo will be evaluated by a single hazard ratio (enzalutamide/placebo) with its 95% confidence interval based on a Cox regression model stratified by the 1 randomization stratification factor. Kaplan-Meier curves will be used to estimate the distribution of time to PSA progression. The 50th percentile of Kaplan-Meier estimates will be used to estimate the median time to PSA progression. A 2-sided 95% confidence interval will be provided for this estimate. The 25th percentile and its 2-sided 95% confidence interval will also be provided.

7.4.2.2 Objective Response Rate:

The best overall radiographic response after randomization will use Investigator assessments of response for soft tissue disease per RECIST 1.1.

Rates of complete response (CR), partial response (PR), stable disease (SD), CR+PR, and CR+PR+SD will be tabulated along with exact binomial confidence intervals (Clopper Pearson).

7.4.2.3 Time to Pain Progression:

Time to pain progression is defined as the interval from randomization to the first date a subject experiences a BPI-SF increase by ≥30% from baseline in the average of BPI-SF pain intensity item scores (items 3, 4, 5, and 6) observed at 2 consecutive evaluations ≥3 weeks apart without decrease in analgesic usage. Only subjects experiencing average pain intensity item scores (items 3, 4, 5 and 6) of ≥4 at the time of progression will be included in the calculation.

The statistical analyses for evaluating treatment effect of enzalutamide compared to placebo on time to pain progression will be the same as that described for time to PSA progression.

7.4.2.4 Time to opiate use for cancer-related pain:

Time to opiate use for cancer-related pain is defined as the interval from randomization to initiation of chronic administration of opiate analgesia (parenteral opiate use for ≥7 days or use of WHO Analgesic Ladder Level 3 oral opiates for ≥3 weeks).

The statistical analyses for evaluating treatment effect of enzalutamide compared to placebo on time to pain progression will be the same as that described for time to PSA progression.

7.4.2.5 Time to First Skeletal Related Event:

Time to first SRE is defined as the interval from randomization to the first date of radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.

The statistical analyses for evaluating treatment effect of enzalutamide compared to placebo on time to first SRE will be the same as that described for time to PSA progression.

7.4.2.6 Quality of Life

Quality of life will be assessed using FACT-P and EQ-5D-5L data and will be summarized descriptively by treatment group and study visit.

7.4.2.7 Cumulative Dose of Docetaxel

Cumulative dose of docetaxel will be summarized descriptively by treatment group.

7.4.2.8 Health Resource Use

Health resource use will be summarized descriptively for both Periods (by treatment group in Period 2).

7.4.3 Analysis of Biomarkers

These will include exploratory studies of blood samples to identify biomarkers that are prognostic and/or predictive of disease progression, response to treatment, and resistance to

study treatment (associations of biomarkers with clinical outcomes). Due to the ongoing rapid advances in the scientific understanding of prostate cancer and enzalutamide resistance, it is currently not possible to pre-define all the biomarkers that are linked to disease progression and treatment response. Therefore, blood samples will be collected, processed and stored frozen at -80 ºC at an accredited central laboratory until further analysis, for a maximum of 10 years after collection (or as specified by local regulatory authorities). Definitive biomarker studies will be performed at a future timepoint and may include, but are not limited to:

- Investigating changes in tumor-derived RNA (single mRNA, whole transciptome, miRNA) and DNA (single genes or whole genome/exome, germ line vs tumour), such as mutations, variants and expression level of the androgen receptor and other prostate cancer related genes in plasma in understanding mechanisms of resistance to enzalutamide.
- Isolation and investigation of Circulating Tumor Cells (CTCs) to identify changes in protein and/or nucleic acid biomarkers that may be related to disease progression or treatment response.
- Investigating other serum biomarkers such as cytokines (eg. IL6, IL8) that may be predictive/prognostic for treatment response.
- Investigations of how enzalutamide works in people with prostate cancer.
- Studies that may help to understand the course of prostate cancer and related diseases.

Subjects may withdraw consent to have their samples analysed at any time prior to the analysis taking place. The treating doctor of the participant will be notified of any analytically or clinically valid findings that may emerge significant to the participant or their family regarding cancer.

The analysis of the exploratory biomarkers will be described in a separate biomarker plan.

7.5 Analysis of Safety

Safety will be assessed separately for Period 1 and Period 2.

7.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to IMP will be summarized by system organ class, preferred term and treatment group. The number and percentage of AEs by severity will also be summarized. All AEs will be listed.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment group and time point. Using the definitions provided in the NCI CTCAE Version 4.03, lab values will be classified as Grade 1 through 5, where possible. Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated regarding either normal ranges or CTC CTCAE grade. Laboratory data will be displayed in listings and summary tables.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time. Vital signs data will be displayed in listings.

7.5.4 Physical Examination

Physical examination results will be listed by treatment group.

7.5.5 ECGs

The 12-lead ECG results will be summarized by treatment group and time point.

7.5.6 Deaths

Deaths will be summarized by treatment group and time point.

7.6 Protocol Deviations

Protocol deviations as defined in **Section 8.1.6 Protocol Deviations** will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

- PD1 - Entered into the study even though they did not satisfy entry criteria;
- PD2 - Developed withdrawal criteria during the study and was not withdrawn;
- PD3 - Received wrong treatment or incorrect dose;
- PD 4- Received excluded concomitant treatment

7.7 Interim Analysis (and Early Discontinuation of the Clinical Study)

No formal interim analysis is planned.

7.8 Handling of Missing Data, Outliers, Visit Windows, and Other Information

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to determine whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

Imputation of partial dates for AEs for treatment emergent determination will follow a worst case scenario where AEs that are possible Treatment Emergent are flagged as such.

See the SAP for details of the definitions for windows to be used for analyses by visit and the clear descriptions of imputation of AE dates.

All “time to” analysis will be right-censored based on one of the following conditions:

- Lost to follow-up since randomization;
- Not known to have the event at the data analysis cut-off;
- Death will also be a censoring condition for all events that do not include death.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The Investigator or site designee will enter data collected using an eCRF. In the interest of collecting data in the most efficient manner, the Investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 5 working days after the subject visit.

The Investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at local and central laboratories. Central laboratory data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

Subject questionnaires will be completed by the subject on paper. The Investigator or site designee should review the questionnaire data while the subject is at the site. The Investigator or site designee will enter the subject questionnaire data directly into the eCRF.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms (ICFs)
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- Adverse events and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the Investigator/Sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The Investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to **Section 8.1.2 Specification of Source Documents**) when they are requested by the Sponsor monitors and auditors, the IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Global Data Science Department of the Sponsor in accordance with the SOPs for data management. All study specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The Investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an Investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn
- Received wrong treatment or incorrect dose.

Received excluded concomitant treatment. When a deviation from the protocol is identified for an individual subject, the Investigator or designee must ensure the Sponsor is notified. The Sponsor will follow up with the Investigator, as applicable, to assess the deviation and the possible impact to the safety and / or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the Investigator must contact the Sponsor immediately.

The Investigator will also assure that deviations meeting IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the Last Subject's Last Visit (LSLV).

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Independent Ethics Committee/Competent Authorities

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the IB, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC. The IEC will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC approval prior to implementation of the changes made to the study design at the site. The Investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible IECs and Competent Authorities (CAs), as required. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC should also be provided to Sponsor.

If required by local regulations, the Investigator shall make accurate and adequate written progress reports to the IEC at appropriate intervals, not exceeding one year. The Investigator shall make an accurate and adequate final report to the IEC within one year after LSLV or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the Investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The Investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
2. The Investigator must update their ICF and submit it for approval to the IEC. The Investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The Investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The Investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number will identify subject data retrieved by the Sponsor. However, the Sponsor requires the Investigator to permit the Sponsor, Sponsor's representative(s), the IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e. Health Insurance Portability and Accountability Act [HIPAA]).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the IB and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The Investigator may use this information for the purpose of the study only. It is understood by the Investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical Investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The Investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. The Investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on the CRFs supplied for each subject.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments/substantial amendments and/or /non-substantial amendments. Depending on the nature of the amendment, either IEC, CA approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the Investigator, the regulatory authority, and the IEC (if applicable).

Amendments to this protocol must be signed by the Sponsor and the Investigator. Written verification of IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IEC approval, but will be submitted to the IEC for their information, if required by local regulations.

If there are changes to the Informed Consent, written verification of IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Insurance of Subjects and Others

The Sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating Investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, CRFs, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee

An IDMC will be charged with reviewing safety data.

A separate charter will describe the activities of this committee.

10.2 Study Steering Committee

A Steering Committee will be implemented to provide oversight of the conduct of the trial. This includes input into design of the study, oversight of the practical aspects of the study, as well as ensuring that the study continues to be run in a way which is both safe for the subjects and will provide appropriate safety and efficacy data to the Investigators and Sponsor. In fulfilling the safety role, the Committee will work in conjunction with an IDMC being established for this trial.

A separate charter will describe the activities of this committee.

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12 APPENDICES

12.1 List of Excluded Concomitant Medications

- Aminoglutethimide;
- Ketoconazole (for the treatment of prostate cancer; treatment for fungal infections is permitted, but refer to **Section 5.1.4 Potential Interactions Between the Test Products and Concomitant Medications**);
- Abiraterone;
- ^{223}Ra, ^{89}Sr, ^{153}Sm, ^{186}Re/^{188}Re;
- Immunomodulatory therapies (e.g. Sipuleucel-T, DCVAC);
- Cytotoxic chemotherapy not required by protocol (e.g. cabazitaxel, mitoxantrone, estramustine);
- Investigational agents;
- Antiandrogens (e.g. bicalutamide, nilutamide, flutamide);
- 5-α reductase inhibitors (e.g. finasteride, dutasteride);
- Estrogens;
- Anabolic steroids;
- Drugs with antiandrogenic properties such as spironolactone > 50 mg/kg;
- Progestational agents.

12.2 Central Laboratory Tests

Samples will be analyzed by Bioanalytical Research Corporation (BARC nv, Gent, Belgium).

Hematology	Red Blood Cell count (RBC) Hemoglobin (Hb) Hematocrit (HCT) White Blood Cell count (WBC) WBC differential Mean Corpuscular Volume (MCV) Platelet Count
Biochemistry	Alanine Aminotransferase (ALT) Albumin Alkaline Phosphatase (ALP) Aspartate Aminotransferase (AST) Bicarbonate Blood Urea Nitrogen (BUN) Calcium Chloride Creatinine Gamma-glutamyl Transferase (GGT) Glucose (non-fasting) Lactate Dehydrogenase (LDH) Phosphate Potassium Sodium Total Bilirubin Total Protein
Other Tests	Testosterone (for eligibility only) Prostate Specific Antigen (see **Section 5.3.2 Prostate Specific Antigen)** Liver Function Tests (see **Appendix 12.3 Liver Safety Monitoring and Assessment)**

12.3 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN (to > 5 × ULN in subjects with liver metastases), or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the Investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 x ULN (in patients without liver metastases), > 5 x ULN (in patients with liver metastases)	or	> 2 x ULN
Severe*	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases)
- ALT or AST > 3 × ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The Investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) that has been developed globally and can be activated for any study or appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above , in the absence of another etiology may be considered an important medical event and may be reported as a Serious Adverse Event (SAE). The Sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the Investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The Investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the (e)CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
  - acute viral hepatitis (A,B, C, D, E or other infectious agents).
  - ultrasound or other imaging to assess biliary tract disease
  - other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, pre-existing or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The Investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metastases)
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and (TBL > 2 × ULN in patients with liver metastases)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant)." The 2 "requirements" for Hy's Law are:1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated patients to be discriminating"). 2. Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-

hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. [Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 Apr;15(4):241-3.]

Reference

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.4 Common Serious Adverse Events

The following is a list of serious adverse events that the Sponsor considers to be associated with the disease state being studied. **The list does NOT change your reporting obligations or prevent the need to report an adverse event meeting the definition of an SAE as detailed in Section 5.5.2 Definition of Serious Adverse Events (SAEs)**. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events". You are required to follow the requirements detailed in **Section 5.5.5 Reporting of Serious Adverse Events (SAEs)**.

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analysis of these events indicate they occur more frequently with study drug, an expedited IND safety report may be submitted to the FDA.

- Anemia
- Anorexia
- Asthenia / Fatigue
- Back pain
- Bone pain
- Catheter related infection
- Dyspnea
- Haematuria
- Hydronephrosis
- Metastases to bone
- Metastases to central nervous system
- Nausea
- Obstructive uropathy
- Pain
- Prostate cancer metastatic
- Renal failure
- Renal failure acute
- Spinal compression fracture
- Spinal cord compression
- Urinary retention
- Urinary tract infection
- Urinary tract obstruction
- Vomiting

SIGNATURES

1. SPONSOR'S SIGNATURE

1.1. PROTOCOL AUTHORS

(GPF 4.00)