A Multicenter Phase 4, Open-label, Single-arm, Safety and Efficacy Study of Enzalutamide in Indian Patients with Progressive Metastatic Castration-Resistant Prostate Cancer (mCRPC) Previously Treated with Docetaxel-Based Chemotherapy

ISN/Protocol 9785-CL-0413

Version <1.0>

31 May 2018

Sponsor:

Astellas Pharma Inc. (API)

2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g. Protocol authors and contributors, etc.) are located in [Section 13 Sponsor's Signatures].

2. INVESTIGATOR'S SIGNATURE

A Multicenter Phase 4, Open-label, Single-arm, Safety and Efficacy Study of Enzalutamide in Indian Patients with Progressive Metastatic Castration-Resistant Prostate Cancer (mCRPC) Previously Treated with Docetaxel-Based Chemotherapy

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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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(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: _____

Date (DD Mmm YYYY)

Printed Name: _____ _____

Address: _____

_____

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See [Section 5.5.5 Reporting of Serious Adverse Events] for SAE Fax Number and Email	**Please fax or email the SAE Worksheet to:** **IQVIA RDS East Asia Pte. Ltd.** **Lifecycle Safety** **Fax number: 000-800001-6750** **Email: QLS_Enzalutamide@iqvia.com**
Medical Monitor/Study Physician:	**Emergency Phone Numbers: +19736596677 OR +15708198565** **Email: MM_Astellas_9785-CL-0413@iqvia.com**
Clinical Research Contacts:	PPD Astellas Pharma Inc. 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo, 103-8411, JAPAN PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

Abbreviations	Description of abbreviations
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
APGD	Astellas Pharma Global Development, Inc.
API	Astellas Pharma Inc.
AR	Androgen receptor
AST	Aspartate aminotransferase
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
CIOMS	Council for International Organizations of Medical Sciences
CLCR	Creatinine clearance
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
CYP	Cytochrome P450
DCGI	Drug Controller General of India
DILI	Drug Induced Liver Injury
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EMA	European Medicines Agency
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAS	Full Analysis Set
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin Releasing Hormone
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data-Monitoring Committee
IEC	Independent Ethics Committee
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International study number

Abbreviations	Description of abbreviations
IUD	Intrauterine Device
IUS	Intrauterine System
J-NDA	Japan New Drug Application
LA-CRF	Liver abnormality case report form
LFT	Liver function test
mCRPC	Metastatic castration-resistant prostate cancer
mHSPC	Metastatic hormone sensitive prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MAA	Marketing Authorization Application
MRI	Magnetic resonance imaging
NA	Not applicable
NCI	National Cancer Institute
NDA	New Drug Application
OS	Overall survival
P-gp	P-glycoprotein
PRES	Posterior reversible encephalopathy syndrome
PSA	Prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SOC	Standard of care
SOP	Standard operating procedure
TBL	Total bilirubin
ULN	Upper limit of normal

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Assessments of subjects as they enter a trial before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a trial.
Enroll	To register or enter a subject into a clinical trial. NOTE: Once a subject has received the study drug or placebo, the clinical trial protocol applies to the subject.
Intervention	The drug, device, 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	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any entity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version No of Protocol Synopsis:	31 May 2018, Version 1.0
Sponsor: Astellas Pharma Inc. (API)	**Protocol Number:** 9785-CL-0413
Name of Study Drug: Enzalutamide	**Phase of Development:** Phase 4
Title of Study: A Multicenter Phase 4, Open-label, Single-arm, Safety and Efficacy Study of Enzalutamide in Indian Patients with Progressive Metastatic Castration-Resistant Prostate Cancer (mCRPC) Previously Treated with Docetaxel-Based Chemotherapy	
Planned Study Period: From 2Q2018	
Study Objective(s)**:** The objective is to evaluate the safety and efficacy of enzalutamide in Indian patients with progressive mCRPC previously treated with docetaxel-based chemotherapy as per locally approved prescribing information. Primary Objective • To evaluate the safety and tolerability of enzalutamide in Indian patients with progressive mCRPC previously treated with docetaxel-based chemotherapy. Secondary Objectives • To evaluate the effect of enzalutamide on prostate-specific antigen (PSA).	
Planned Total Number of Study Centers and Location(s): Approximately 7 centers in India	
Study Population: Indian patients with progressive mCRPC previously treated with docetaxel-based chemotherapy	
Number of Subjects to be Enrolled / Randomized: Approximately 50 subjects	
Study Design Overview: This study is a multicenter Phase 4, open-label, single-arm, safety and efficacy study of enzalutamide (160 mg/day) in patients with progressive mCRPC who have previously been treated with docetaxel-based chemotherapy. Approximately 50 patients will be enrolled and treated with enzalutamide 160 mg once daily until study discontinuation criteria is met. Safety and tolerability will be assessed by the collection of adverse events, vital signs, physical examinations, and safety laboratory evaluations. PSA will be collected for assessment of prostate cancer status on Screening Visit, Days 1, 29, 57, 85, 169, every subsequent 84 days and Safety Follow-up Visit. Subjects will have a safety follow-up visit 30 days after their last dose of study drug or prior to initiation of another investigational agent or new therapy including commercial enzalutamide for prostate cancer, whichever occurs first.	
Inclusion/Exclusion Criteria: *Inclusion:* Subject is eligible for the study if all of the following apply: 1. Institutional Review Board (IRB)-/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).
2. Subject is 18 years or more at the time of signing informed consent.
3. Subject is diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell or small cell histology.
4. Subject with established diagnosis of metastatic castration-resistant prostate carcinoma.
5. Being newly initiated on Xtandi treatment (Enzalutamide) based on independent clinical judgment of treating physicians as per locally approved prescribing information.
6. Subject has an estimated life expectancy of ≥ 6 months as assessed by the Investigator.
7. A sexually active male subject with female partner(s) who are of childbearing potential is eligible if:
    - Agree to use a male condom starting at screening and continue throughout study treatment and for 3 months after the final study drug administration.
    - If the male subject has not had a vasectomy or is not sterile as defined below their female partner(s) is utilizing 1 form of highly effective birth control starting at screening and continue throughout study treatment and for 3 months after the final study drug administration.
    - Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
    - Established intrauterine device (IUD) or intrauterine system (IUS).
    - Bilateral tubal occlusion
    - Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
    - Male is sterile due to a bilateral orchiectomy
    - Sexual Abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant
8. Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for 3 months after the final study drug administration.
9. Male subject must not donate sperm starting at screening and throughout the study period, and for 3 months after the final study drug administration.
10. Subject agrees not to participate in another interventional study while participating in the present study.

Exclusion:
Subject will be excluded from participation if any of the following apply:
1. Subject who is not eligible to receive Xtandi as per the locally approved prescribing information.
2. Subject participating or planning to participate in any interventional drug trial during the course of this trial.
3. Subject has received investigational study within 28 days or 5 half-lives, whichever is longer, prior to screening.
4. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.

Investigational Product(s):
Enzalutamide 40 mg capsule
Drug(s):

160 mg once daily until study discontinuation criteria is met.

Mode of Administration:
Oral, with or without food

Comparative Drug(s):
Not applicable

Enzalutamide Dose Reduction / Dose Adjustment

Subjects who experience a grade 3 or higher toxicity that is attributed to the study drug and cannot be ameliorated by the use of adequate medical intervention and/or dose reduction may interrupt study drug treatment for 1 week or until the toxicity grade improves to grade 2 or lower in severity. Study drug may be restarted at the original dose (160 mg/day) or a reduced dose (120 mg or 80 mg/day). If restarted at a lower dose or if interrupted for > 2 weeks, the Medical Monitor must be consulted.

Other Treatment for Prostate Cancer during the Study:
ADT (Androgen deprivation therapy), either bilateral orchiectomy or GnRH agonist or antagonist, which must be maintained during study treatment. A GnRH agonist/antagonist will be provided from the site's pharmacy stock and administered in accordance with the prescribing information.

Concomitant Medication Restrictions or Requirements:

Required Concomitant Treatment

All subjects will be required to maintain ADT during study treatment, either using a GnRH agonist/antagonist or having a history of bilateral orchiectomy.

Prohibited Concomitant Treatments

The following medications are prohibited within 4 weeks of day 1 and during the study treatment period:

- 5 α-reductase inhibitors (finasteride, dutasteride);
- Estrogens;
- Cyproterone acetate;
- Abiraterone
- Biologic or other agents with antitumor activity against prostate cancer (with the exception of those therapies identified in inclusion/exclusion criteria);
- Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone intended for the treatment of prostate cancer;
- Herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease PSA levels (i.e., saw palmetto);
- Androgens (testosterone, dehydroepiandrosterone, etc.);
- Investigational agents.

In addition, bisphosphonates and denosumab are prohibited unless stabilized for 2 weeks prior to day 1 and held constant throughout study treatment or administered for diagnosis of osteoporosis.

Enzalutamide Drug Interaction

There is a potential for enzalutamide to affect exposures to other medicinal products, or for other medicinal products to affect exposure to enzalutamide:

- Strong cytochrome P450 (CYP) 2C8 inhibitors (e.g., gemfibrozil) are to be avoided. If subject must be coadministered a strong CYP2C8 inhibitor, the dose of enzalutamide 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.
- Strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin) or

moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin, St. John's Wort) should be avoided if possible as they may reduce enzalutamide plasma concentration if coadministered. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended.

- Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), or CYP2C19, or UGT1A1 (e.g., S-mephenytoin) should be avoided if possible, as enzalutamide may decrease their exposure.
- If enzalutamide coadministration with warfarin cannot be avoided, additional international normalized ratio (INR) monitoring should be conducted.
- Enzalutamide is an inhibitor of human P-glycoprotein (P-gp) and may increase exposure to medicines that are P-gp substrates. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., digoxin, colchicine, dabigatran etexilate) should be used with caution when administered concomitantly with enzalutamide.

Permitted Concomitant Treatment

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

- Blood transfusions and growth factor support per standard of care and institutional guidelines;
- Steroid use (for indication other than prostate cancer) per standard of care;
- Pain therapy per standard of care and institutional guidelines;
- Palliative radiation therapy including external beam radiotherapy or systemic radionuclides (e.g., Samarium or Strontium);
- Vaccine therapy that has prior market authorization and is not intended to treat prostate cancer;
- Palliative surgical procedures to treat skeletal-related events.

Duration of Treatment:

Until study discontinuation criteria is met.

Discontinuation Criteria:

The subject is free to withdraw from the study treatment 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.

Subject will be discontinued from the study drug treatment if any of the following occur:

- Any adverse event that is intolerable to the subject which cannot be ameliorated by the use of adequate medical intervention and/or dose reduction or that in the opinion of the Investigator would lead to undue risk to the subject if dosing is continued.
- Subject who experiences a seizure or any condition that significantly predisposes the subject to seizure such as brain metastasis or clinically evident stroke.
- Subject who experiences a confirmed event of posterior reversible encephalopathy syndrome (PRES) by brain imaging, preferably by MRI.
- Subject initiates an investigational agent or new therapy for prostate cancer.
- Subject who has evidence of radiological disease progression and/or PSA progression as confirmed by the investigator and is no longer deriving clinical benefit. Imaging test can be done at the discretion of the investigator and are not part of the study.
- Subject has discontinued ADT (GnRH agonist/antagonist) and has a testosterone value in the noncastrate range (> 50 ng/dL).
- Subject who is, in the opinion of the Investigator or the Medical Monitor, noncompliant with

the protocol requirements. • Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject. • Subject withdraws consent for the study. Subject will be discontinued from the 30 day study follow-up if any of the following occur: • Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject. • Subject withdraws consent for further follow-up. • Death. • Study termination by the Sponsor.
Endpoints for Evaluation: **Primary:** <u>Safety</u> • Nature, frequency and severity of adverse events • Safety laboratory tests: biochemistry and hematology • Physical examination • Vital signs (blood pressure, pulse and temperature) **Secondary:** <u>Efficacy</u> • PSA response rate (≥50% reduction from baseline)
Statistical Methods: **Sample size justification:** The sample size of 50 subjects is not based on a statistical power calculation. **Safety:** Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent AEs, serious AEs (SAEs), AEs leading to withdrawal of treatment, and AEs possibly related to the study drug will be calculated. Changes in laboratory parameters, vital signs, and weight over time will be tabulated. **Efficacy:** The PSA response rate will be summarized by time point. **Pharmacokinetics:** Not applicable **Pharmacodynamics:** Not applicable **Interim analyses:** An interim assessment will be conducted at 6 month from first subject enrollment, with respect to safety. The report will be submitted to the health authority.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

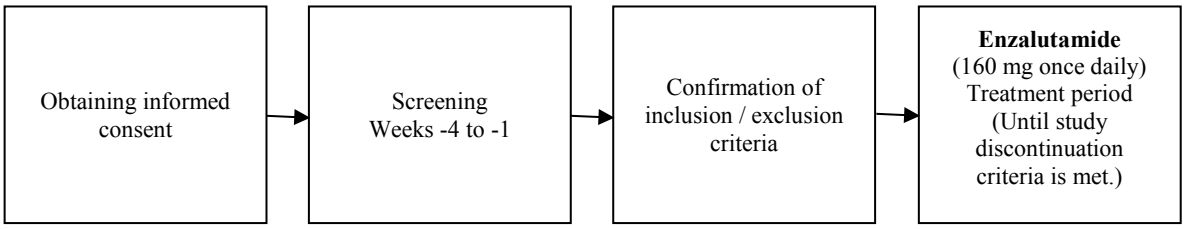

Table 1: Schedule of Assessments

Study Day	**Screening Visit**	**1**	**29**	**57**	**85**	**169 & every subsequent 84 days**	**Safety Follow-up**	**Unscheduled Visit†**
Study Week	**-4 to -1 (28 Days)**	**1**	**5**	**9**	**13**	**25**	**30 Days after Last Dose§**	
Window (Days)			± 7	± 7	± 7	± 7	± 7	NA
Informed Consent	X							
Medical History	X							
Inclusion/Exclusion Criteria	X	X						
IRT		X						
Vital Signs	X	X	X	X	X	X	X	X
Physical Examination including Weight¶	X	X	X	X	X	X	X	X
Height	X							
Clinical Labs ‡	X	X	X	X	X	X	X	X
PSA	X	X	X	X	X	X	X	
ECOG Performance Status	X							
Adverse Events§§	X	X	X	X	X	X	X	X
Previous and Concomitant Medications	X	X	X	X	X	X	X	X
Study Drug Dispensing		X	X	X	X	X		
Study Drug Treatment		X	X	X	X	X		

ECOG: Eastern Cooperative Oncology Group; IRT: Interactive Response Technology; NA: not applicable; PSA: prostate-specific antigen

† Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events at the subject's request or if deemed necessary by the Investigator. Procedures and assessments are to be performed as clinically indicated.

§ Or prior to initiation of an investigational agent or new therapy for prostate cancer, whichever occurs first.

¶ A brief physical examination is required at each visit, with the exception of the screening visit during which a complete physical examination will be completed.

‡ Laboratory assessments include serum chemistries and hematology.

§§ Adverse events will be collected from the time the subject signs the consent form until the end of the safety reporting period (or until screen failure). The safety reporting period ends at the time of the safety follow-up visit, 30 days after last dose of study drug or initiation of an investigational agent or new therapy for prostate cancer.

1 INTRODUCTION

1.1 Background

Worldwide, prostate cancer ranks second in cancer incidence and fifth in cancer mortality in men [Globocan, 2012]. Prostate cancer growth is dependent on androgens, and androgen deprivation therapy (i.e., treatment with a GnRH analogue or bilateral orchiectomy) is the cornerstone of treatment of men with metastatic prostate cancer. Although initial response rates are high, the disease can progress despite castrate levels of testosterone at which point it is considered castration resistant (i.e., CRPC). CRPC represents a lethal transition in the natural history of prostate cancer, with most patients dying of disease progression.

While the precise mechanism through which tumors progress from being castration sensitive to castration resistant is unknown, it is widely believed that a key step includes the development of continuous activation of androgen signaling. This activation may arise through androgen receptor gene amplification, androgen receptor overexpression, androgen receptor mutations, and/or aberrant androgen receptor coregulation [Scher & Sawyers, 2005]. In addition, studies have demonstrated that tumor cells display increased sensitivity to androgen-mediated cell growth and intratumoral production of androgens. These findings suggest that despite androgen deprivation therapy, androgen receptor signaling remains an important mediator of tumor cell growth in CRPC and as such, treatment strategies that target the androgen receptor may have important therapeutic potential.

The treatment of patients with metastatic CRPC often includes antiandrogens such as bicalutamide, nilutamide, or flutamide; however, these agents have the potential to stimulate androgen receptor signaling and can accelerate tumor cell growth [Bohl et al, 2005]. In 2010, immunotherapy with sipuleucel-T was shown to be associated with a statistically significant improvement in overall survival compared with placebo in men with asymptomatic or minimally symptomatic metastatic CRPC [Kantoff et al, 2010]; however, this therapy was not associated with improvement in other markers of disease progression such as objective radiographic response or prostate-specific antigen (PSA) response. In 2012, abiraterone acetate (abiraterone) plus prednisone was shown to significantly improve radiographic progression-free survival (rPFS) in asymptomatic or mildly symptomatic chemotherapy-naïve patients with metastatic CRPC compared with prednisone alone. A strong trend toward improvement in overall survival was observed in that study, but results did not meet statistical significance [Ryan et al, 2013]. Recently, radium Ra 223 dichloride (radium-223) was shown to improve overall survival in the chemotherapy-naïve subgroup in a study enrolling patients with metastatic CRPC and symptomatic bone metastases [Parker et al, 2013].

Over time, patients with metastatic CRPC generally experience continued disease progression, worsening pain, and become eligible for chemotherapy. Although first-line chemotherapy with docetaxel plus prednisone demonstrated a survival benefit in these patients [Tannock et al, 2004], its use leads to substantial morbidity from severe neutropenia, diarrhea, and other toxicities. Other treatment options that have demonstrated a survival

improvement in patients with metastatic CRPC after docetaxel include cabazitaxel plus prednisone [de Bono et al, 2010] and abiraterone plus prednisone [de Bono et al, 2011]. Because of its potential side effects, many patients are denied chemotherapy. Recently published data from the Swedish Prostate Cancer database indicate that a majority of men younger than 70 years with CRPC were treated with chemotherapy. In contrast, only half as many men between 70 and 79 received chemotherapy. In addition, chemotherapy treatment was often administered shortly prior to death [Lissbrant et al, 2013]. Therefore, additional treatment options are needed to improve clinical outcomes in patients with metastatic CRPC.

In India, prostate cancer ranks eight in cancer incidence and 10th in cancer mortality in men with Age-Standardized Rate (ASR) of 4.2/100000. Total incidence of prostate cancer is around 19000 patients [Globocan, 2012]. Patients with prostate cancer are frequently elderly with the median age of death in the 7th to 8th decade of life, which emphasizes the importance of treatments with tolerable safety profiles for this patient population. Current treatment modalities of early disease predominantly are surgery and radiation. However, for the advanced disease, it is predominantly hormonal therapy (Androgen Deprivation Therapy) and once the disease becomes refractory to hormonal manipulations, the options are very limited. Interventions like Docetaxel, Mitoxantrone and Estramustine with or without steroids form the main stay in first line hormone refractory prostate cancer therapy.

Enzalutamide is a second generation AR (Androgen receptor) inhibitor that competitively binds the AR with great potency. Additionally, enzalutamide inhibits nuclear translocation of AR, inhibits the association of AR with DNA [Tran et al, 2009], and has no known agonist activity when the AR is overexpressed. Enzalutamide is currently being developed in multiple prostate cancer indications. The clinical development program initially focused on metastatic disease that progressed on androgen deprivation therapy. For this indication, completed phase 3 studies include CRPC2 (AFFIRM) in patients with metastatic CRPC who previously received docetaxel and MDV3100-03 (PREVAIL) in chemotherapy-naïve patients with metastatic CRPC. CRPC2 was the pivotal study that supported the initial approval of enzalutamide in the United States (US) and European Union (EU) and MDV3100-03 was the pivotal study that supports the use of enzalutamide in chemotherapy-naïve patients. For India, Enzalutamide for post-chemo mCRPC has been approved in April 2016 by the Health Authorities.

The purpose of this study is to evaluate the safety, efficacy and exposure of enzalutamide and its major metabolites in Indian patients with progressive mCRPC previously treated with docetaxel-based chemotherapy as per locally approved prescribing information.

1.2 Nonclinical and Clinical Data

1.2.1 Nonclinical Data

The primary pharmacodynamic effect of enzalutamide is inhibition of the AR signaling pathway. Primary pharmacodynamics have been defined in experiments that demonstrated inhibition of AR binding, inhibition of AR nuclear translocation, inhibition of AR chromatin association, inhibition of AR-dependent transcription and cancer cell proliferation, induction

of cell death and tumor regression. The nonclinical data on the primary pharmacodynamics of enzalutamide show that it is an AR inhibitor and further, that it is distinct from other antiandrogens in affecting multiple steps in the AR signaling pathway in the setting of AR overexpression. A major human metabolite of enzalutamide, *N*-desmethyl enzalutamide, demonstrated key primary pharmacodynamics with similar potency to the parent molecule.

Enzalutamide and *N*-desmethyl enzalutamide bind to and antagonize the γ-aminobutyric acid (GABA)-gated chloride channel. Enzalutamide given at high doses to mice induced dose-dependent convulsions, an observation that parallels the clinical data showing that dose appears to be an important predictor of the risk of seizure in subjects. As some molecules that antagonize the GABA-gated chloride channel are associated with convulsions, enzalutamide and *N*-desmethyl enzalutamide may both contribute to the convulsions that were observed in nonclinical studies. Safety pharmacology studies evaluating the central nervous, respiratory and cardiovascular systems did not identify any additional acute effects at exposures relevant to the human clinical dose of 160 mg/day.

Following oral administration in animals, enzalutamide is eliminated slowly from plasma with a long $t_{1/2}$ across species. In vitro studies showed that enzalutamide is metabolized by human recombinant cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4/5. Enzalutamide and/or its major human metabolites caused direct in vitro inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. In vitro, enzalutamide caused time-dependent inhibition of CYP1A2. Based on in vitro data, enzalutamide is an inducer of CYP3A4 but is not expected to induce CYP1A2 at therapeutically relevant concentrations.

In vitro data show that enzalutamide and its active metabolite *N*-desmethyl enzalutamide are potential inhibitors, but not substrates, of the efflux transporter P-glycoprotein (P-gp).

Overall, enzalutamide was generally well tolerated in nonclinical species with the most prominent effects occurring in reproductive and hormone sensitive tissues. In studies 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. Additional changes related to reproductive and hormone sensitive tissues included hypertrophy/hyperplasia of the pituitary gland and atrophy in seminal vesicles in rats and testicular hypospermia, seminiferous tubule degeneration and hypertrophy/hyperplasia of the Leydig cells in dogs. Gender differences were noted in rat mammary glands (i.e., 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.

Hepatocellular toxicity is commonly associated with other antiandrogen compounds such as flutamide and nilutamide and both compounds are associated with liver injury in humans [Brahm et al, 2011; Gomez et al, 1992]. In contrast to other antiandrogens, enzalutamide showed no evidence of hepatotoxicity in animals or in the clinical program.

ECG and cardiovascular assessments in a toxicity study in dogs showed no treatment-related effects. In vivo and in vitro safety pharmacology studies also demonstrated the absence of cardiovascular enzalutamide-related effects.

Enzalutamide was nonmutagenic in bacteria, nonclastogenic in mammalian cells and nongenotoxic in vivo in mice. The 2 major human metabolites (*N*-desmethyl enzalutamide and an inactive carboxylic acid derivative) were negative for mutagenicity in the bacterial reverse mutation assay (refer to the current Investigator's Brochure).

1.2.2 Clinical Data

As of the data cutoff date of 28 February 2016, over 5500 subjects with prostate cancer, over 400 women with breast cancer, and over 300 subjects with no known cancer including healthy male subjects and subjects with hepatic impairment have received at least 1 dose of enzalutamide in completed and ongoing clinical studies (not including the expanded access program or 2 compassionate use programs). Enzalutamide was approved by DCGI for treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy on 28 April 2016 and commercially available on July 2016. As of 26 March 2017, 174 patients have received the treatment.

The pharmacokinetics and metabolism of enzalutamide have been evaluated in more than 2500 subjects with prostate cancer and in more than 200 healthy male subjects and subjects with mild, moderate, or severe hepatic impairment. Individual daily doses have ranged from 30 to 600 mg.

The pharmacokinetics of a single oral 160 mg dose of enzalutamide were examined in subjects with baseline mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, and C, respectively) and in matched control subjects with normal hepatic function (Study 9785-CL-0009 and Study 9785-CL-0404). Mild, moderate or severe hepatic impairment did not have a clinically relevant effect on the composite AUC of enzalutamide plus *N*-desmethyl enzalutamide. Therefore, the results indicate that no starting dose adjustment is necessary for subjects with baseline mild, moderate or severe hepatic impairment.

After oral administration to subjects with CRPC, the median time to reach maximum enzalutamide plasma concentrations was 1 hour, and the mean terminal half-life was 5.8 days. Enzalutamide steady state was achieved by day 28, and the accumulation ratio was 8.3-fold. At steady state, enzalutamide showed approximately dose-proportional pharmacokinetics over the range of 30 to 360 mg/day. Steady-state plasma levels of the active metabolite are similar to those of enzalutamide.

A mass balance and biotransformation study in healthy male volunteers showed that enzalutamide is primarily eliminated by hepatic metabolism. A food-effect study showed that food does not have a clinically relevant effect on the AUC of enzalutamide or *N*-desmethyl enzalutamide; therefore, enzalutamide can be taken with or without food.

Based on population pharmacokinetics modeling, age, weight and renal function (creatinine clearance [CLCR ≥ 30 mL/minute] do not have clinically meaningful effects on enzalutamide

exposures; therefore, no dose adjustments are indicated for these covariates. Based on pharmacokinetic data from a study in Japanese subjects with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Caucasian subjects. Clinical data are insufficient to assess the potential effect of severe renal impairment (CLCR < 30 mL/minute) and end-stage renal disease on enzalutamide pharmacokinetics.

A clinical drug-drug interaction study in prostate cancer subjects showed that enzalutamide can affect exposures to certain comedications. At steady state, enzalutamide reduced the AUC of oral midazolam (CYP3A4 substrate), S-warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) by 86%, 56% and 70%, respectively. Therefore, enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Substrates of CYP3A4, CYP2C9 and CYP2C19 with a narrow therapeutic index are to be avoided, as enzalutamide may decrease plasma exposure of these drugs. If enzalutamide is coadministered with warfarin (CYP2C9 substrate), additional international normalized ratio (INR) monitoring needs to be conducted. Enzalutamide (160 mg/day) did not have a clinically relevant effect on exposure to intravenous docetaxel (CYP3A4 substrate) or to oral caffeine (CYP1A2 substrate), dextromethorphan (CYP2D6 substrate) or pioglitazone (CYP2C8 substrate).

Another clinical drug-drug interaction study in healthy subjects showed that concomitant medications can affect exposure to enzalutamide. Coadministration of gemfibrozil (a strong CYP2C8 inhibitor) increased the composite AUC of enzalutamide plus *N*-desmethyl enzalutamide by 2.2-fold; therefore, strong CYP2C8 inhibitors are to be avoided. If coadministration with a strong CYP2C8 inhibitor is necessary, the dose of enzalutamide needs to be reduced to 80 mg once daily. Coadministration of itraconazole (strong CYP3A4 inhibitor) increased the composite AUC of enzalutamide plus *N*-desmethyl enzalutamide by 1.3-fold; as this small change is not clinically meaningful, no starting dose adjustment is needed when coadministering enzalutamide with CYP3A4 inhibitors. Coadministration of rifampin (strong CYP3A4 and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus *N*-desmethyl enzalutamide by 37%, while C_{max} remained unchanged (Study 9785-CL-0405); as these changes are not considered clinically relevant, no starting dose adjustment is needed when coadministering enzalutamide with moderate CYP2C8 inducers or CYP3A4 inducers.

The potential for enzalutamide to affect the pharmacokinetics of other drugs via effects on drug transporters was assessed through a series of in vitro experiments. Based on in vitro data, enzalutamide, *N*-desmethyl enzalutamide and/or the carboxylic acid metabolite may be inhibitors of BCRP, MRP2 and OAT3 at clinically relevant systemic concentrations or in the gastrointestinal wall during absorption. Thus, enzalutamide may increase the plasma concentrations of coadministered medicinal products that are BCRP, MRP2 or OAT3 substrates. In vitro experiments also suggest enzalutamide, *N*-desmethyl enzalutamide and the carboxylic acid metabolite do not inhibit OATP1B1, OAT1B3, OCT1, OCT2, OAT1 and OAT3-mediated transport at clinically relevant concentrations. Enzalutamide is not a substrate for OATP1B1, OATP1B3 or OCT1, and *N*-desmethyl enzalutamide is not a substrate for P-gp or BCRP. Based on in vitro data, enzalutamide is an inhibitor but not a

substrate for P-gp; however, under conditions of clinical use, enzalutamide may be an inducer of P-gp via activation of pregnane X receptor. Thus, enzalutamide may alter the plasma concentrations of coadministered medicinal products that are P-gp substrates (refer to current Investigator's Brochure).

1.3 Summary of Key Safety Information for Study Drugs

Enzalutamide has been approved by FDA and EMA and approved in 95 countries including India for CRPC. The safety profile of enzalutamide in subjects with CRPC is derived primarily from 2 phase 3 studies. Study CRPC2 (AFFIRM) was a randomized, double-blind, placebo-controlled, efficacy and safety clinical study of enzalutamide (160 mg daily) in 1199 subjects with progressive metastatic CRPC (mCRPC) previously treated with docetaxel-based chemotherapy. MDV3100-03 (PREVAIL) was a multinational, randomized, double-blind, placebo-controlled, efficacy and safety clinical study of enzalutamide in 1717 chemotherapy naïve subjects with mCRPC who have failed ADT (Androgen deprivation therapy).

Findings from the 2 phase 3 CRPC studies showed that adverse events (AEs) occurring in at least 5% of the subjects treated with 160 mg/day enzalutamide (n = 1671) and at an incidence of at least 2% greater than in placebo subjects were: asthenia, fatigue, back pain, diarrhea, constipation, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, muscular weakness, insomnia, spinal cord compression, dysgeusia, hematuria, anxiety, hypertension, fall, decreased appetite and weight decreased. The proportion of subjects with AEs associated with discontinuation of study drug in the combined controlled population was 17.7% in the enzalutamide group and 23.5% in the placebo group. Seizures occurred in 7 (0.9%) of the enzalutamide-treated subjects and none (0%) of the placebo-treated subjects in the blinded CRPC2 (AFFIRM) study. A lower seizure rate was observed in MDV3100-03 (PREVAIL) study (1 enzalutamide-treated subject [0.1%]).

There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in subjects receiving enzalutamide. PRES is a rare, reversible, neurological disorder that can present with rapidly evolving symptoms including seizure, headache, confusion, blindness and other visual and neurological disturbances, with or without associated hypertension.

For more information on the investigational product enzalutamide and on the clinical study experience, refer to the current Investigator's Brochure of enzalutamide.

1.4 Risk Benefit Assessment

Enzalutamide is a novel small molecule designed to have an increased affinity for the AR and more effective suppression of the androgen pathway in the setting of androgen overexpression [Tran et al, 2009]. Enzalutamide has a higher binding affinity to the AR (8 times greater), has no agonist activity and has demonstrated superior AR downstream effects in the setting of androgen overexpression compared to bicalutamide in preclinical studies.

The efficacy of enzalutamide in subjects with metastatic prostate cancer who progressed on ADT has been demonstrated in 2 randomized controlled phase 3 studies including MDV3100-03 (PREVAIL) in asymptomatic or mildly symptomatic subjects and CRPC2 (AFFIRM) in subjects with more advanced disease who previously received docetaxel. Regardless of study arm, subjects remained on ADT in both PREVAIL and AFFIRM studies. Both studies showed a statistically significant advantage of enzalutamide treatment over placebo across multiple clinically relevant endpoints such as Overall survival (OS), rPFS, time to first skeletal-related event, time to PSA progression, PSA response rate, best overall soft tissue response, and QoL as measured by the Functional Assessment of Cancer Therapy-Prostate (FACT-P). Notably, Study MDV3100-03 (PREVAIL) showed a significant benefit of enzalutamide in time to initiation of cytotoxic chemotherapy.

Study MDV3100-03 (PREVAIL; chemotherapy naïve mCRPC subjects) was stopped after a planned interim analysis (conducted when 540 deaths had been reported) and showed a benefit of the active treatment. The rate of rPFS at 12 months was 65% among subjects treated with enzalutamide, as compared with 14% among subjects receiving placebo (81% risk reduction; Hazard ratio (HR) in the enzalutamide group, 0.19; 95% CI, 0.15 to 0.23; $P < 0.001$). A total of 626 subjects (72%) in the enzalutamide group, as compared with 532 subjects (63%) in the placebo group, were alive at the data cutoff date (29% reduction in the risk of death; HR, 0.71; 95% CI, 0.60 to 0.84; $P < 0.0001$). The benefit of enzalutamide was shown with respect to all secondary endpoints, including the time until the initiation of cytotoxic chemotherapy (HR, 0.35), the time until the first skeletal-related event (HR, 0.72), a complete or partial soft tissue response (59% versus 5%), the time until PSA progression (HR, 0.17), and a rate of decline of at least 50% in PSA (78% versus 3%) ($P < 0.001$ for all comparisons). The updated analysis of overall survival was consistent with the interim analysis and showed a clinically meaningful and statistically significant decrease in the risk of death in patients randomized to enzalutamide compared with placebo (hazard ratio 0.767 [95% CI: 0.666, 0.882]). The updated median overall survival was 35.3 months (95% CI: 32.2, NYR) in the enzalutamide group and 31.3 months (95% CI: 28.8, 34.2) in the placebo group (cutoff date of 01 Jun 2014 with a total of 784 deaths).

Study CRPC2 (AFFIRM; postchemotherapy mCRPC subjects) demonstrated that enzalutamide treatment decreased the risk of death by 37% (HR, 0.631; $P < 0.0001$) compared with placebo treatment. The median survival was 18.4 months in the enzalutamide arm and 13.6 months in the placebo arm (difference = 4.8 months). The statistically significant and clinically meaningful benefit of enzalutamide treatment as measured by OS was seen in all prespecified subject subgroups and observed despite 42.0% of enzalutamide-treated and 61.4% of placebo-treated subjects receiving subsequent therapies to treat prostate cancer, including abiraterone (20.9% versus 24.3%) and cabazitaxel (9.8% versus 13.8%), both shown to improve OS following docetaxel treatment. Enzalutamide treatment also resulted in significant improvements over placebo treatment in all key secondary efficacy endpoints.

In addition, in a phase 2, open-label, single-arm study (9785-CL-0321) in patients with hormone-naïve prostate cancer, 92.5% (62 of 67) of patients had a ≥ 80% decline in PSA

from baseline at week 25. Of the 54 patients who were on treatment for 1 year (week 49), 100% had a ≥ 80% decline in PSA from baseline. Eleven (42.3%) of 26 evaluable patients with metastatic disease at study entry had a derived objective response (confirmed complete response + confirmed partial response), 8 (30.8%) patients with confirmed complete response, and 3 (11.5%) patients with confirmed partial response.

Based on the safety information collected to date in clinical trials and in commercial use, the safety profile experienced by patients remains consistent with the approved product label as well as events that can be seen in patients with prostate cancer. The safety profile in mHSPC (Metastatic hormone sensitive prostate cancer) patients in this study is expected to be consistent with the established safety profile for enzalutamide. To date, there are 9 important identified risks associated with enzalutamide (seizure, PRES, hypertension, fall, neutrophil count decreased, nonpathological fracture, cognitive/memory impairment, interactions with strong inhibitors or inducers of CYP2C8 and interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19).

While serious adverse events (SAEs) such as seizure and PRES have occurred in patients receiving treatment with enzalutamide, these events have been rare. To mitigate the risk of seizure, subjects with a history of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma, brain arteriovenous malformation) are excluded from the trial. Study drug discontinuation is required for subjects experiencing either seizure or PRES.

Based on the information known about the drug and the efficacy results that have been consistently demonstrated in both PREVAIL and AFFIRM, the risk-benefit assessment supports the investigation of enzalutamide plus ADT in Indian men with progressive mCRPC previously treated with docetaxel-based chemotherapy.

The totality of the efficacy and safety data demonstrate a favorable benefit-risk balance for the use of enzalutamide in Indian men with progressive mCRPC previously treated with docetaxel-based chemotherapy.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objective(s)

The objective is to evaluate the safety and efficacy of enzalutamide in Indian patients with progressive mCRPC previously treated with docetaxel-based chemotherapy as per locally approved prescribing information.

2.1.1 Primary Objective

To evaluate the safety and tolerability of enzalutamide in Indian patients with progressive mCRPC previously treated with docetaxel-based chemotherapy.

2.1.2 Secondary Objective

- To evaluate the effect of enzalutamide on PSA.

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This study is a multicenter Phase 4, open-label, single-arm, safety and efficacy study of enzalutamide (160 mg/day) in patients with progressive mCRPC who have previously been treated with docetaxel-based chemotherapy. Approximately 50 patients will be enrolled and treated with enzalutamide 160 mg once daily until study discontinuation criteria is met.

Safety and tolerability will be assessed by the collection of adverse events, vital signs, physical examinations and safety laboratory evaluations.

PSA will be collected for assessment of prostate cancer status on Screening Visit, Days 1, 29, 57, 85, 169, every subsequent 84 days and Safety Follow-up Visit.

Subjects will have a safety follow-up visit 30 days after their last dose of study drug or prior to initiation of another investigational agent or new therapy including commercial enzalutamide for prostate cancer, whichever occurs first.

2.2.2 Dose Rationale

Enzalutamide 160 mg administered orally, once daily, is the daily dose recommended by regulatory agencies in India where enzalutamide is approved.

2.3 Endpoints

2.3.1 Primary Endpoints

Safety

- Nature, frequency and severity of adverse events
- Safety laboratory tests: biochemistry and hematology
- Physical examination
- Vital signs (blood pressure, pulse and temperature)

2.3.2 Secondary Endpoints

Efficacy

- PSA response rate (≥ 50% reduction from baseline)

3 STUDY POPULATION

3.1 Selection of Study Population

The study population will include approximately 50 men with progressive mCRPC previously treated with docetaxel-based chemotherapy.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-/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).
2. Subject is 18 years or more at the time of signing informed consent.
3. Subject is diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell or small cell histology.
4. Subject with established diagnosis of metastatic castration-resistant prostate carcinoma.
5. Being newly initiated on Xtandi treatment (Enzalutamide) based on independent clinical judgment of treating physicians as per locally approved prescribing information.
6. Subject has an estimated life expectancy of ≥ 6 months as assessed by the Investigator.
7. A sexually active male subject with female partner(s) who are of childbearing potential is eligible if:
    - Agree to use a male condom starting at screening and continue throughout study treatment and for 3 months after the final study drug administration.
    - If the male subject has not had a vasectomy or is not sterile as defined below their female partner(s) is utilizing 1 form of highly effective birth control starting at screening and continue throughout study treatment and for 3 months after the final study drug administration.
    - Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
    - Established intrauterine device (IUD) or intrauterine system (IUS).
    - Bilateral tubal occlusion
    - Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
    - Male is sterile due to a bilateral orchiectomy
    - Sexual Abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant
8. Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for 3 months after the final study drug administration.
9. Male subject must not donate sperm starting at screening and throughout the study period, and for 3 months after the final study drug administration.
10. Subject agrees not to participate in another interventional study while participating in the present study.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:
1. Subject who is not eligible to receive Xtandi as per the locally approved prescribing information.
2. Subject participating or planning to participate in any interventional drug trial during the course of this trial.
3. Subject has received investigational study within 28 days or 5 half-lives, whichever is longer, prior to screening.
4. Subject has any condition which, in the investigator's opinion, makes the subject

unsuitable for study participation.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Study Drug(s)

Enzalutamide will be supplied to sites as 40 mg white to off-white oblong capsules. The oral soft gelatin capsules are filled with a clear, yellowish solution that contains the 2 antioxidants, BHA and BHT, and enzalutamide active ingredient (40 mg), all dissolved in the nonionic surfactant, Labrasol (caprylocaproyl polyoxylglycerides).

4.2 Packaging and Labeling

The clinical materials are blister packaged according to this study design using the appropriate transparent thermo formable film(s) with foil backing and placed in wallets for individual subject dispensing. The capsules should be stored in the original package in a secure location with limited access at room temperature.

All study drug(s) used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at Astellas Pharma Inc. (API) or Sponsor's designee in accordance with API or Sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH-GCP guidelines, and applicable local laws/regulations.

Each blister sheet will bear a label conforming to regulatory guidelines, GMP and local laws and regulations, which identifies the contents as investigational drug.

The study centers will be provided wallet-type cardboard integrated blister packaging containing 28 capsules of enzalutamide 40 mg capsules.

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;
- Study drug is handled and stored according to labeled storage conditions;
- Study drug with appropriate expiry/retest only is dispensed to study subjects in accordance with the protocol, and;
- Any unused study drug is returned to the Sponsor, unless prior approval is received from the Sponsor allowing local standard procedures for the alternative disposition of unused study drug.

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

- The Investigator or designee agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator, head of study site 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 study drugs.
- A study drug inventory will be maintained by the investigator, head of study site 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 for this responsibility.
- The site staff must return study drug to the sponsor or designee at the end of the study or upon expiration unless otherwise approved by the sponsor.

4.4 Blinding

This section is not applicable as this is an open label study.

4.5 Assignment and Allocation

Subjects will be entered into the IRT system at screening and assigned a subject number. Randomization will be not performed as this is single-arm study.

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

Study drug consists of enzalutamide provided as 40 mg capsules to be taken as 160 mg (4 capsules) orally once daily. Study drug is to be taken until disease progression, unacceptable toxicity or any other discontinuation criteria are met.

Study drug will be self-administered at home by the subject and taken as close to the same time each day as possible. Study drug can be taken with or without food. Subjects should not make up missed or vomited doses; dosing should resume the following day unless otherwise instructed.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

During the study, subjects who experience a National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) guidelines (version 4.03) grade 3 or higher AE (except liver function test [LFT] AE) toxicity that is attributed to the study drug and cannot be ameliorated by the use of adequate medical intervention and/or dose reduction may interrupt study drug treatment for 1 week or until the toxicity grade improves to grade 2 or lower in severity. Study drug may be restarted at the original dose (160 mg/day) or a reduced dose (120 mg or 80 mg/day). If restarted at a lower dose or if interrupted for > 2 weeks, the Medical Monitor must be consulted. After dose reduction, based on subject tolerance, study drug may be increased to a maximum dose of 160 mg/day per Investigator discretion.

Enzalutamide must be interrupted during the evaluation of symptoms suspicious of PRES (headache, lethargy, confusion, blindness and other visual and neurological disturbances, with or without associated hypertension).

5.1.3 Previous and Concomitant Treatment (Medication and NonMedication Therapy)

Medications taken within 28 days prior to the screening visit and up to the first dose of study medication will be documented on the appropriate case report form (CRF) as a prior medication.

Medications taken after the first dose of study medication up until the final follow-up visit will be documented on the appropriate CRF as concomitant medication.

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

5.1.3.1 Required Concomitant Treatment

All subjects are required to receive background therapy with ADT, either bilateral orchiectomy or a GnRH agonist or antagonist, which must be maintained during study treatment, as per standard of care (SOC).

A GnRH agonist or antagonist will be provided from the site's stock and administered in accordance with prescribing information.

5.1.3.2 Prohibited Concomitant Treatment

A list of excluded concomitant medications is provided in [Appendix 12.1 List of Excluded Concomitant Medications]. The following medications are prohibited within 4 weeks of day 1 and during the study treatment period:

- 5 α-reductase inhibitors (finasteride, dutasteride);
- Estrogens;
- Cyproterone acetate;
- Abiraterone
- Biologic or other agents with antitumor activity against prostate cancer (with the exception of those therapies identified in inclusion/exclusion criteria);

- Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone intended for the treatment of prostate cancer;
- Herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease PSA levels (i.e., saw palmetto);
- Androgens (testosterone, dehydroepiandrosterone, etc.);
- Investigational agents.

In addition, bisphosphonates and denosumab are prohibited unless stabilized for 2 weeks prior to day 1 and held constant throughout study treatment or administered for diagnosis of osteoporosis.

5.1.3.3 Enzalutamide Drug Interaction

There is a potential for enzalutamide to affect exposures to other medicinal products, or for other medicinal products to affect exposure to enzalutamide:

- Strong CYP2C8 inhibitors (e.g., gemfibrozil) are to be avoided. If subject must be coadministered a strong CYP2C8 inhibitor, the dose of enzalutamide 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.
- Strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin) or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin, St. John's Wort) should be avoided if possible as they may reduce enzalutamide plasma concentration if coadministered. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended.
- Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), or CYP2C19, or UGT1A1 (e.g., S-mephenytoin) should be avoided if possible, as enzalutamide may decrease their exposure.
- If enzalutamide coadministration with warfarin cannot be avoided, additional international normalized ratio (INR) monitoring should be conducted.
- Enzalutamide is an inhibitor of human P-glycoprotein (P-gp) and may increase exposure to medicines that are P-gp substrates. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., digoxin, colchicine, dabigatran etexilate) should be used with caution when administered concomitantly with enzalutamide.

5.1.3.4 Permitted Concomitant Treatment

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

- Blood transfusions and growth factor support per SOC and institutional guidelines;
- Steroid use (for indication other than prostate cancer) per SOC;

- Pain therapy per SOC and institutional guidelines;
- Palliative radiation therapy including external beam radiotherapy or systemic radionuclides (e.g., Samarium or Strontium);
- Vaccine therapy that has prior market authorization and is not intended to treat prostate cancer;
- Palliative surgical procedures to treat skeletal-related events.

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug unless study drug is withheld for a toxicity. Investigator or designee should ensure that study subjects meet this goal throughout the study period. Compliance will be verified by the accounting of study drug. When study drug is administered at the research facility, it will be administered under the supervision of study personnel. If compliance is less than 80% and study drug was not withheld and there were no study drug reductions, the Investigator or designee is to counsel the subject on the importance of taking the study drug.

Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject at visits. Compliance will be documented.

5.1.5 Criteria for Continuation of Treatment

This study does not set an expansion cohort, and long-term study in which this study's subject can participate is not scheduled either.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information will be collected at the screening visit for all subjects and will include age or date of birth, gender, race and ethnicity (as local regulations allow).

5.2.2 Medical History

Medical history will be collected at the screening visit for all subjects and includes all significant medical conditions that have occurred or are currently ongoing at time of consent. The condition, onset date and recovery date will be collected. NCI-CTCAE (version 4.03) grade will be collected for conditions that are ongoing at time of consent.

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

Prostate cancer history will be collected at the screening visit and will include histological or cytological diagnosis, date of diagnosis, Gleason score and associated treatment. Date of diagnosis of metastatic disease, location of metastatic disease lesions, and all previous and/or ongoing treatment will also be documented during screening visit.

5.3 Efficacy and Pharmacokinetics Assessments

5.3.1 Efficacy Assessments

PSA response ≥ 50% is defined as ≥ 50% reductions in PSA level from baseline to the lowest post-baseline PSA result as determined by the central laboratory, with a consecutive assessment conducted at least 3 weeks later to confirm the PSA response.

5.3.2 Pharmacokinetics Assessments

Not applicable

5.4 Safety Assessment

5.4.1 Vital Signs

Routine vital signs, including blood pressure, pulse and temperature will be assessed at the screening visit, at every clinic visit while on study drug and at the safety follow-up visit.

5.4.2 Adverse Events

AE collection will begin at the time the informed consent form (ICF) is signed and continue until subject is determined to be ineligible for study entry, or initiation of new therapy for prostate cancer including commercial enzalutamide, or 30 days after the last dose of study drug, whichever occurs first.

See [Section 5.5 Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See [Appendix 12.2 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 LFTs (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

Routine laboratory samples for hematology, chemistry and PSA will be collected at the screening visit, at every clinic visit while on study drug and at the safety follow-up visit. Other laboratory assessments will be collected according to the schedule of assessments [Table 1]. Samples will be analyzed at Sponsor designated central laboratory. Analytes included are identified in [Table 2].

Table 2: Laboratory Assessments

Hematology	Biochemistry	Other
Red blood cell count White blood cell count White blood cell differential Hemoglobin	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase	PSA

Hematology	Biochemistry	Other
Hematocrit Platelet count	Blood urea nitrogen Calcium Creatinine Glucose Phosphorus Potassium Sodium Total bilirubin Total protein	

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

5.4.4 Physical Examination

Complete physical examination will be performed at the screening visit to assess weight, height, general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, respiratory, gastrointestinal, musculoskeletal, neurologic status, mental status, lymphatic and genitourinary systems.

A brief physical examination with weight will be performed at day 1, all subsequent clinic visits while on study drug and at the safety follow-up visit. New or worsening clinically significant findings on physical examination will be recorded as AEs if they meet the criteria in [Section 5.5.1 Definition of Adverse Events].

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received study drug treatment. AE collection begins after the signing of the informed consent and will be collected until subject is determined to be ineligible for study entry, or initiation of new therapy for prostate cancer including commercial enzalutamide, or 30 days after the last dose of study drug, whichever occurs first.

5.5.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g. hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., ECGs, radiographic scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

5.5.1.2 Potential Cases of Drug-Induced Liver Injury

Refer to **[Appendix 12.2 Liver Safety Monitoring and Assessment]** for detailed instructions on Drug Induced Liver Injury (DILI). Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent or with abnormal elevations in total bilirubin that meet the criteria outlined in **[Appendix 12.2 Liver Safety Monitoring and Assessment]**, in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Section 5.5.5 Reporting of Serious Adverse Events].

5.5.1.3 Disease Progression and Study Endpoints

Under this protocol, the following event(s) will not be considered as an(S)AE:

- Disease Progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs. These data will be captured as efficacy assessment data as outlined in Section 5.3.1. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the study drug and the event, it should be reported as an (S)AE.
- Pre-planned and elective hospitalizations or procedures for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of the clinical trial. These procedures are collected per the eCRFs Completion Guidelines.

5.5.2 Definition of Serious Adverse Events (SAEs)

An AE 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 (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is

not caused by an AE). Hospitalization for treatment/observation/examination caused by AE is to be considered as serious.)

- Other medically important events (defined in paragraph below)

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 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are 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.

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 Study Drug

The investigator is obligated to assess the relationship between the study drug and each occurrence of each (S)AE. The investigator will use clinical judgment to determine the relationship. The investigator should also use the Investigator's Brochure (IB). The investigator is requested to provide an explanation for the causality assessment for each SAE (Serious adverse event) and must document this on the SAE worksheet. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF (Electronic case report form) with the new information and updated causality assessment. Following a review of the relevant data, the causal relationship between the study drug and each (S)AE will be assessed by answering '**yes**' or '**no**' to the question "**Do you consider that there is a reasonable possibility that the event may have been caused by the study drug**".
When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a 'reasonable possibility' that an (S)AE may have been caused by the study drug (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study drug and (S)AE onset and/or resolution. Has the subject actually received the study drug? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study drug?

- Plausibility; i.e., could the event been caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.

- Dechallenge/Dose reduction/Rechallenge:

  - Did the (S)AE resolve or improve after stopping or reducing the dose of the suspect drug? Also consider the impact of treatment for the event when evaluating a dechallenge experience.
  - Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?

- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the (S)AE and the study drug (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study drug exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to delegated CRO. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to delegated CRO. With limited or insufficient information about the event to make an informed judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of 'no' is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information.

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the 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 noted; intervention not indicated.
2-Moderate	Local or noninvasive intervention indicated.
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to AE

5.5.5 Reporting of Serious Adverse Events (SAEs)

The collection of AEs and the expedited reporting of SAEs will start following receipt of the informed consent and will continue to safety follow-up visit.

In the case of a SAE, the investigator must contact delegated CRO by fax or email immediately (within 24 hours of awareness).

The investigator must complete and submit a SAE worksheet containing all information that is required by local and/or regional regulations to delegated CRO by email or fax immediately (within 24 hours of awareness).

For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE Worksheet to:

IQVIA RDS East Asia Pte. Ltd.

Lifecycle Safety

Fax number: 000-800001-6750
Email: QLS_Enzalutamide@iqvia.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's Medical Monitor/Study Physician or his/her designee [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, SAE Worksheet 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 criteria),
- Causal relationship to the study drug (including reason), and
- The drug provided (if any)

The sponsor or sponsor's designee will submit expedited safety reports (e.g., IND Safety Reports, CIOMS-I) to Competent Authorities (CA) and concerned Ethics Committee (cEC) per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/local IEC within timelines set by regional regulations (e.g., EU, FDA) where required. Documentation of the submission to and receipt by the IRB/ local IEC of expedited safety reports should be retained by the site.

The sponsor or designee will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements.

The heads of the study sites/investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

The investigator may contact the sponsor's Medical Monitor/Study Physician for any other problem related to the safety, welfare, or rights of the subject.

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 by the investigator.

If after the protocol defined AE collection period [see Section 5.5.1 Definition of Adverse Events], an AE progresses to a SAE, or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the study drug treatment or study participation, the investigator must promptly notify the sponsor.

5.5.7 Special Situations

Certain Special Situations observed in association with the study drug(s), such as incorrect administration (e.g., wrong dose of study drug, comparator, or background therapy) are collected in the eCRF, as Protocol Deviation per [Section 8.1.6 Major Protocol Deviations] or may require special reporting, as described below. These Special Situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a Special Situation is associated with, or results in, an AE, the AE is to be assessed separately from the Special Situation and captured as an AE in eCRF. If the AE meets the definition of a SAE, the SAE is to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] and the details of the associated Special Situation are to be included in the clinical description on the SAE worksheet.

The Special Situations are:

- Pregnancy
- Medication Error, Overdose and “Off label use”
- Misuse/abuse
- Occupational exposure
- Suspected Drug-Drug interaction

5.5.7.1 Pregnancy

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 90 days from the discontinuation of dosing and report the information to delegated CRO according to the timelines in [Section 5.5.5 Reporting of Serious Adverse Event**s**] using the Pregnancy Reporting Form.

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.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female study subject as an AE in the eCRF or SAE per [Section 5.5.5 Reporting of Serious Adverse Events]. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the Pregnancy Reporting Form. Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion.
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the study drug.
- If an infant who dies more than 1 month after the birth, is to be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator.
- Congenital anomaly (including anomaly in miscarried fetus)

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination. (S)AEs experienced by the newborn/infant should be reported via the Pregnancy Reporting Form. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

5.5.7.2 Medication Error, Overdose and “Off-Label Use”

If a Medication Error, Overdose or “Off label Use” (i.e. use outside of what is stated in the protocol) is suspected, refer to [Section 8.1.6 Major Protocol Deviations]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with the details of the medication error, overdose or “Off-Label Use”.

An overdose is defined as any dose greater than the protocol specified dose of enzalutamide 160 mg once daily. In the event of an enzalutamide overdose, the study drug should be stopped and subject should receive supportive care and monitoring. The Medical Monitor should be contacted.

Neither the effects of overdose of enzalutamide or an antidote to overdose are known. Subjects may be at increased risk of seizures following an overdose of enzalutamide.

5.5.7.3 Misuse/Abuse

If misuse or abuse of the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to delegated CRO by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with details of the misuse or abuse of the study drug(s).

5.5.7.4 Occupational Exposure

If occupational exposure (e.g. inadvertent exposure to the study drug(s) of site staff whilst preparing it for administration to the patient) to the study drug(s) occurs, the investigator

must forward the Special Situation worksheet to delegated CRO by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the Special Situation are to be reported on the Special Situations worksheet.

5.5.7.5 Suspected Drug-Drug Interaction

If a suspected drug-drug interaction associated with the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to delegated CRO by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with details of the suspected drug-drug interaction.

5.5.8 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 IRB/IEC of such information when needed.

The investigator will also inform the subjects, who will be required to sign an updated informed consent form in order to continue in the clinical study.

5.6 Test Drug Concentration

Not applicable

5.7 Other Measurements, Assessments or Methods

Not applicable

5.8 Total Amount of Blood

The total amount of blood to be drawn for a subject will vary depending on the course of their disease and their duration on study treatment. At any time during the study, if laboratory values are determined to be abnormal, additional blood samples may be required for monitoring subject safety. The maximum amount of blood estimated to be collected from screening visit through day 169/week 25 visit is approximately 50 mL.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

The subject is free to withdraw from the study treatment 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.

Discontinuation Criteria from Study Drug Treatment for Individual Subjects:

- Any AE that is intolerable to the subject which cannot be ameliorated by the use of adequate medical intervention and/or dose reduction or that in the opinion of the Investigator would lead to undue risk to the subject if dosing is continued.
- Subject who experiences a seizure or any condition that significantly predisposes the subject to seizure such as brain metastasis or clinically evident stroke.
- Subject who experiences a confirmed event of PRES by brain imaging, preferably by MRI.
- Subject initiates an investigational agent or new therapy for prostate cancer.
- Subject who has evidence of radiological disease progression and/or PSA progression as confirmed by the Investigator and is no longer deriving clinical benefit. Imaging test can be done at the discretion of the investigator and are not part of the study.
- Subject has discontinued ADT (GnRH agonist/antagonist) and has a testosterone value in the noncastrate range (> 50 ng/dL).
- Subject who is, in the opinion of the Investigator or the Medical Monitor, non-compliant with the protocol requirements.
- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject.
- Subject withdraws consent for the study.

Subject will be discontinued from the 30 day study follow-up (Safety or Long-term Follow-up) if any of the following occur:

- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject.
- Subject withdraws consent for further follow-up.
- Death.
- Study termination by the Sponsor.

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

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 hard lock at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

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

7.1 Sample Size

The sample size of 50 subjects is not based on a statistical power calculation.

7.2 Analysis Sets

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 received at least one dose of study drug and have at least one post baseline measurement. This will be the primary analysis set for efficacy analyses.

7.2.2 Safety Analysis Set (SAF)

The SAF consists of all subjects who took at least 1 dose of study drug, and will be used for safety analyses.

For the statistical summary of the safety data, the safety analysis set (SAF) will be used.

7.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the FAS and SAF.

7.3.1 Subject Disposition

The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented. Similar tables for screening disposition, investigational period disposition and follow-up disposition will also be presented. All disposition details and dates of first and last evaluations for each subject will be listed.

7.3.2 Previous and Concomitant Medications

All previous and concomitant medications will be presented in a listing.

7.3.3 Medical History

Medical history for each subject will be presented in a listing.

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS.

PSA response ≥ 50% will be calculated for subjects with PSA values at the baseline assessment and at least 1 post-baseline assessment.

7.5 Analysis of Safety

Safety analysis will be conducted on the SAF.

7.5.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of subjects with AEs, SAEs, AEs leading to withdrawal of treatment, and AEs related to study drug will be summarized by system organ class, preferred term. 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 for subjects in the SAF.

Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings.

7.5.3 Physical Examination

Physical examination will be listed.

7.5.4 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for subjects in the SAF. Vital signs data will be displayed in listings.

7.6 Analysis of Pharmacokinetics

Not applicable

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

An interim assessment will be conducted at 6 month from first subject enrollment, with respect to safety. The report will be submitted to the health authority.

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

The final decision on handling of missing data, outliers, and the visit windows for analysis will be made before hard lock.

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 Electronic Data Capture (EDC) system. 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 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 the sponsor designated central laboratory. 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 minimum demographic data (gender, birth date or age, race and informed consent date) and reason for screen failure will be collected in the eCRF and the screen failure log, if applicable. This information will be entered into the study database.

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
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, as specified in the protocol
- AEs and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts
- Details of dispensing and return of study drug
- Reason for premature discontinuation
- Assigned subject number
- Staff notes and telephone conversation documentation;

- Medical records from other departments or hospitals (photocopy or faxed document of original record is acceptable if obtained from an outside institution).

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 IRB/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 IRB/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 Japan-Asia Data Science or designee of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Data Management. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary, respectively.

8.1.6 Major Protocol Deviations

A major 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 study 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.

The major protocol deviation criteria are 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,

PD4 - Received excluded concomitant treatment.

When a major 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 major deviation impacts the safety of a subject, the investigator must contact the sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the sponsor and maintained within the trial master file (TMF).

8.1.7 End of Trial in All Participating Countries

The end of trial is defined as the last subject's last visit or last subject's last contact, whichever is longer.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, 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/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB 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/IRB 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 ethics committees and regulatory agencies, 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/IRB 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/IRB should also be provided to sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding 1 year.

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 informed consent form 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 whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update their ICF and submit it for approval to the IRB/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 reconsent 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 informed consent form. A copy of the signed informed consent form 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 and Privacy

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.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/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 agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and Privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then sponsor shall serve as the controller of such data, as defined by the European Union (EU) Data Protection Directive, and Investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data If sponsor is not based in the EEA, sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the Directive.

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 Investigator's Brochure 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 sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, where applicable)

- Investigator's Brochure (and amendments, where applicable)
- eCRFs
- Study drug with all necessary documentation
- Study contract

In order to start the study, the investigator and/or study site is required to provide the following documentation to the sponsor:

- Signed Investigator's Statement in this protocol and eCRF
- Current Curricula Vitae of all investigators
- List of sub-investigators and collaborators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Study contract
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)

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 IRB/IEC, Competent Authority 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 IRB/IEC (if applicable).

Amendments to this protocol must be signed by the sponsor and the investigator. Written verification of IRB/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 IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the informed consent, written verification of IRB/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 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 studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s). Where applicable, the quality assurance and quality control systems and written SOPs of the CRO will be applied.

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, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC) | Data and Safety Monitoring Board (DSMB) | Monitoring Committee | Other Evaluation Committee(s)

Not applicable

10.2 Other Study Organization

Not applicable

11 REFERENCES

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12 APPENDICES

12.1 List of Excluded Concomitant Medications

The following medications are prohibited within 4 weeks of day 1 and during the study treatment period:

- 5 α-reductase inhibitors (finasteride, dutasteride);
- Estrogens;
- Cyproterone acetate;
- Abiraterone
- Biologic or other agents with antitumor activity against prostate cancer (with the exception of those therapies identified in inclusion/exclusion criteria);
- Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone intended for the treatment of prostate cancer;
- Herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease PSA levels (i.e., saw palmetto);
- Androgens (testosterone, dehydroepiandrosterone, etc.);
- Investigational agents.

In addition, bisphosphonates and denosumab are prohibited unless stabilized for 2 weeks prior to day 1 and held constant throughout study treatment or administered for diagnosis of osteoporosis.

12.2 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 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory 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 International Normalized Ratio (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 to 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 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 is to be recorded as ”AEs” in the (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, including dose, is to be entered in 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, preexisting 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:

[Temple, 2006]
1. Evidence that a drug can cause hepatocellular-type injury, generally shown by a higher rate than control of people with 3 X and greater transaminase elevations over the upper limit of normal (2 X elevations are too common in treated and untreated patients to be discriminating).
2. Cases of increased bilirubin (to at least 2X ULN) in people with concomitant transaminase elevation to at least 3 X ULN (but it is almost invariably higher) and no evidence of intra-or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome.

[Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009]
1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

References

Temple R. Hy's law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 April;15(Suppl 4):241-3.

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

12.3 Common Serious Adverse Events

Not applicable

12.4 ECOG Performance Status Scale

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference

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(GPF v.6.0)

13 SPONSOR'S SIGNATURES

PPD