A Randomized Study of Enzalutamide in Patients with Localized Prostate Cancer Undergoing Active Surveillance (ENACT)

ISN/Protocol 9785-MA-1010

Version 1.0

18-Dec-2015

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Sponsor:

Astellas Pharma Global Development Inc.
Medical Affairs, Americas
1 Astellas Way
Northbrook, IL 60062

Investigator:

Investigator information is on file at Astellas.

Table of Contents

I. SIGNATURES

1. SPONSOR'S SIGNATURE

A Randomized Study of Enzalutamide in Patients with Localized Prostate Cancer Undergoing Active Surveillance (ENACT)

ISN/Protocol 9785-MA-1010 / Version 1.0 dated 18 Dec 2015

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

2. INVESTIGATOR'S SIGNATURE

A Randomized Study of Enzalutamide in Patients with Localized Prostate Cancer Undergoing Active Surveillance (ENACT)

ISN/Protocol 9785-MA-1010 / Version 1.0 dated 18 Dec 2015

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

Principal Investigator:

Signature: .....

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

Printed Name: .....

Address: .....

.....

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See Section 0	PPD Astellas Pharma Global Development Inc. Medical Affairs, Americas 1 Astellas Way Northbrook, IL 60062 PPD **Please fax or email the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Product Safety & Pharmacovigilance** **North America telefax numbers:** **888-396-3750 (alternate 847-317-1241)** **Email: Safety-US@astellas.com**
Medical Monitor/Medical Expert:	PPD Astellas Pharma Global Development Inc. Medical Affairs, Americas 1 Astellas Way Northbrook, IL 60062 PPD
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III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ADT	Androgen Deprivation Therapy
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APGD	Astellas Pharma Global Development
AR	Androgen Receptor
AS	Active Surveillance
AST	Aspartate Aminotransferase
AT	Aminotransferases
BCRP	Breast Cancer Resistance Protein
BFI	Brief Fatigue Index
BMI	Body Mass Index
CA	Competent Authorities
CBC	Complete Blood Count
CLCR	Creatinine Clearance
CRO	Contract Research Organization
CRPC	Castration Resistant Prostate Cancer
CSR	Clinical Study Report
CT	Computerized Tomography
CTL	Cytotoxic T Lymphocyte
DDI	Drug-Drug Interaction
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EPIC	Expanded Prostate Cancer Index Composite
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GS	Gleason Score
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviations	Description of abbreviations
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International Study Number
LA-CRF	Liver Abnormality Case Report Form
LBD	Ligand Binding Domain
LFT	Liver Function Testing
LS	Least Square
LSO	Last Subject Out
LVEF	Left Ventricular Ejection Fraction
MAX-PC	Memorial Anxiety Scale for Prostate Cancer
mCRPC	Metastatic Castration Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Authorities
mpMRI	Multiparametric Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging
MUGA	Multi Gated Acquisition Scan
NASH	Non-Alcoholic Steatohepatitis
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NYHA	New York Heart Association
PD	Protocol Deviation
PHI	Protected Health Information
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PRO	Patient Reported Outcomes
PSA	Prostate Specific Antigen
QOL	Quality of Life
rPFS	Radiographic Progression Free Survival
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SEER	Surveillance, Epidemiology and End Results
SF-12	Medical Outcomes Study 12-Item Short Form Survey
SOP	Standard Operating Procedures
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings and Figures

Abbreviations	Description of abbreviations
TMF	Trial Master File
TREC	T-Cell Receptor Excision Circles
TRUS	Transrectal Ultrasonography
ULN	Upper Limit of Normal
WHO	World Health Organization

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet one or more criteria required for participation in a trial.
Study period	Period of time from the first site initiation date to the last site completing the study.
Therapeutic progression	The institution of definite therapy (prostatectomy, radiation therapy or systemic therapy) for prostate cancer.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Sponsor: Astellas Pharma Global Development Inc. (APGD) Medical Affairs, Americas	**Protocol Number: 9785-MA-1010**
Name of Study Drug: Enzalutamide	**Phase of Development:** 2
Title of Study: A Randomized Study of Enzalutamide in Patients with Localized Prostate Cancer Undergoing Active Surveillance (ENACT)	
Planned Study Period: From Q1 2016 to Q1 2019	
Study Objective(s): Primary: ○ To compare the time to prostate cancer progression (pathological or therapeutic progression) between patients treated with enzalutamide versus patients undergoing active surveillance Secondary: To evaluate: ○ Safety ○ Proportion of patients with negative biopsy for cancer at 1 year and 2 years ○ Percent of cancer positive cores at 1 year and 2 years ○ Time to prostate specific antigen (PSA) progression (secondary rise in serum PSA≥25% above baseline or ≥25% above nadir or absolute increase ≥ 2 ng/mL) ○ Proportion of patients with secondary rise in serum PSA≥25% above baseline or ≥25% above nadir or absolute increase ≥ 2 ng/mL at 1 year and 2 years ○ Brief fatigue index (BFI) ○ Medical outcomes study 12-item short form survey (SF-12) ○ Expanded Prostate Cancer Index Composite (EPIC) questionnaire- urinary, sexual and hormonal domains ○ Memorial Anxiety Scale for Prostate Cancer (MAX-PC) questionnaire [redacted] CCI [redacted]	
Planned Total Number of Study Centers and Location(s): Approximately 50 centers in the US and in Canada	
Study Population: Patients with clinically localized, histologically proven prostate cancer who are considered low risk or intermediate risk AND undergoing active surveillance (AS).	
Number of Subjects to be Enrolled / Randomized: 222	
Study Design Overview: This is a multicenter, randomized, open label exploratory study, evaluating the efficacy and safety of enzalutamide for extension of time to prostate cancer progression (pathological or therapeutic) in patients with clinically localized, histologically proven prostate cancer that is categorized as low risk or intermediate risk and who are under AS. Patients are eligible if they were diagnosed within 6 months of screening and have been on AS. A minimum of ten cores from transrectal ultrasound-guided prostate biopsy (with or without multiparametric magnetic resonance imaging [mpMRI]	

targeting) is required. Low risk is defined as T1c-T2a, PSA<10, N0, M0 (or presumed N0, M0 if CT/bone scan not done due to low risk of metastases), Gleason score (GS) ≤ 6 and ECOG status ≤2 with a life expectancy >5 years. Intermediate risk is defined as T2b-T2c, PSA<20, N0, M0 (or presumed N0, M0 if computerized tomography [CT]/bone scan not done), GS ≤7 (3+4 pattern only), ECOG status ≤2 and estimated life expectancy > 5 years. Prostate cancer progression is defined as either therapeutic progression or pathological progression. Pathological progression is defined as increase in primary or secondary Gleason pattern by ≥ 1 or higher proportion of cancer positive cores (≥15% increase).Therapeutic progression is defined as the earliest occurrence of primary therapy for prostate cancer (prostatectomy/radiation/focal therapy/systemic therapy). Patients will be stratified by low versus intermediate risk and type of biopsy performed (mpMRI targeted versus non mpMRI targeted). With regards to the use of mpMRI targeting, each site must be consistent with their method of biopsy throughout the study, for all subjects they enroll.

Subjects will be randomized to receive treatment with enzalutamide (160 mg), administered as four 40 mg capsules, by mouth, once daily, or to AS during the one year study treatment period. Following the one year treatment period, all subjects will be followed for one additional year (without any treatment). Subjects will be followed up every 3 months for these 2 years. Serum PSA will be measured at baseline and every 3 months during subsequent follow-up visits. Digital rectal examination will be done at baseline and every 6 months during subsequent follow-up visits. All subjects will have transrectal ultrasound-guided prostate biopsy (with or without mpMRI targeting) at 12 months and 24 months with a standard of 12 cores required. Systematic biopsies (12 core transrectal ultrasonography [TRUS] guided systematic biopsies including six lateral and six mid lobar cores from the base, middle and apex of the gland) are required even if mpMRI targeted technique is performed; mpMRI targeting should consist of two cores from any targeted lesion. All sites will be consistent with their method of biopsy (with regards to the use of mpMRI targeting) throughout the study for all patients enrolled at that site. If there is a significant clinical reason such as adverse changes on digital rectal examination or increase in PSA, biopsy is allowed based on investigator's decision. If at any time during the study the patient considers intervention for prostate cancer, biopsy is allowed and recommended. Treatment decisions based on pathological progression are at the discretion of the individual investigator. Hormonal levels (testosterone, DHT, dihydroepiandrosterone, androstenedione and estradiol) will also be collected at baseline, 12 months and 24 months. Quality of life/sexual function questionnaires (EPIC), anxiety measures (MAX-PC), BFI and SF-12 assessments will also be done at baseline, 6 months, 12 months, 18 months and 24 months. An additional BFI assessment will be done at 3 months. Subjects who withdraw from the study before the 24 Month Visit will be asked to complete the EPIC, MAX-PC, BFI and SF-12 assessments at their final study visit.

Subjects will be followed beyond the two year study period until the last patient has completed the 24 Month Visit. This additional follow up will entail biannual visits (every 6 months) that include measurement of serum PSA and digital rectal examination.

All biopsy samples will be centrally read by a designated pathologist blinded to treatment allocation. CT, magnetic resonance imaging (MRI) and bone scan will be performed at the discretion of the investigator based on clinical need and will be read locally.

Throughout the study, safety and tolerability will be assessed by the recording of adverse events (AEs), monitoring of vital signs, physical examinations and safety laboratory evaluations.

Inclusion/Exclusion Criteria:

Inclusion:

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

1. Age 18 years or older and willing and able to provide informed consent
2. Histologically proven adenocarcinoma of the prostate diagnosed (with ≥10 core biopsy) within 6 months of screening. The biopsy that was used for this diagnosis must be submitted for central pathology review.
3. Prostate cancer categorized (as determined by central pathology review) as low risk is defined as T1c-T2a, PSA<10, N0, M0 (or presumed N0, M0 if CT/bone scan not done due to low risk of metastases), GS ≤ 6, ECOG status ≤2 and estimated life expectancy >5 years **OR** intermediate risk is defined as T2b-T2c, PSA<20, N0, M0 (or presumed N0, M0 if CT/bone scan not done), GS ≤7 (3+4 pattern only), ECOG status ≤ 2 and estimated life expectancy > 5 years. Prostate cancer categorized (as determined by central pathology review) to the very low risk category (T1c, GS ≤6, PSA <10 ng/mL, fewer than 3 prostate biopsy cores positive, ≤50% cancer in any core, PSA density <0.15 ng/mL/g) is not included.
4. Ability to swallow study drugs and to comply with study requirements throughout the study
5. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable)
6. Throughout study, male subject and a female partner who is of childbearing potential must use two acceptable methods of birth control (one of which must include a condom barrier method of contraception) starting at screening and continuing throughout the study period and for three months after the final study drug administration. Two acceptable methods of birth control thus include the following:
    a. Condom (barrier method of contraception)
    AND
    b. One of the following is required:
        i. Established use of oral, injected or implanted hormonal methods of contraception by the female partner;
        ii. Placement of an intrauterine device or intrauterine system by the female partner;
        iii. Additional barrier method: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam / gel / film / cream / suppository by the female partner;
        iv. Tubal ligation in the female partner.
7. Must not donate sperm starting at screening throughout the study period and for 90 days after the final study drug administration
8. Subject agrees not to participate in another interventional study while on treatment

Waivers to the inclusion criteria will NOT be allowed

Exclusion:

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

1. Prior radiotherapy, surgery, chemotherapy, or hormonal therapy for prostate cancer
2. Very low risk category (T1c, GS ≤6, PSA <10 ng/mL, fewer than 3 prostate biopsy cores positive, ≤50% cancer in any core, PSA density <0.15 ng/mL/g)
3. Prior transurethral resection of the prostate or prior transurethral microwave thermotherapy of the prostate
4. Use of oral glucocorticoids within 1 month of screening
5. Use of 5 alpha reductase inhibitor within 1 month of screening or total use, within the last two

years prior to screening, of >3 months
6. Presence of metastatic disease
7. History of seizure or any condition that may predispose to seizures (e.g., prior cortical stroke or significant brain trauma) at any time in the past. History of loss of consciousness or transient ischemic attack within 12 months of screening
8. Absolute neutrophil count < 1,500/μL, platelet count < 100,000/μL, or hemoglobin < 6.2 mmol/L (10 g/dL) at screening
9. Total bilirubin >1.5 times the upper limit of normal (ULN) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 X ULN at screening
10. Creatinine > 177 μmol/L (> 2 mg/dL) at screening
11. Albumin < 30 g/L (3.0 g/dL) at screening
12. Major surgery within 4 weeks prior to Randomization Visit
13. Clinically significant cardiovascular disease including:
    a. Myocardial infarction or uncontrolled angina within 6 months
    b. Congestive heart failure New York Heart Association (NYHA) class 3 or 4
    c. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)
    d. History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place
    e. Hypotension as indicated by systolic blood pressure < 86 millimeters of mercury (mm Hg) at screening
    f. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram (ECG) and on physical examination
    g. Uncontrolled hypertension as indicated by at least 2 consecutive measurements of a resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at the Screening Visit
14. Known hypersensitivity to enzalutamide or any of its components.
15. Subject has received investigational therapy within 28 days or 5 half lives, whichever is longer, prior to screening.
16. Any condition (e.g., non-prostate malignancy or other active non-malignant disease) which, in the investigator's opinion, makes the subject unsuitable for study participation.

Waivers to the exclusion criteria will NOT be allowed.

Investigational Product(s):
Enzalutamide 40 mg soft gelatin capsules
Dose(s):
Enzalutamide 160 mg/day.
Mode of Administration:
Enzalutamide capsules are administered orally with or without food.

Comparative Drug(s): NA
Dose(s): NA
Mode of Administration: NA

Concomitant Medication Restrictions or Requirements:

Prohibited Medications

The following medications are prohibited in the absence of disease progression:

- 5α-reductase inhibitors (finasteride, dutasteride)
- Estrogens
- Cyproterone acetate
- Androgens (testosterone, dehydroepiandrosterone [DHEA], etc.)
- Antiestrogens or other medications to manage gynecomastia / breast complications
- Any other investigational agent

Restricted Medications

Usage of the following medications is restricted for subjects receiving enzalutamide:

- Co-administration of strong CYP2C8 inhibitors should be avoided if possible. If subjects must be co-administered a strong CYP2C8 inhibitor, reduce the enzalutamide dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor
- Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) should be avoided if possible. St John's Wort may decrease enzalutamide exposure and should be avoided. If subjects must be co-administered a strong CYP3A4 inducer, increase the enzalutamide dose from 160 mg to 240 mg once daily. If co-administration of the strong CYP3A4 inducer is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer.
- Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional international normalized ratio (INR) monitoring.

Restrictions on Concomitant Treatment

At initiation of the study, the options to manage gynecomastia/breast complications of enzalutamide treatment, which may occur in subjects randomized to the enzalutamide treatment arm, should be discussed with the study subjects and a strategy should be decided between each individual investigator and subject. Options to be offered are prophylactic breast irradiation (to be performed locally according to local standard of care), breast irradiation as needed for symptoms or dose reduction / interruption of medication as needed for symptoms. Antiestrogens or other medications are prohibited to manage these conditions.

Duration of Treatment:

Treatment on study drug will be 1 year or until disease progression or unacceptable toxicity, whichever occurs first.

Endpoints for Evaluation:

Primary:

- Time to prostate cancer progression (pathological or therapeutic progression)

Secondary:

To evaluate:

- Safety
- Incidence of negative biopsies for cancer at 1 year and 2 years
- Percent of cancer positive cores at 1 year and 2 years
- Time to PSA progression (secondary rise in serum PSA≥25% of baseline or ≥25% above nadir or absolute increase ≥ 2 ng/mL)
- Incidence of secondary rise in serum PSA≥25% baseline or ≥25% above nadir or absolute increase ≥ 2 ng/mL at 1 year and 2 years
- BFI
- SF-12 assessments
- EPIC questionnaire (urinary, sexual and hormonal domains)
- MAX-PC questionnaire

CCI

Statistical Methods:

Sample size justification:

A sample size of 222 subjects randomized in a 1 to 1 manner accrued over one year, with a study duration of 3 years, loss to follow-up of 16%, an assumed underlying hazard ratio of 0.52 and a three year median time-to-progression for the Control group (0.2310 rate) will result in 72 events (Fleshner et al., 2012). This sample size is sufficient to power this study at 80% with a two-sided type one error rate of 5%.

Efficacy:

The primary efficacy endpoint is time to prostate cancer progression (pathological or therapeutic) and the hypothesis for analysis is:

H0: The times to progression for enzalutamide and AS are the same

H1: The times to progression for enzalutamide and AS are not the same

Median and 95% confidence intervals for time to prostate cancer progression (pathological or therapeutic) will be calculated with the Kaplan-Meier method for each treatment group. Subjects with no cancer progression at the time of trial completion, discontinuation or death will be censored at the last assessment date. Additionally, subjects switching therapy during the study will be censored at the time of the initial therapy switch, but subjects discontinuing therapy will not be censored until the time of study discontinuation. If less than 50% of subjects progress by study cut-off time, the 25th percentile and its two-sided 95% confidence interval will be reported.

Treatment group differences between enzalutamide versus AS will be based on a Cox regression model. The resulting Hazard ratio (enzalutamide/AS) and 95% confidence interval will be included in the summary. Censoring assumptions will follow the same rules as applied for the KM estimates.

Fixed effects for the model will include the treatment groups, stratification factors, race, and time since prostate cancer diagnosis. Complete details of the model and all covariates will be included in the statistical analysis plan.

The proportional hazards assumption will be investigated graphically by the log on the negative log of the estimated survival versus the log on time to progression.

The secondary endpoints of treatment-emergent adverse events, negative biopsy for cancer, percent of positive cores, secondary rise in serum PSA, BFI, SF-12, EPIC and MAX-PC questionnaire scoring will be summarized with descriptive statistics or frequencies and percentages, as appropriate. Appropriate statistical analyses of treatment group differences will be included for all secondary endpoints.

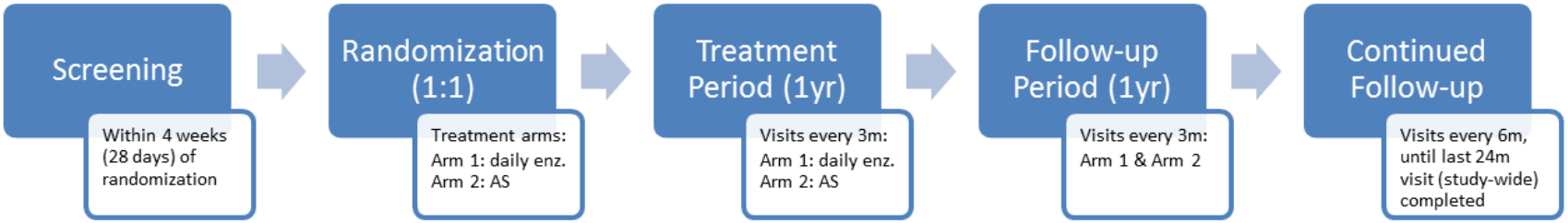
Time to PSA progression will be analyzed using methods analogous to those detailed above for the primary endpoint.

Pharmacokinetics:
NA
Pharmacodynamics:
NA
Safety:
All AEs will be collected and the severity the AEs will be evaluated by the investigator based on the latest version of National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE). All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) to preferred term, high level term and system organ class. AEs will be presented by the number and percentage of subjects by MedDRA system organ class and preferred term, relationship to study treatment and severity. The latest version of NCI-CTCAE will be used to classify laboratory values by toxicity grade. Descriptive statistics will be used for AEs.

Interim analyses:
NA

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



Abbreviations: AS = active surveillance, enz. = enzalutamide (160 mg PO daily), yr = year, m = months

Table 1 Schedule of Assessments

Study Visit Name	Screening	Randomization	3m	6m	9m	12m	15m	18m	21m	24m	>24m, q6m[1]	Unscheduled[2]
Study Day	**-28 to -7**	**1**	**85**	**176**	**267**	**358**	**455**	**545**	**635**	**730**	**>730**	**n/a**
Week	**-4 to -1**	**1**	**13**	**26**	**39**	**52**	**65**	**78**	**91**	**104**	**>104**	**n/a**
Window (days)			± 7	± 7	± 7	± 7	+7	+7	+7	+7	± 7	**n/a**
Informed Consent	X											
Medical History[3]	X	X[3]										
Inclusion/Exclusion Criteria	X	X										
Randomization		X										
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination, Weight[4]	X		X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X[5]											
MUGA/Echocardiogram[6]	X[5]											
Clinical Labs[7]	X	X	X	X	X	X	X	X	X	X	X	X
Serum hormone levels[8]		X				X				X		X
Serum PSA[9]	X	X	X	X	X	X	X	X	X	X	X	X[10]
Digital Rectal Examination	X			X		X		X		X	X	X[10]
[redacted] CCI	[redacted]			[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
Transrectal ultrasound-guided prostate biopsy (12 core)[12]	X[13]					X				X		X[10]
BFI[14]		X	X	X		X		X		X		
SF-12[14]		X		X		X		X		X		
EPIC[14, 15]		X		X		X		X		X		
MAX-PC[14]		X		X		X		X		X		
Adverse Events[16]		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Therapies and Outcomes Review		X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing[17]		X	X	X	X	X						
Blood Sample for Potential Future Analysis (optional)[18]		X	X	X	X	X	X	X	X	X	X	X

1. Subjects will be followed every 6 months until the last subject (study-wide) has completed the 24m Visit.
2. Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events (AEs), at the patient's request or if deemed necessary by the investigator.

Footnotes continued on next page

3. Medical history will include capturing information about any first degree relatives with prostate cancer. Any updates to the subject's medical history will be recorded at the Randomization Visit (Study Day 1) prior to randomization.
4. A complete physical examination will be completed at the Screening Visit. For all visits after the Randomization visit, only a brief physical examination is required.
5. This procedure (if required) must be done within 28 days prior to randomization.
6. A multi-gated acquisition (MUGA) scan or echocardiogram is only required if the patient has a history of anthracycline or anthracenedione (mitoxantrone) treatment.
7. Clinical labs, which will be assessed by the study's central laboratory, include serum chemistries (comprehensive metabolic panel) and hematology (CBC with differential).
8. Serum hormonal levels to be measured are testosterone, DHT, dihydroepiandrosterone, androstenedione and estradiol.
9. Serum PSA will be measured by the study's central laboratory.
10. If warranted per Investigator's clinical opinion or per standard of care.
11. [redacted]
12. Biopsies may be done with or without mpMRI targeting. Sites must use a consistent method (either with or without mpMRI targeting) for all of their study patients. Any biopsy performed during the patient's study participation will be analyzed centrally (for histological reading, [redacted]).
13. Biopsy must be done within 6 months prior to the Screening Visit, and submitted for central analysis (histological reading, [redacted]). For this biopsy, a minimum of 10 cores is required.
14. Subjects who withdraw from the study prior to the 24m Visit will be asked to complete all patient reported outcomes questionnaires (BFI, SF-12, EPIC, MAX-PC) at their final study visit.
15. Only the urinary, sexual and hormonal domains will be used.
16. Adverse events (serious and non-serious) will be collected from the time the patient signs the consent form until the patient completes the study.
17. Study drug is only applicable to subjects randomized to the enzalutamide arm; subjects randomized to AS will not be dispensed any study drug.
18. Subjects will have the option of having an additional sample collected at each phlebotomy session for storage and analysis in future trials of future trials of biomarker discovery for localized prostate cancer.

1 INTRODUCTION

1.1 Background

Prostate cancer is the most commonly diagnosed cancer (other than skin cancer) among men. In 2015 the American Cancer Society estimates that 220,800 men will develop prostate cancer in the United States and about 27,540 will die of prostate cancer (American Cancer Society, 2015). Of those diagnosed, 80% will be diagnosed with localized disease according to Surveillance, Epidemiology and End Results (SEER) data (SEER 18 2005-2011). For localized disease, there are multiple options – active surveillance (AS), radical prostatectomy and external beam radiotherapy / brachytherapy (NCCN, 2015). Interventional options, however, carry risks. Radical prostatectomy (open or robotic) has long term risks of erectile dysfunction and urinary incontinence. External beam radiation therapy and brachytherapy also carry risks, such as erectile dysfunction, urinary incontinence and bowel complications. AS has emerged as one of the recommended options for localized prostate cancer (Mohler et al, 2010; Thompson et al, 2007). AS use is increasing for low risk disease over the years 2010-2013 compared to the years before then (Cooperberg & Carroll, 2015; Ritch et al, 2015; Weiner et al, 2015). Ritch et al (2015) also noted increasing use of observation for low risk prostate cancer in an analysis of the SEER-Medicare database. This increase in AS is mostly due to concern that clinically low risk prostate cancer is over-treated, and AS may reduce unnecessary treatment in these patients. (Lane et al, 2014; Wilt, 2014; Wilt et al, 2012; Bill-Axelson et al, 2011;). AS studies have also included men with higher risk features including Gleason pattern 4 (Klotz et al, 2015; Cooperberg et al, 2011).

There are major differences, however, in the criteria for entering AS and the routines that are followed. There are still significant numbers of men whose cancer is upgraded on subsequent biopsies (pathological progression) and who are thus considered for an interventional treatment due to this. In a low risk population, one recent study demonstrated upgrading of the initial Gleason score (GS) in 42% of patients with a median time to initial upgrade of 23 months (Hussein et al, 2015) and 76% of those eventually received treatment for this upgrade or progression. Another study that included 20% intermediate risk patients in addition to the low risk patients demonstrated upgrading in 31% of the patients with a median time to upgrading of 1.8 years. Of those who were upgraded, 62% had active interventional treatment (Jain et al, 2015). Another study with low risk patients undergoing AS demonstrated upgrading in 32.7% of patients with a median follow-up of 2.3 years (Tseng et al, 2010). A further study of long-term follow up also concurs with this general range of reclassification or upgrading during the course of AS follow up (Klotz et al, 2010). Higher upgrading rates are found when radical prostatectomy specimens are used as the reference (Shaw et al, 2014). Pathological upgrading may occur due to a variety of reasons—biological progression/cancer dedifferentiation, sampling error at diagnosis, changes in pathological classification over time and /or inter observer variability (Jain et al, 2015). Whether this upgrading represents true progression or tumor missed at diagnosis is not definitively known and may be influenced by the type of biopsy performed (multiparametric magnetic resonance imaging [mpMRI] targeted versus non-mpMRI targeted systematic biopsy) and some studies show that significant numbers of men are excluded from AS protocols after undergoing

targeted biopsy (Hu et al, 2014). To date, there have been few studies with pharmacologic interventions for AS. The REDEEM study investigated the effect of dutasteride (5 alpha reductase inhibitor) on low risk prostate cancer patients who chose an AS protocol (Fleshner et al, 2012). Dutasteride delayed the progression of prostate cancer; by 3 years, 54 (38%) of 144 men in the dutasteride group and 70 (48%) of 145 controls had prostate cancer progression (pathological or therapeutic; hazard ratio 0.62, 95% CI 0.43–0.89; p=0.009). Most other ongoing AS studies offer only behavioral interventions or interventions with dietary or herbal supplements (http://clinicaltrials.gov).

1.2 Non-clinical and Clinical Data

Enzalutamide (formerly known as MDV3100) competitively binds to the ligand binding domain (LBD) of the androgen receptor (AR) and inhibits AR translocation to the cell nucleus, recruitment of cofactors and binding to DNA (Tran et al, 2009). Enzalutamide has been shown in two phase 3 randomized trials to have significant activity in metastatic castration resistant prostate cancer (mCRPC). In the phase 3 AFFIRM trial (Scher et al, 2012), 1199 men with prior chemotherapy exposure who were randomly assigned to receive enzalutamide versus placebo, a statistically significant improvement in overall survival of 18.4 versus 13.6 months was detected with enzalutamide (HR, 0.63; 95% CI, 0.53 to 0.75; $P < 0.001$). Radiographic progression free survival (rPFS) was 8.3 versus 2.9 months (HR, 0.40; $P < 0.001$), prostate specific antigen (PSA) response was 54% versus 2% ($P< 0.001$), time to PSA progression was 8.3 versus 3.0 months (HR, 0.25; $P < 0.001$) and time to first skeletal-related event was 16.7 versus 13.3 months (HR, 0.69; $P < 0.001$), all in favor of enzalutamide. Overall quality of life (QOL) benefit was observed in 43% versus 18% ($P < 0.001$) of patients receiving enzalutamide compared with placebo, whereas fatigue, diarrhea and hot flushes were more common with enzalutamide. Five patients (0.6%) experienced seizures in the enzalutamide group. In the phase 3 PREVAIL trial (Beer et al, 2014), 1717 men without prior chemotherapy exposure were randomized to receive enzalutamide or placebo. Compared to placebo, enzalutamide improved rPFS (rPFS rate at 12-month: 65% versus 12%; HR= 0.19; 95% CI, 0.15 to 0.23; $P<0.001$) and overall survival (HR=0.71; 95% CI, 0.60 to 0.84; $P<0.001$). 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). Fatigue and hypertension were the most common clinically relevant adverse events (AEs) associated with enzalutamide treatment.

Enzalutamide was studied in the neoadjuvant setting before radical prostatectomy (Montgomery et al, 2015). However, these were patients with features of high risk localized disease (Gleason 8, etc) who would not be candidates for AS.

An open-label, single-arm, phase 2 study was conducted in the European Union to assess the efficacy and safety of enzalutamide monotherapy in male patients with localized, locally advanced, or metastatic prostate cancer who had never received hormone therapy (Tombal et

al, 2015). The study enrolled 67 patients who presented with hormone-naïve prostate cancer requiring hormonal therapy and presented with non-castrate testosterone levels (≥230 ng/dL). The primary endpoint was PSA response, defined as a decline in baseline PSA of ≥ 80% at Week 25. Pre-specified secondary and exploratory endpoints included change from baseline in hormone levels, safety, objective disease response and change from baseline in lipids, insulin sensitivity, bone mineral density, body composition and health related quality of life (HRQoL). Sixty-two patients (92.5%; 95% CI, 86.2-98.8) achieved the primary endpoint of PSA response at Week 25 with a median maximum decline in PSA of -99.6% (IQR: -100.0% to -97.8%), with a tolerable risk/benefit profile and minimal effects on total body bone mineral density.

Pharmacokinetics

The pharmacokinetics and metabolism of enzalutamide have been evaluated in patients with castration resistant prostate cancer (CRPC), hormone-naïve prostate cancer patients, healthy male volunteers and subjects with mild or moderate hepatic impairment. Individual doses have ranged from 30 to 600 mg. Pharmacokinetic studies of enzalutamide in women have not been completed.

After oral administration to patients 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. Enzalutamide is primarily eliminated by hepatic metabolism. Food does not have a clinically relevant effect on the AUC of enzalutamide and its active metabolite so it can be taken with or without food. Composite AUC of enzalutamide plus its active metabolite after single-dose enzalutamide was similar in subjects with impaired baseline hepatic function (i.e. Child-Pugh Class A, B, or C) relative to subjects with normal hepatic function, and no starting dose adjustment is needed.

Based on population pharmacokinetics modeling, age, weight and renal function (creatinine clearance [CLCR] ≥ 30 mL/min) do not have clinically meaningful effects on enzalutamide exposures; therefore, no dose adjustments are indicated for these covariates. Clinical data are insufficient to assess the potential effect of severe renal impairment (CLCR < 30 mL/min) and end-stage renal disease on enzalutamide pharmacokinetics.

Drug-Drug Interaction (DDI) studies in prostate cancer patients showed that enzalutamide can affect exposures to other co-medications. At steady state, enzalutamide is a strong CYP3A4 inducer and moderate CYP2C9 and CYP2C19 inhibitor, and was shown to have reduced the AUC of oral midazolam (CYP3A4 substrate), S-warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) by 86%, 56% and 70%, respectively. Enzalutamide (160 mg/day) did not have a clinically relevant effect on exposure to intravenous docetaxel (CYP3A4 substrate) or oral pioglitazone (CYP2C8 substrate).

In vivo data shows that, at steady state, enzalutamide did not cause clinically meaningful changes in exposure to the CYP1A2 or CYP2D6 substrates.

In vitro data shows that enzalutamide caused direct inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP3A4/5; however, subsequent clinical data showed that enzalutamide is an inducer of CYP2C9, CYP2C19 and CYP3A4 and had no clinically meaningful effect on CYP2C8. In vitro, enzalutamide caused time-dependent inhibition of CYP1A2.

In vitro studies showed that enzalutamide induces CYP2B6 and CYP3A4 and does not induce CYP1A2 at therapeutically relevant concentrations.

DDI studies 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.

Coadministration of itraconazole (strong CYP3A4 inhibitor) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold.

Coadminstration of rifampin (moderate CYP2C8 inducer and strong CYP3A4 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%.

In vitro data indicate that enzalutamide and its major metabolites are not substrates for human P-glycoprotein (P-gp); enzalutamide and N-desmethyl enzalutamide are inhibitors for P-gp.

In vitro data also show that enzalutamide and N-desmethyl enazlutamide do not appear to be substrates for human breast cancer resistance protein (BCRP), however, enzalutamide and N-desmethyl enzalutamide are inhibitors of BCRP at clinically relevant concentrations.

Rationale for study

Patients who progress on AS are at risk for sequelae of their prostate cancer and often receive interventions which carry significant risks and side effects. To date, no studies have been published with an intervention of a known anti-cancer agent in an AS population. Because of this, novel approaches are needed to both stratify and offer options for those on AS as well as to offer an intervention that might affect progression. Also, current AS groups encompass different patient populations. Some populations with certain characteristics (related to medical or family history [redacted]) might progress more often on AS than other populations. This study will allow us to examine these issues, as well as to examine any effect of enzalutamide on these different subsets of patients. The use of enzalutamide monotherapy will potentially allow for optimal tumor treatment without the side effects and effects on quality of life inherent to androgen deprivation therapy (ADT). Treatment duration that would be applicable to this study group has also not been directly studied. One study using enzalutamide in the neoadjuvant setting before radical prostatectomy utilized 6 months of enzalutamide in prostate cancer patients considered for radical prostatectomy with PSA >10 and Gleason ≥7. This demonstrated 0/25 patients with pathologic complete response (as assessed by radical prostatectomy specimen). Because of this limited response in relatively higher risk patients than our current study, 12 months of enzalutamide was felt to be more appropriate in this group with lower risk disease characteristics in order to demonstrate a significant treatment difference.

Rationale for mpMRI targeted biopsies

Newer tools and techniques such as multiparametric magnetic resonance imaging (mpMRI) and biopsy based biomarker assessments are being reported in localized prostate cancer patients on AS (Lin et al, 2013; Stamatakis et al, 2013). These not only help to predict progression but also can assist in the accurate initial and ongoing assessment of the tumor, as there is evidence that early tumor progression (in the first few years after diagnosis) is due to inadequate initial assessment of the tumor (Cooperberg et al, 2011), with one study estimating this rate of inaccurate initial assessment at 30% (Conti et al, 2009) while another study estimated a 10% reclassification of patients (from those eligible for AS to those not eligible) based on mpMRI targeted biopsy (Ouzzane et al, 2015). Having a mix of patients being followed with and without mpMRI will also help predict the utility of this test in our dataset. mpMRI profiling can also possibly help identify aggressive versus indolent tumors and aid the clinician in deciding on possible therapy in patients who progress on AS (Hussein et al, 2015). While the detection rate for higher grade tumors has been found with the use of mpMRI, clinically significant tumors have also been found with systematic biopsy which justifies our use of both techniques in this study (de Gorski et al, 2015). While mpMRI use is increasing in prostate cancer detection and management of those with recently diagnosed prostate cancer, the question as to how to apply this in clinical practice remains unanswered at this time. There is variability in the use of mpMRI targeted biopsies and the utility and yield of mpMRI targeted biopsies versus standard systematic biopsies depends largely on the biopsy history of the included men (Taneja, 2015) and the relative benefit of an mpMRI targeted approach is not fully defined at this time.

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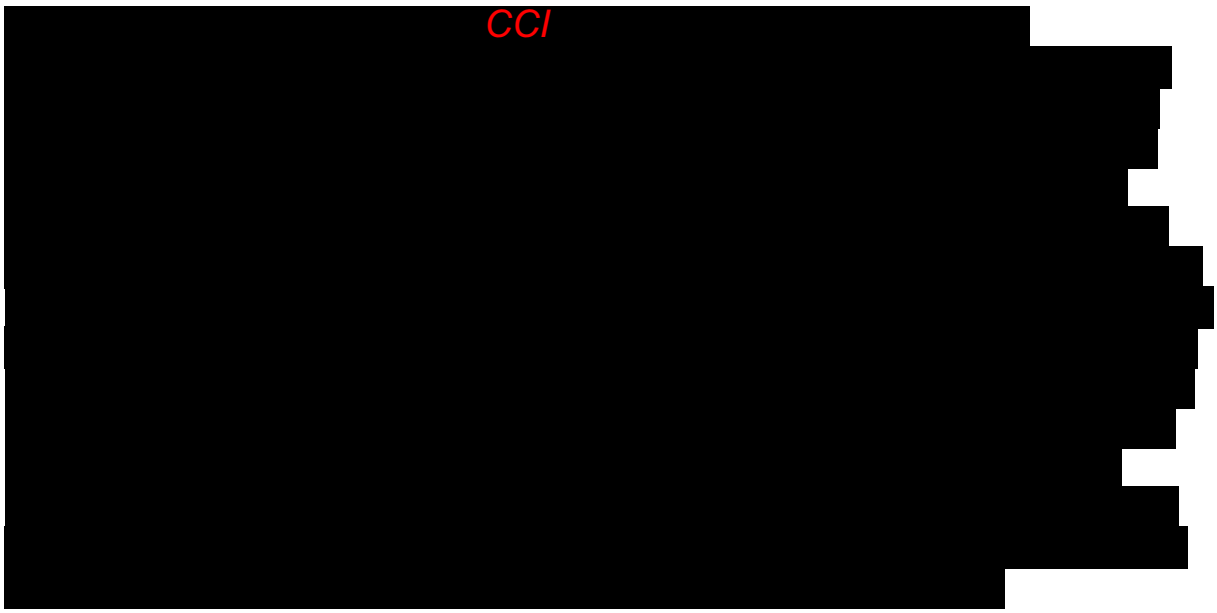

1.3 Summary of Key Safety Information for Study Drugs

Please reference the current Investigator Brochure (IB) for the safety profile of enzalutamide. The following information is summarized from the IB (Edition 8 dated 09 June 2015) unless otherwise noted.

Briefly, the safety profile of enzalutamide in patients with CRPC is primarily derived from two randomized, placebo-controlled phase 3 studies (MDV3100-03 [PREVAIL] and CRPC2 [AFFIRM]). Additional studies of enzalutamide in patients with prostate cancer, as well as studies of enzalutamide in patients with breast cancer and in healthy volunteers, contribute to the available enzalutamide safety data. Generally, the emerging data from open-label breast cancer studies and from the other individual studies is consistent with what was observed in patients with CRPC via the combined controlled population, which consists of both PREVAIL and AFFIRM.

Summary of safety information from the combined controlled population (CRPC)

In the combined controlled population, the enzalutamide group included patients with more advanced disease at study entry compared with the placebo group due to the differing randomization allocation ratios of PREVAIL and AFFIRM. In this population, AEs more common in the enzalutamide treatment group with at least a 2% higher absolute incidence over placebo are the following: constipation (23.9% versus 20.7%), diarrhea (19.2% versus 15.4%), fatigue (35.1% versus 27.0%), asthenia (15.8% versus 10.9%), edema peripheral (12.8% versus 9.3%), fall (8.8% versus 4.0%), weight decreased (12.3% versus 9.2%), decreased appetite (23.8% versus 20.8%), back pain (27.5% versus 23.0%), arthralgia (20.9% versus 16.5%), musculoskeletal pain (12.7% versus 9.6%), muscular weakness (6.9% versus 4.4%), headache (11.5% versus 6.5%), dysgeusia (6.1% versus 3.6%), spinal cord compression (5.9% versus 3.9%), insomnia (8.4% versus 5.8%), anxiety (5.2% versus 3.1%), hematuria (7.9% versus 5.4%), hot flush (19.1% versus 8.6%) and hypertension (10.5% versus 3.7%). Overall, in this population, study drug-related SAEs were reported infrequently

with no meaningful difference between treatment groups. SAEs with at least a 0.5% higher absolute incidence in the enzalutamide group compared with the placebo group included anemia, general physical health deterioration, pathological fracture, spinal cord compression and cauda equine syndrome. Expected adverse drug reactions (ADR) identified in this population include: seizure, hypertension, fatigue, hot flush, falls, mental impairment disorders, neutropenia, headache, anxiety, hallucination, dry skin and gynecomastia.

Summary of safety information in patients with hormone naïve prostate cancer

In a study of enzalutamide monotherapy in hormone naïve prostate cancer (9785-CL-0321), sixty-seven patients enrolled and received ≥1 dose of enzalutamide. Fifty-four patients (81%) completed the study through Week 49, and 45 (67%) remained on treatment at and after Week 97 (Tombal et al, 2015). Sixty-two (92.5%) patients experienced treatment-emergent adverse events (TEAEs) assessed as related to the study drug regimen. The most frequently reported TEAEs were gynecomastia, fatigue, nipple pain, hot flush, diarrhea, hypertension, nausea, back pain, pain in extremity and constipation. The majority of these TEAEs were NCI-CTCAE Grade 1 or 2.

Thirty-one SAEs were reported; five of these SAEs were deemed to be related to the study drug regimen: worsening of arrhythmia (Grade 3), atrial fibrillation (two patients, Grade 3), tachycardia (Grade 2) and chronic fatigue syndrome (Grade 3). Anoxic seizure was reported in one patient following a cardiac arrest.

Summary of safety information in patients with localized intermediate or high-risk prostate cancer

In a study of single-agent enzalutamide therapy versus triple therapy (enzalutamide, leuprolide, dutasteride) in patients with localized intermediate or high-risk prostate cancer who had not received prior ADT, chemotherapy, surgery, or radiation for prostate cancer (MDV3100-07), fifty-two patients enrolled and received at least one dose of enzalutamide (twenty-five patients received triple therapy and twenty-seven received single-agent enzalutamide). All of these patients experienced at least one TEAE; the most common (≥24% in either treatment group) were fatigue (60.0% triple therapy and 70.4% enzalutamide), hot flush (96.0% and 25.9%), gynecomastia (12.0% and 63.0%), insomnia (36.0% and 22.2%), libido decreased (32.0% and 14.8%), breast tenderness (8.0% and 33.3%), diarrhea (24.0% and 18.5%) and pollakiuria (24.0% and 14.8%). Grade 3 or higher AEs occurred in nine patients (diarrhea, medical device pain, clostridial infection, pelvic abscess [Grade 4], procedural pain, hyperglycemia, hyponatremia, hot flush, lymphocele [more than one patient]). All SAEs (lymphocele [two patients], postoperative ileus, pelvic abscess, clostridial infection) occurred after the radical prostatectomy procedure that was done following six months of study treatment.

1.4 Risk-Benefit Assessment

Cumulatively through the data lock point of 30 Aug 2015, 343 healthy volunteers and over 7800 patients had been enrolled in enzalutamide clinical studies, of whom approximately 6290 received enzalutamide. The safety and tolerability of enzalutamide continues to be

evaluated on an ongoing basis for all enzalutamide program studies. None of these studies have been terminated early for safety reasons. The risk benefit assessment for enzalutamide in the mCRPC setting remains favorable.

The benefit of treating patients with localized (low risk or intermediate risk) prostate cancer with enzalutamide monotherapy has not been established. Considering the scientific gap of studying interventions in the AS setting, especially those with anti-cancer activity, and the well-tolerated safety profile for enzalutamide, this study of treatment with enzalutamide during AS is warranted.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

The primary objective is to compare the time to prostate cancer progression (pathological or therapeutic progression) between patients treated with enzalutamide versus patients undergoing active surveillance.

The secondary objectives are to evaluate:

- Safety
- Proportion of patients with negative biopsy for cancer at 1 year and 2 years
- Percent of cancer positive cores at 1 year and 2 years
- Time to PSA progression (secondary rise in serum PSA≥25% above baseline or ≥25% above nadir or absolute increase ≥ 2 ng/mL)
- Proportion of patients with secondary rise in serum PSA≥25% above baseline or ≥25% above nadir or absolute increase ≥ 2 ng/mL at 1 year and 2 years
- Brief fatigue index (BFI)
- Medical outcomes study 12-item short form survey (SF-12)
- Expanded Prostate Cancer Index Composite (EPIC) questionnaire- urinary, sexual and hormonal domains
- Memorial Anxiety Scale for Prostate Cancer (MAX-PC) questionnaire

[redacted]

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a multicenter, randomized, open label exploratory study, conducted in the US and Canada, evaluating the efficacy and safety of enzalutamide for extension of time to prostate cancer progression (pathological or therapeutic) in patients with clinically localized, histologically proven prostate cancer that is categorized as low risk or intermediate risk and who are under AS. A total of 222 patients from approximately 50 centers will be enrolled. Patients are eligible if they were diagnosed within 6 months of screening and have been on

AS. A minimum of ten cores from transrectal ultrasound-guided prostate biopsy (mpMRI targeted versus non mpMRI targeted) are required; confirmatory biopsy before entering the study is not required and is done at the discretion of the investigator. Low risk is defined as T1c-T2a, PSA<10, N0, M0 (or presumed N0, M0 if computerized tomography [CT]/bone scan not done due to low risk of metastases), GS ≤ 6, ECOG status ≤2 and estimated life expectancy >5 years. Intermediate risk is defined as T2b-T2c, PSA<20, N0, M0 (or presumed N0, M0 if CT/bone scan not done), GS ≤7 (3+4 pattern only), ECOG status ≤2 and estimated life expectancy > 5 years. Prostate cancer progression is defined as either therapeutic progression or pathological progression. Therapeutic progression is defined as the earliest occurrence of primary therapy for prostate cancer (prostatectomy / radiation / focal therapy / systemic therapy). Pathological progression is defined as increase in primary or secondary Gleason pattern by > 1 or higher proportion of cancer positive cores (>15% increase). Patients will be stratified by low versus intermediate risk and type of biopsy performed (mpMRI targeted versus non mpMRI targeted).

Subjects will be randomized (1:1) either to receive treatment with enzalutamide (160 mg), administered as four 40 mg capsules, by mouth, once daily or to AS during the one year study treatment period. Following the one year treatment period, all subjects will be followed for one additional year. Subjects will be followed up every 3 months for these 2 years. Serum PSA will be measured at baseline and every 3 months during subsequent follow-up visits. Digital rectal examination will be done at baseline and every 6 months during subsequent follow-up visits. All subjects will have transrectal ultrasound-guided prostate biopsy (with or without mpMRI targeting) at 12 months and 24 months with a standard of 12 cores required; two biopsies are required from each target site (if mpMRI is used) as well as 12 systematic biopsies (12 core transrectal ultrasonography [TRUS] guided systematic biopsies including six lateral and six mid lobar cores from the base, middle and apex of the gland) at the same time. All sites will be consistent with their method of biopsy (with regards to the use of mpMRI targeting) throughout the study for all patients enrolled at that site. If there is a significant clinical reason such as adverse changes on digital rectal examination or increase in PSA, biopsy is allowed based on investigator's decision. If at any time during the study the patient considers intervention for prostate cancer, biopsy is allowed and recommended. Treatment decisions based on pathological progression are at the discretion of the individual investigator. Hormonal levels (testosterone, DHT, dihydroepiandrosterone, androstenedione and estradiol) will be collected at baseline, 12 months and 24 months. Quality of life/sexual function questionnaires (EPIC), anxiety measures (MAX-PC), BFI, SF-12 assessments will also be done at baseline, 6 months, 12 months, 18 months and 24 months. An additional BFI assessment will be done at 3 months. Subjects who withdraw from the study before the 24 Month visit will be asked to complete the EPIC, MAX-PC, BFI and SF-12 assessments at their final study visit.

Subjects will be followed beyond the two year study period until the last patient has completed the 24 month visit. This additional follow up will entail biannual visits (every 6 months) that include measurement of serum PSA and digital rectal exam.

All biopsy samples, including those collected for-cause or per standard of care, will be centrally read by a designated pathologist blinded to treatment allocation. CT, magnetic resonance imaging (MRI) and bone scan will be performed at the discretion of the investigator based on clinical need; when performed, these assessments will be read locally and recorded in the electronic case report form (eCRF).

Throughout the study, safety and tolerability will be assessed by the recording of AEs, monitoring of vital signs, physical examinations and safety laboratory evaluations.

2.2.2 Dose Rationale

A dose of 160 mg enzalutamide (four 40 mg capsules) once daily, administered orally, is the FDA approved daily dose for the indications in the approved labeling.

2.3 Endpoints

2.3.1 Primary Endpoints

The primary endpoint is time to prostate cancer progression (pathological or therapeutic progression).

2.3.2 Secondary Endpoints

The secondary endpoints are:

- Safety
- Incidence of negative biopsies for cancer at 1 year and 2 years
- Percent of cancer positive cores at 1 year and 2 years
- Time to PSA progression (secondary rise in serum PSA≥25% of baseline or ≥25% above nadir or absolute increase ≥ 2ng/mL)
- Incidence of secondary rise in serum PSA≥25% baseline or ≥25% above nadir or absolute increase ≥ 2ng/mL at 1 year and 2 years
- BFI
- SF-12 assessments
- EPIC questionnaire (urinary, sexual and hormonal domains)
- MAX-PC questionnaire

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3 STUDY POPULATION

3.1 Selection of Study Population

This study will enroll 222 patients with clinically localized, histologically proven prostate cancer who are considered National Comprehensive Cancer Network (NCCN) low risk or intermediate risk (as described in inclusion criteria) AND undergoing AS.

3.2 Inclusion Criteria

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

1. Age 18 years or older and willing and able to provide informed consent
2. Histologically proven adenocarcinoma of the prostate diagnosed (with ≥10 core biopsy) within 6 months of screening. The biopsy that was used for this diagnosis must be submitted for central pathology review.
3. Prostate cancer categorized (as determined by central pathology review) as low risk is defined as T1c-T2a, PSA<10, N0, M0 (or presumed N0, M0 if CT/bone scan not done due to low risk of metastases), GS ≤ 6, ECOG status ≤2, and estimated life expectancy > 5 years **OR** intermediate risk is defined as T2b-T2c, PSA<20, N0, M0 (or presumed N0, M0 if CT/bone scan not done), GS ≤7 (3+4 pattern only), ECOG status ≤2 and estimated life expectancy > 5 years. Prostate cancer categorized (as determined by central pathology review) to the very low risk category (T1c, GS ≤6, PSA <10 ng/mL, fewer than 3 prostate biopsy cores positive, ≤50% cancer in any core, PSA density <0.15 ng/mL/g) is not included.
4. Ability to swallow study drugs and to comply with study requirements throughout the study
5. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
6. Throughout study, male subject and a female partner who is of childbearing potential must use two acceptable methods of birth control (one of which must include a condom barrier method of contraception) starting at screening and continuing throughout the study period and for three months after the final study drug administration. Two acceptable methods of birth control thus include the following:
    a. Condom (barrier method of contraception)
    AND
    b. One of the following is required:
        i. Established use of oral, injected or implanted hormonal methods of contraception by the female partner;
        ii. Placement of an intrauterine device or intrauterine system by the female partner;

iii. Additional barrier method: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam / gel / film / cream / suppository by the female partner;
iv. Tubal ligation in the female partner.

7. Must not donate sperm starting at screening and throughout the study period and for 90 days after the final study drug administration
8. Subject agrees not to participate in another interventional study while on treatment.

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

3.3 Exclusion Criteria

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

1. Prior radiotherapy, surgery, chemotherapy, or hormonal therapy for prostate cancer
2. Very low risk category (T1c, GS ≤6, PSA <10 ng/mL, fewer than 3 prostate biopsy cores positive, ≤50% cancer in any core, PSA density <0.15 ng/mL/g)
3. Prior transurethral resection of the prostate or prior transurethral microwave thermotherapy of the prostate
4. Use of oral glucocorticoids within 1 month of screening
5. Use of 5 alpha reductase inhibitor within 1 month of screening or total use, within the last two years prior to screening, of >3 months
6. Presence of metastatic disease
7. History of seizure or any condition that may predispose to seizures (e.g., prior cortical stroke or significant brain trauma) at any time in the past. History of loss of consciousness or transient ischemic attack within 12 months of screening
8. Absolute neutrophil count < 1,500/μL, platelet count < 100,000/μL, or hemoglobin < 6.2 mmol/L (10 g/dL) at screening
9. Total bilirubin >1.5 times the upper limit of normal (ULN) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 X ULN at screening
10. Creatinine > 177 μmol/L (> 2 mg/dL) at screening
11. Albumin < 30 g/L (3.0 g/dL) at screening
12. Major surgery within 4 weeks prior to Randomization Visit
13. Clinically significant cardiovascular disease including:
    a. Myocardial infarction or uncontrolled angina within 6 months
    b. Congestive heart failure New York Heart Association (NYHA) class 3 or 4
    c. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)
    d. History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place
    e. Hypotension as indicated by systolic blood pressure < 86 millimeters of mercury (mm Hg) at screening
    f. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram (ECG) and on physical examination

g. Uncontrolled hypertension as indicated by at least 2 consecutive measurements of a resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at the Screening Visit

14. Known hypersensitivity to enzalutamide or any of its components.
15. Subject has received investigational therapy within 28 days or 5 half lives, whichever is longer, prior to screening.
16. Any condition (e.g., non-prostate malignancy or other active non-malignant disease) which, in the investigator's opinion, makes the subject unsuitable for study participation.

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

Enzalutamide capsules are opaque white to off-white oblong liquid filled soft gelatin capsules for oral administration. Each capsule contains 40 mg enzalutamide.

4.2 Comparative Drug(s)

Not applicable.

4.3 Packaging and Labeling

Enzalutamide is supplied by Astellas Pharma Global Development (APGD), Medical Affairs, Americas. Enzalutamide capsules will be packaged in high-density polyethylene bottles with child-resistant induction seal closure.

Enzalutamide used in this study will be prepared, packaged and labeled under the responsibility of qualified staff at Astellas or Sponsor's designee in accordance with Astellas or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines and applicable local laws/regulations.

Each bottle will have a label conforming to regulatory guidelines, Good Manufacturing Practice and local laws and regulations which identifies the contents as investigational drug.

4.4 Study Drug Handling

Enzalutamide will be stored in a secure, dry location with limited access at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Subjects will be instructed to store study drug at room temperature and out of the reach of children.

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

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

- that any unused study drug is returned to the Sponsor.

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

- The investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return study drugs to the Sponsor or designee at the end of the study or upon expiration.
- Study drugs provided by Astellas will not be destroyed on-site, unless considered hazardous materials or drugs for which the clinical unit SOP dictates destruction must be handled by the institution. Destruction must not occur until final study drug accountability reconciliation has been performed and Sponsor has approved destruction in writing.

4.5 Blinding

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

4.6 Assignment and Allocation

Randomization will be performed on Study Day 1 via Interactive Response Technology (IRT). Prior to the initiation of the study treatment, the site staff will contact the IRT in order to determine the randomly assigned treatment. Specific procedures for randomization through the IRT are contained in the study procedures manual.

The randomization allocation will consist of 1:1 ratio for once daily enzalutamide or AS. The randomization will be stratified according to the following two factors:

- Low versus intermediate risk
- Type of biopsy performed (mpMRI targeted versus non mpMRI targeted)

Additionally, enrollment of subjects with low risk prostate cancer will be capped to not exceed 80% of the study population.

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

Subjects randomized to the enzalutamide treatment arm will receive treatment with enzalutamide (160 mg daily), administered as four 40 mg capsules, by mouth, once daily for one year. Subjects in the enzalutamide treatment arm will be instructed to swallow the enzalutamide capsules whole, either with or without food and to take the drug as close to the same time each day as possible.

Subjects randomized to the AS arm will not receive any study drug.

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

If a subject in the enzalutamide treatment arm experiences a Grade 3 or greater toxicity or intolerable adverse side effect, withhold dosing for one week or until symptoms improve to Grade 2 or lower severity or become tolerable, then resume at the same or reduced dose (120 mg or 80 mg per day) if warranted.

Enzalutamide dosing may be reduced to 120 mg or 80 mg per day if needed to manage gynecomastia / breast complications. Enzalutamide dosing may also be reduced or held, if warranted per Investigator's discretion, to manage adverse side effects.

Dose reductions will be captured in the eCRF.

5.1.3 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

Concomitant treatments will be captured on the eCRF at every study visit, beginning with the Screening Visit. At the Screening Visit, treatments taken within four weeks prior to the visit will also be captured in the eCRF.

Treatments captured in the eCRF will include both drug and non-drug therapies, prescribed and over-the-counter and all alternative medicines.

Subjects must be instructed not to start any new medication, prescribed or over-the-counter, without consulting the Investigator, unless the new medication is required for emergency use. Subjects must be instructed to notify the Investigator immediately if medications were required for emergency use.

Prohibited Medications

The following medications are prohibited in the absence of disease progression:

- 5α-reductase inhibitors (finasteride, dutasteride)
- Estrogens
- Cyproterone acetate
- Androgens (testosterone, dehydroepiandrosterone [DHEA], etc.)
- Antiestrogens or other medications to manage gynecomastia / breast complications

- Any other investigational agent

Restricted Medications

Usage of the following medications is restricted for subjects receiving enzalutamide:

- Co-administration of strong CYP2C8 inhibitors should be avoided if possible. If subjects must be co-administered a strong CYP2C8 inhibitor, reduce the enzalutamide dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.
- Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) should be avoided if possible. St John's Wort may decrease enzalutamide exposure and should be avoided. If subjects must be co-administered a strong CYP3A4 inducer, increase the enzalutamide dose from 160 mg to 240 mg once daily. If co-administration of the strong CYP3A4 inducer is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer.
- Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional international normalized ratio (INR) monitoring.

Restrictions on Concomitant Treatment

At initiation of the study, the options to manage gynecomastia/breast complications of enzalutamide treatment, which may occur in subjects randomized to the enzalutamide treatment arm, should be discussed with the study subjects and a strategy should be decided between each individual investigator and subject. Options to be offered are prophylactic breast irradiation (to be performed locally according to local standard of care), breast irradiation as needed for symptoms or dose reduction/interruption of medication as needed for symptoms. Antiestrogens or other medications are prohibited to manage these conditions.

5.1.4 Treatment Compliance

Study subjects randomized to enzalutamide treatment should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study.

The dose and schedule of enzalutamide administered to each subject will be recorded on the appropriate form at each study visit. At each study visit after Randomization, the subject will be required to bring all unused study medication and empty study medication bottles to each visit. The quantity of study medication returned by the subject will be counted and recorded in the eCRF.

Treatment compliance will be verified by the accounting of study drug at each study visit during the one year treatment period. Reasons for dose delay, reduction or omission will be recorded. This information about enzalutamide will be used to assess subject compliance with the treatment.

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

Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject at the 3 Month, 6 Month, 9 Month and 12 Month Visits. Compliance will be documented.

5.1.5 Criteria for Continuation of Treatment

Not applicable

5.1.6 Restrictions During the Study

From the Screening Visit until the subject's completion or discontinuation of the study, genomic tests on prostate biopsy specimens – [redacted] – are prohibited.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

The subject's date of birth, sex, race, ethnicity, height and weight will be recorded at the Screening Visit.

5.2.2 Medical History

Medical history will be obtained at the Screening Visit from each subject. All relevant past and present conditions, as well as prior surgical procedures and information about first degree relatives with prostate cancer, will be recorded. Any updates to the subject's medical history will be recorded at the Randomization Visit (Study Day 1) prior to randomization.

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

A detailed prostate cancer history for each subject will be obtained at the Screening Visit. This will include documenting the subject's initial diagnosis of histologically proven adenocarcinoma of the prostate, GS at time of diagnosis, any prostate cancer-related biomarker testing done (as per standard of care) on biopsy samples or other samples from the time of diagnosis until the Screening Visit and other disease specific information as designated in the eCRF.

5.3 Efficacy Assessment

5.3.1 Histopathology

Transrectal ultrasound-guided prostate biopsies (with or without mpMRI targeting) are required for the Screening, 12 Month and 24 Month Visits. Additional transrectal ultrasound-

guided prostate biopsies may be obtained based on investigator's decision or local standard of care.

All prostate biopsy samples obtained during a subject's participation in the study will be submitted to the designated pathologist for central review. The central pathologist will be blinded to treatment allocation.

After 20 patients (total from both treatment arms) have had the one year biopsy completed, a feasibility assessment of the biopsy specimens will be performed. This will be done to assess for any possible treatment related effects on the histopathology of the biopsy specimens and implications this may have on the completion of the study.

With regards to the use of mpMRI targeting, each site must be consistent with their method of biopsy throughout the study, for all subjects they enroll. If mpMRI targeted biopsies are utilized, two biopsies are required from each target site as well as 12 systematic biopsies (12 core TRUS guided systematic biopsies including six lateral and six mid lobar cores from the base, middle and apex of the gland) at the same time. Before the start of the study, sample preparation and shipment procedures will be provided in a histopathology manual.

The biopsy utilized for the Screening Visit must have been done within 6 months prior to the visit. A minimum of ten cores is required for this biopsy. A confirmatory biopsy before entering the study is not required, but may be done at the discretion of the investigator. The biopsy utilized for the Screening Visit must be submitted for central reading by the designated pathologist. Should there be disagreement between the local and central pathology reports regarding the subject's eligibility per Inclusion Criteria 3 and Exclusion Criteria 2, the subject's eligibility will be defined using categorization from the central pathologist.

If there is a significant clinical reason such as adverse changes on digital rectal examination or increase in PSA, biopsy is allowed based on investigator's decision. If at any time during the study the patient considers intervention for prostate cancer, biopsy is allowed and recommended. Treatment decisions based on pathological progression are at the discretion of the individual investigator.

Genomic tests on prostate biopsy specimens – [redacted] – are prohibited during the subject's participation in this study.

For all biopsies obtained during the study, published criteria will be used to centrally diagnose pathological progression as defined above. Treatment decisions based on the biopsy results will be at the discretion of the investigator.

5.3.2 Therapeutic progression

At each study visit from the Randomization visit through the subject's discontinuation, therapy for prostate cancer will be assessed. The subject will be considered as having therapeutic progression at the earliest occurrence of primary therapy for prostate cancer (prostatectomy / radiation / focal therapy / systemic therapy).

5.3.3 Prostate-Specific Antigen (PSA)

Serum samples for assessment of PSA levels will be collected at all study visits and analyzed by the designated central laboratory. Additional assessments of PSA levels during the subject's participation in the study, either done for-cause or per standard of care, should be done through the designated central laboratory as well.

Before the start of the study, sampling and shipment procedures will be provided in a laboratory manual.

5.3.4 Brief Fatigue Inventory (BFI)

BFI consists of 5 questions to rapidly assess the severity and impact of cancer-related fatigue.

BFI will be completed by study subjects on paper during the Randomization (Day 1), 3 Month, 6 Month, 12 Month, 18 Month and 24 Month Visits. Subjects who withdraw from the study before the 24 Month Visit will be asked to complete BFI at their final study visit. Subjects should complete the BFI during the study visit instead of taking it home for completion. Before the start of the study, patient reported outcomes (PRO) instructions will be provided in a study PRO guidelines document. Site personnel should ensure subjects complete BFI in accordance with the BFI instructions and study PRO guidelines, and are responsible for entering the subjects' responses into the eCRF.

5.3.5 Expanded Prostate Cancer Index Composite (EPIC)

EPIC is a multi-domain instrument that measures patient function and concerns following prostate cancer treatment.

The urinary, sexual and hormonal domains of EPIC will be completed by study subjects on paper at the Randomization (Day 1), 6 Month, 12 Month, 18 Month and 24 Month Visits. Subjects who withdraw from the study before the 24 Month Visit will be asked to complete the EPIC assessments at their final study visit. Subjects should complete these components of EPIC during the study visit instead of taking them home for completion. Before the start of the study, PRO instructions will be provided in a study PRO guidelines document. Site personnel should ensure subjects complete these components of EPIC in accordance with the EPIC instructions and study PRO guidelines, and are responsible for entering the subjects' responses into the eCRF.

5.3.6 Memorial Anxiety Scale for Prostate Cancer (MAX-PC)

MAX-PC is an instrument that measures anxiety in men with prostate cancer.

MAX-PC will be completed by study subjects at the Randomization (Day 1), 6 Month, 12 Month, 18 Month and 24 Month Visits. Subjects who withdraw from the study before the 24 Month Visit will be asked to complete the MAX-PC assessments at their final study visit. Subjects should complete the MAX-PC during the study visit instead of taking them home for completion. Before the start of the study, PRO instructions will be provided in a study PRO guidelines document. Site personnel should ensure subjects complete these components

of MAX-PC in accordance with the MAX-PC instructions and study PRO guidelines, and are responsible for entering the subjects' responses into the eCRF.

5.3.7 Medical Outcomes Study 12-Item Short Form Survey (SF-12)

SF-12 is a 12 item instrument that measures overall health related quality of life.

SF-12 will be completed by study subjects at the Randomization (Day 1), 6 Month, 12 Month, 18 Month and 24 Month Visits. Subjects who withdraw from the study before the 24 Month Visit will be asked to complete the SF-12 at their final study visit. Subjects should complete the SF-12during the study visit instead of taking them home for completion. Before the start of the study, PRO instructions will be provided in a study PRO guidelines document. Site personnel should ensure subjects complete the SF-12 in accordance with the SF-12 instructions and study PRO guidelines, and are responsible for entering the subjects' responses into the eCRF.

5.4 Safety Assessment

The safety evaluations including vital signs, adverse event recording, clinical laboratory assessments and physical examination will be performed according to Table 1 Study Schedule of Assessments. Measurements obtained during the Screening and Randomization Visits will be considered baseline values.

5.4.1 Vital Signs

Vital signs including blood pressure, heart rate and temperature will be assessed at the Screening Visit, at each 3 monthly visit (between the Randomization and 24 Month Visits, inclusive), at each 6 monthly visit (after the 24 Month Visit, until the last subject has completed the 24 Month Visit), and at any unscheduled study visits (see Table 1 Study Schedule of Assessments).

For each blood pressure measurement, the subject should be seated comfortably for at least 5 minutes with the back supported, feet on the floor, arm supported in a horizontal position and the blood pressure cuff at heart level. The Investigator will use the same device model and cuff size throughout the study. The same arm should be used throughout the study.

5.4.2 Adverse Events

See **Section 5.5 Adverse Events and Other Safety Aspects** for information regarding adverse event collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See **Appendix 12.2 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 liver function testing (LFT, e.g.: AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AE's of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

Clinical laboratory assessments will be done at every scheduled visit, as well as at any unscheduled visits. Assessments of serum hormonal levels will be done at the Randomization, 6 Month and 12 Month Visits, at each 6 monthly visit (after the 24 Month Visit, until the last subject has completed the 24 Month Visit) and at any unscheduled study visits.

Below is a table of the laboratory tests that will be performed during the conduct of the study. See Table 1: Schedule of Assessments for study visit collection dates.

Serum chemistries	Glucose Calcium Total protein Albumin Sodium Potassium CO2 Chloride BUN Creatinine ALP ALT AST Bilirubin
Hematology	WBC count WBC differential RBC count RDW HCT HgB MCV MCH MCHC Platelet count MPV PDW
Hormonal levels	Testosterone DHT Dihydroepiandrosterone Androstenedione Estradiol

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician. Any changes in laboratory values are to be evaluated by the Investigator. Clinically relevant changes must be recorded as AEs in the eCRF (see Section 5.5: Adverse Events and Other Safety Aspects).

Before the start of the study, sampling and shipment procedures will be provided in a laboratory manual.

The Investigator may decide to repeat a laboratory assessment, should the results be outside normal ranges and considered clinically relevant, or if the original sample could not be analyzed.

If the blood sample at the Screening Visit cannot be analyzed, the test results are considered a lab error or the test results are increased related to a temporary condition unrelated to prostate cancer and likely to resolve at short notice, it is acceptable to repeat the laboratory tests to check eligibility criteria. The subject should be requested to come for an unscheduled visit between the Screening and Randomization Visits. If the repeat test results are still exclusionary, the subject should not be randomized. Repeat test to check eligibility criteria can only be repeated once before Randomization.

5.4.4 Physical Examination

Each subject will have a physical examination performed at the Screening Visit and at all study visits except the Randomization Visit. A brief physical examination is required at each study visit except the Randomization Visit according to Table 1 Study Schedule of Activities, with the exception of the Screening Visit during which a complete physical examination will be completed. Date of physical examination and any clinically relevant adverse changes will be recorded as an AE in the eCRF. Weight will be recorded at each study visit.

Digital rectal examination will be done at the Screening, 6 Month, 12 Month, 18 Month and 24 Month Visits, as well as at the biannual (every 6 months) visits following the 24 Month Visit.

5.4.5 Electrocardiogram (ECG)

A 12-lead ECG will be recorded as part of the Screening Visit procedures. The ECG must be done within 28 days prior to Randomization, and will be taken with the subject in the supine position.

All tracings will be read locally by the Investigator or referral physician or Investigator's designee to ensure patient safety and care management. Any abnormalities must be evaluated in clinical context (based on subject's medical history and concomitant medication) and the Investigator must determine if it is clinically significant. A copy of the original ECG traces should be maintained in the study file with the subject's source records. Pertinent results from the locally read ECG report will be captured on the eCRF.

5.4.6 Imaging

A multi gated acquisition (MUGA) scan or echocardiogram showing left ventricular ejection fraction (LVEF) $\geq$ 45% is required as part of the Screening Visit procedures only for subjects with a history of anthracycline or anthracenedione (mitoxantrone) treatment. For these subjects, a MUGA scan or echocardiogram must be done by the Investigator or referral physician or Investigator's designee within 28 days prior to Randomization. A copy of the original MUGA scan or echocardiogram should be maintained in the study file with the

subject's source records. Pertinent results from the locally read MUGA scan or echocardiogram will be captured on the eCRF.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

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

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

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

5.5.2 Definition of Serious Adverse Events (SAEs)

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

- Results in death
- Is life threatening (an adverse event 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 adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in

an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

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

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

All of the special situations noted above should be recorded on the (e)CRF. Any situation involving these special situations that also meet the criteria for an SAE should be recorded on the AE page of the (e)CRF and marked 'serious' and the SAE worksheet.

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

5.5.3 Criteria for Causal Relationship to the Study Drug

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

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

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Event (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)

In the case of a serious adverse event (SAE), the investigator must contact the Sponsor by telephone or fax immediately (within 24 hours of awareness).

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

For contact details, see Section II Contact Details of Key Sponsor's Personnel. Please fax the SAE Worksheet to:

Astellas Pharma Global Development – United States
Product Safety & Pharmacovigilance,
Fax number 888-396-3750 (alternate fax: 847-317-1241)
Email: Safety-US@astellas.com

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

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

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

The following minimum information is required:

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

The Sponsor or Sponsor's designee will submit expedited safety reports (i.e. IND Safety Reports) to the regulatory agencies (i.e. FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within timelines set by regional regulations (i.e. EU, (e)CTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The Sponsor or Sponsor's designee will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements /IRB/IEC / head of the study site.

The investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

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

5.5.6 Follow-up of Adverse Events

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

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

Please refer to **Appendix 12.2 Liver Safety Monitoring and Assessment** for detailed instructions on Drug Induced Liver Injury (DILI).

5.5.7 Monitoring of Common Serious Adverse Events

Common serious adverse events are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in **Appendix 12.3 Common Serious Adverse Events** for your reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events" as specified in **Appendix 12.3 Common Serious Adverse Events**. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in **Section 5.5.5 Reporting of Serious Adverse Events.**

5.5.8 Procedure in Case of Pregnancy

If a partner of a male subject becomes pregnant during the study dosing period or within 90 days from the discontinuation of dosing, the investigator should report the information to the Sponsor as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

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

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

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

If during the conduct of a clinical trial, a male subject makes his partner pregnant, the subject should report the pregnancy to the investigator. The investigator will report the pregnancy to the Sponsor as an SAE.

5.5.9 Emergency Procedures and Management of Overdose

There is no antidote for enzalutamide. In the event of an overdose, stop treatment with enzalutamide and initiate general supportive measures based on the clinical presentation of the patient. Subjects may be at increased risk of seizures following an overdose.

5.5.10 Supply of New Information Affecting the Conduct of the Study

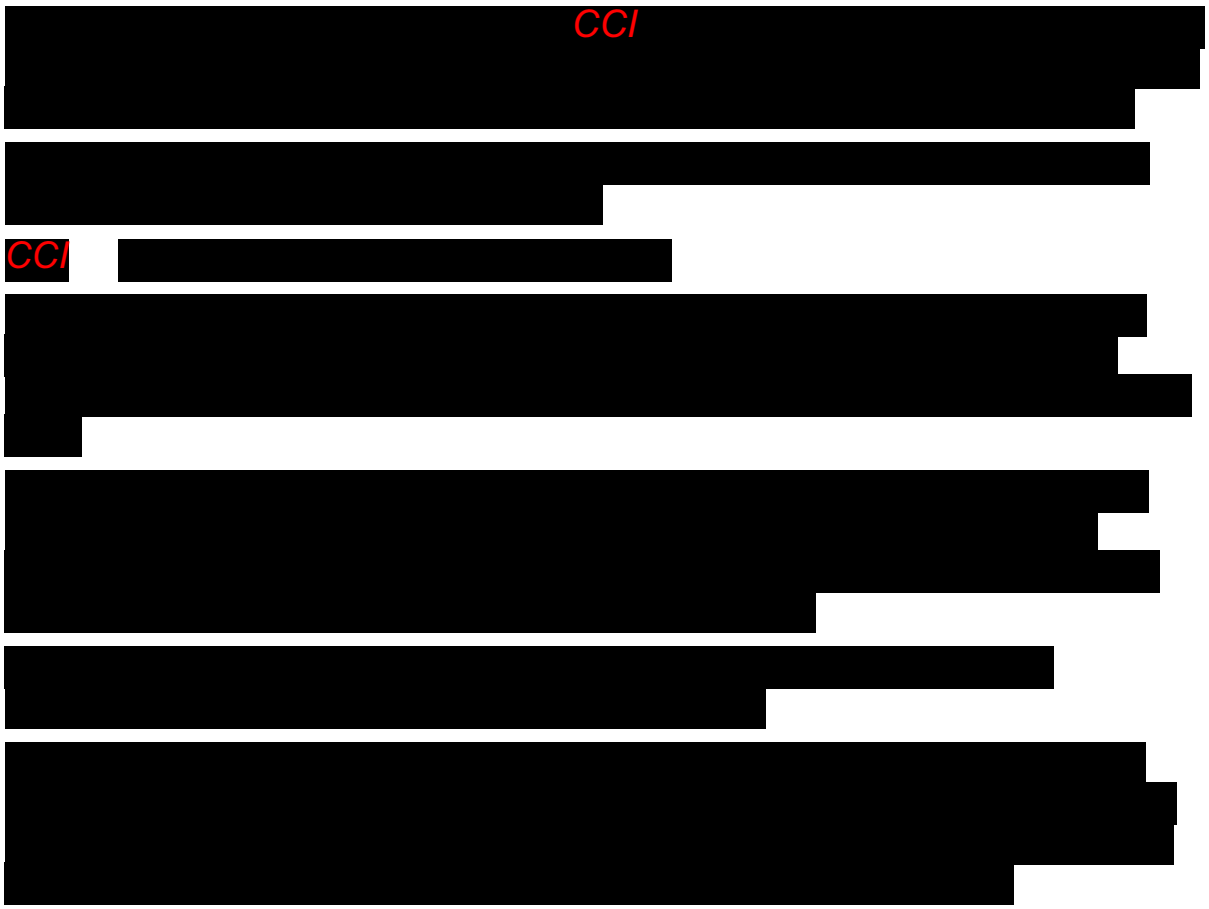
When new information becomes available necessary for conducting the clinical study properly, the Sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

5.6 Test Drug Concentration

Not applicable

5.7 Other Measurements, Assessments or Methods

CCI [redacted]



5.7.3 Banking of Blood Samples for Future Studies (Optional)

Patients participating in ENACT will be provided, through the informed consent process, the option of having an additional sample (5 ml) collected at each phlebotomy session for storage and future analyses related to biomarker discovery for localized prostate cancer. In the event additional investigations beyond these are contemplated, patients will be re-consented for this additional use of their biological material. Samples will be stored for a maximum of 5 years and then destroyed thereafter. Samples will be stored at -80°C at a facility designated by the Sponsor.

5.8 Total Amount of Blood

Blood samples will be taken for the purposes of assessing serum hormone levels at the Randomization, 12 Month and 24 Month Visits, as well as at any unscheduled visits. Blood samples will be taken for the purpose of assessing PSA as well as hematology and chemistry levels at all scheduled study visits as well as at any unscheduled visits.

The total amount of blood taken per subject solely for scheduled visits up to the 24 Month Visit is anticipated to be 150-165 ml. An additional 50 ml (5 ml per scheduled visit) will be collected if the subject chooses to provide blood samples for future analyses.

During the 6 monthly visits after the 24 Month Visit (which continue until the last subject has completed the 24 Month Visit), an anticipated 15 ml will be collected per visit, with an

additional 5 ml per visit collected if the subject chooses to provide blood samples for future analyses.

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

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

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

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. The medical monitor must be notified when an investigator terminates a subject’s involvement in the study due to the subject’s clinical condition.

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

Study Discontinuation Criteria for Individual Subjects (during any study period):

- Subject starts new anti-cancer therapy
- Subject develops radiological progressive disease
- Subject is lost to follow up despite reasonable efforts by the investigator to locate the subject
- Subject withdraws consent
- Gross noncompliance with protocol: The medical monitor or investigator may request permanent treatment discontinuation in the event of a major protocol deviation such as administration of prohibited concomitant medication, lack of cooperation, or noncompliance.
- Death

Subjects who are discontinued from enzalutamide treatment due to the below criteria should remain in the study and continue with the scheduled study visits for follow-up of their outcomes.

Criteria for Discontinuation of Enzalutamide Treatment for Individual Subjects:

- Subject develops unacceptable toxicity
- Subject withdraws consent for enzalutamide treatment but consents to continued study follow-up

Reasonable effort should be made to contact any subject lost to follow-up during the course of the study in order to complete study related assessments and retrieve any outstanding data

and study drug. Following unsuccessful telephone contact, an effort to contact the subject by mail using a method that provides proof of receipt should be attempted. Such efforts should be documented in the source documents.

6.2 Discontinuation of the Site

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

6.3 Discontinuation of the Study

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

7 STATISTICAL METHODOLOGY

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

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

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

Unless otherwise specified, all statistical testing will be conducted using two-sided tests with a significance level of 0.05.

7.1 Sample Size

This study is designed to evaluate time to prostate cancer progression (pathological or therapeutic progression) as the primary end point. The overall two-sided type I error for this study is set at 0.05 level. The characteristics of time to prostate cancer progression (pathological or therapeutic progression) are used to determine the total sample size and overall duration.

A sample size of 222 subjects randomized in a 1 to 1 manner accrued over one year, a study duration of 3 years, loss-to follow-up of 16%, an assumed underlying hazard ratio of 0.52 and a three year median time-to-progression for the Control group (0.2310 rate) will result in

72 events (Fleshner et al., 2012). This sample size is sufficient to power this study at 80% with a two-sided type I error rate of 5%.

The assumed hazard ratio of 0.52 is consistent with Fleshner et al. (2012). Specifically, the Fleshner study is powered to detect a 39% failure rate reduction in the treated group with respect to a three year 45% failure rate in the control group. We used a more conservative 30% failure rate reduction for the treated group and a 50% three year failure rate for the control group. This resulted in parameter estimates of 0.2310 for the Control group and 0.1189 for the Treatment group, and thus, resulted in the hazard rate of 0.52.

7.2 Analysis Set

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

7.2.1 Full Analysis Set (FAS)

The full analysis set will consist of all subjects who are randomized. This will be the primary analysis set for efficacy analyses.

7.2.2 Per Protocol Set (PPS)

The per protocol set will consist of patients who adhere to the protocol. The criteria defining adherence to the protocol will be defined in the SAP.

7.2.3 Safety Analysis Set (SAF)

For the statistical summary and analysis of safety data, the safety analysis set (SAF) will be used. The SAF consists of all subjects who enrolled into the study and were randomized. Therefore, the SAF is equivalent to the FAS.

7.2.4 Pharmacokinetic Analysis Set (PKAS)

Not applicable

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for the SAF. Descriptive statistics will be included for continuous endpoints and frequency and percentage for categorical endpoints.

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS and PPS. The interpretation of results from statistical tests will be based on the FAS. The PPS will be used to assess the robustness of the results from the statistical tests based on the FAS.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

The primary efficacy endpoint is time to prostate cancer progression (pathological or therapeutic), and the hypothesis for analysis is:

H0: The times to progression for enzalutamide and AS are the same

H1: The times to progression for enzalutamide and AS are not the same

Median and 95% confidence intervals for time to prostate cancer progression (pathological or therapeutic) will be calculated with the Kaplan-Meier (KM) method for each treatment group. Subjects with no cancer progression at the time of trial completion, discontinuation or death will be censored at the last assessment date. Additionally, subjects switching therapy during the study will be censored at the time of the initial therapy switch, but subjects discontinuing therapy will not be censored until the time of study discontinuation. If less than 50% of subjects progress by study cut-off time, the 25th percentile and its two-sided 95% confidence interval will be reported.

Treatment group differences between enzalutamide versus AS will be based on a Cox regression model. The resulting Hazard ratio (enzalutamide/AS) and 95% confidence interval will be included in the summary. Censoring assumptions will follow the same rules as applied for the KM estimates. Fixed effects for the model will include the treatment groups, stratification factors, race, and time since prostate cancer diagnosis. Complete details of the model and all covariates will be included in the SAP.

The proportional hazards assumption will be investigated graphically by the log on the negative log of the estimated survival versus the log on time to progression.

7.4.1.2 Secondary Analysis

The incidence of subjects with prostate cancer progression (pathological or therapeutic) will be summarized with frequencies and percentages. Treatment group differences will be assessed using logistic regression and include two-sided 95% confidence interval estimates of the odds ratio.

7.4.1.3 Subgroup Analysis

Subgroup analyses of time to progression will be performed to evaluate the treatment effect based on the following subgroups: age, and race. Further subgroups may be defined in the SAP.

7.4.2 Analysis of Secondary Endpoints

The incidence of negative biopsy for cancer and secondary rise in serum PSA will be summarized with frequencies and percentages at one and two years by treatment group, subgroup and overall.

Inferences will include 95% confidence intervals of the odds ratio for the primary endpoint between treatment groups. Comparison between enzalutamide and AS will be evaluated by logistic regression using the randomization stratification factors as fixed effects.

Time to PSA progression will be analyzed with the same methods as detailed for the primary endpoint analysis in Section 7.4.1.1.

BFI scores and change from baseline will be summarized with descriptive statistics by treatment group, stratification factors, subgroups and overall. Analyses of treatment group

differences will be analyzed with repeated measures linear models using subject as a random factor. Fixed effects will include the stratification factors as appropriate (for the overall analysis), time, time-by-treatment interaction and baseline scores. If the normality assumption is not valid, rank-based scoring will be used for inferences. Estimates will include 95% confidence intervals of least square means (LS Means) for each treatment group with and without stratification factors as appropriate. If the normal assumption is rejected, estimates will include the 25th and 75th percentiles.

Percent positive cores, SF-12 subdomain and the physical and mental component scores, QOL/sexual function EPIC domains (urinary, sexual and hormonal), and MAX-PC total and subscale scores, and the respective change from baseline assessments for all will be analyzed by time point in the same manner as the BFI scores.

7.4.3 Analysis of Exploratory Endpoints

The SAP will detail exploratory endpoint analyses.

7.5 Analysis of Safety

7.5.1 Adverse Events

All AEs will be collected and the severity of the AEs will be evaluated by the investigator based on the latest version of NCI-CTCAE. All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) to preferred term, high level term and system organ class. AEs, SAEs, AEs leading to discontinuation and AEs related to study drug will be presented by the number and percentage of subjects by MedDRA system organ class and preferred term, relationship to study treatment and severity. The latest version of NCI-CTCAE will be used to classify laboratory values by toxicity grade. Descriptive statistics will be used for AEs.

7.5.2 Laboratory Assessments

Laboratory data in this study consist of hematology, serum chemistry, PSA levels and hormonal levels. [redacted]

Normal ranges will be applied to identify values that are outside the normal ranges and create NCI toxicity grade using the latest NCI-CTCAE. Parameters that have criteria available for both low and high values will be summarized for both criteria (low and high).

7.5.3 Vital Signs

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

7.6 Analysis of Pharmacokinetics

Not applicable

7.7 Protocol Deviations and Other Analyses

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

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

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

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

No formal interim analysis is planned.

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

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medication and visit windows that will be detailed in the SAP.

Subjects who do not receive the study drug to which they have been randomized will be analyzed as treated.

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 7 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.

Laboratory tests on serum samples will be analyzed at the designated central laboratory. The central laboratory will compile the results and electronically transfer the data to Astellas or designee for inclusion in the clinical study database.

All transrectal prostate biopsy samples will be submitted, in accordance with the guidelines in the histopathology manual, for central pathology review and [redacted] by designated central laboratories. The designated centers performing these assessments will compile the results and electronically transfer the data to Astellas or designee for inclusion in the clinical study database.

For all central assessments of biopsy and serum samples, the results for each subject will be shared with the corresponding Investigator.

Subject questionnaires (BFI; SF-12; EPIC urinary, sexual and hormonal domains; MAX-PC) will be completed by the subject on paper during the study visit. The investigator or site designee should review the questionnaires for completion while the subject is at the site. The investigator or site designee will enter the responses from the completed subject questionnaire into the EDC system. The monitor will collect the paper questionnaires, and submit them to the Sponsor or designee, ensuring a copy remains at site. For screen failures, the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

8.1.2 Specification of Source Documents

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

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

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

8.1.3 Clinical Study Monitoring

The Sponsor or delegated Contract Research Organization (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 Good Clinical Practice (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 Sponsor or designated CRO of Sponsor in accordance with their standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. (e)CRF completion will be described in the (e)CRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary respectively.

8.1.6 Protocol Deviations

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

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

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

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

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

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

The investigator will also assure that deviations meeting 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).

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

8.1.7 End of Trial in All Participating Countries

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

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 serious adverse events 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 one year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-sponsored studies, or for APEB/APEL-sponsored studies within one year after last subject out (LSO) or termination of the study.

8.2.2 Ethical Conduct of the Study

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

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed 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 must document whether the subject is willing to remain in the study or not.
2. The investigator must update their ICF and submit it for approval to the 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

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

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

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number 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 will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e. HIPAA).

8.3 Administrative Matters

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

Information concerning the study drug, patent applications, processes, unpublished scientific data, the 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 investigator will archive all study data (e.g., Subject Identification Code List, source data, eCRFs and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, two years after approval of the NDA or discontinuation of the IND). The Sponsor will notify the site/investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPD/CHIKEN TODOKE is discontinued. 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 eCRFs supplied for each subject.

The investigator and sponsor will mutually agree upon the storage format for the retention of electronic data.

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, 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 trials are conducted and data are generated, documented, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirement(s).

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

10 STUDY ORGANIZATION

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

Not applicable

10.1 Other Study Organization

Not applicable

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12 APPENDICES

12.1 List of Excluded Concomitant Medications

Prohibited Medications

The following medications are prohibited in the absence of disease progression:

- 5α-reductase inhibitors (finasteride, dutasteride)
- Estrogens
- Cyproterone acetate
- Androgens (testosterone, dehydroepiandrosterone [DHEA], etc.)
- Antiestrogens or other medications to manage gynecomastia / breast complications
- Any other investigational agent

Restricted Medications

The following medications are restricted for subjects receiving enzalutamide; please reference Section 5.1.3 for more details regarding these restrictions:

- Strong CYP2C8 inhibitors
- Strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine), St. John's Wort
- Narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus)
- Narrow therapeutic index drugs that are metabolized by CYP2C9 (e.g., phenytoin, warfarin)
- Narrow therapeutic index drugs that are metabolized by CYP2C19 (e.g., S-mephenytoin)

Restrictions on Concomitant Treatment

Antiestrogens or other medications to manage gynecomastia/breast complications of enzalutamide treatment are prohibited; please reference Section 5.1.3 for more details on management of gynecomastia/breast complications.

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 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

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

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

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

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

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

Follow-up Procedures

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

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

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology may be considered an important medical event and may be reported as a Serious Adverse

Event (SAE). The Sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

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

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

Study Discontinuation

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

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metasteses
- 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 metasteses)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

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

*Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant)." The two "requirements" for Hy's Law are: 1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated patients to be discriminating"). 2. Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. [Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 Apr;15(4):241-3.]

Reference

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

12.3 Common Serious Adverse Events

For this protocol, there is no list of common serious adverse events anticipated for the study population for the purposes of IND safety reporting.

13 SIGNATURES

(GPF 4.00)