

**A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study  
to Assess the Efficacy and Safety of Enzalutamide in Subjects  
with Advanced Hepatocellular Carcinoma**

**ISN/Protocol 9785-CL-3021**

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**Date of Protocol v5.0: 08 Mar 2018**

**Sponsor: Astellas Pharma Global Development, Inc. (APGD)**

1 Astellas Way  
Northbrook, IL 60062

**A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study  
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**Protocol for Phase 2 Study of Enzalutamide**

**ISN/Protocol 9785-CL-3021**

**Version 5.0**

**Incorporating Substantial Amendment 4 [See Section 13]**

**08 March 2018**

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Sponsor:

**Astellas Pharma Global Development, Inc. (APGD)**

1 Astellas Way

Northbrook, IL 60062

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## **I. SIGNATURES**

### **1. SPONSOR'S SIGNATURE**

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



## 2. INVESTIGATOR'S SIGNATURE

### **A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Enzalutamide in Subjects with Advanced Hepatocellular Carcinoma**

**ISN/Protocol 9785-CL-3021**

**Version 5.0 / Incorporating Substantial Amendment 4**

**08 March 2018**

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (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: \_\_\_\_\_

\_\_\_\_\_  
Date (DD Mmm YYYY)

Printed Name: \_\_\_\_\_

*<Insert name and qualifications of the Investigator>*

Institution: \_\_\_\_\_

Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

## II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

<b>24h-Contact for Serious Adverse Events (SAEs)</b>  See Section <a href="#">5.5.5</a> Reporting of Serious Adverse Events	<b>Please fax or email the SAE Worksheet to:</b>  <b>Astellas Pharma Global Development – United States Pharmacovigilance</b> <b>Fax number:</b> <b>North America: +1 847 317 1241 (alternate +1 888 396 3750)</b> <b>Europe: +44 800 471 5263</b> <b>Email: <a href="mailto:safety-us@astellas.com">safety-us@astellas.com</a></b>
<b>Medical Monitor/Medical Expert</b>	<div>[REDACTED]</div> <div>Astellas Pharma Global Development, Inc.</div> <div>Telephone: [REDACTED]</div> <div>Mobile: [REDACTED]</div> <div>Email: [REDACTED]</div>
<b>Clinical Research Contact:</b>	<div>[REDACTED]</div> <div>Phone: [REDACTED]</div> <div>Mobile: [REDACTED]</div> <div>Email: [REDACTED]</div>

### III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

Abbreviations used for laboratory or electrocardiogram assessments and commonly used abbreviations are not included in this list.

#### List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse event
ALT	Alanine Aminotransferase (GPT)
APEBV	Astellas Pharma Europe B.V.
APGD	Astellas Pharma Global Development, Inc.
AR	Androgen Receptor
AST	Aspartate Aminotransferase (GOT)
AUST	Astellas United States Technologies
BCLC	Barcelona Clinic Liver Cancer
CCRK	Cell Cycle-related Kinase
CIOMS	Council for International Organizations of Medical Sciences
CL <sub>CR</sub>	Creatinine Clearance
CR	Complete Response
CRO	Contract Research Organization
CRPC	Castration-resistant Prostate Cancer
CT	Computed Tomography
CYP	Cytochrome P450
DCR	Disease Control Rate
DSMB	Data Safety Monitoring Board
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full Analysis Set
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response System
ISN	International Study Number
IUD	Intrauterine Device
IUS	Intrauterine System

Abbreviations	Description of abbreviations
LD	Longest Diameter
LFT	Liver Function Tests
mCRPC	Metastatic Castration-resistant Prostate Cancer
MRI	Magnetic Resonance Imaging
NASH	Nonalcoholic steatohepatitis
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NDA	New Drug Application
NYHA	New York Heart Association
PD	Progressive Disease
PDAS	Pharmacodynamic Analysis Set
PFS	Progression Free Survival
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PKAS	Pharmacokinetic Analysis Set
PR	Partial Response
■	■
OS	Overall Survival
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TACE	Transarterial Chemoembolization
TBL	Total Bilirubin
TEAE	Treatment-emergent Adverse Event
■	■
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

## Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
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 clinical 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.
Screening period	Period of time before entering the investigational period, from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet one or more criteria required for participation in a trial.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.
Source data	All information in original records and certified copies of the original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the clinical study. Source data exist in source documents (original records or certified copies) or in an electronic data capture system.
Source documents	Original documents, data and records including source data.

## IV. SYNOPSIS

<b>Date and Version # of Protocol Synopsis:</b>	08 March 2018 / Version 5.0
<b>Sponsor:</b> Astellas Pharma Global Development Inc (APGD)	<b>Protocol Number:</b> 9785-CL-3021
<b>Name of Study Drug:</b> Enzalutamide	<b>Phase of Development:</b> Phase 2
<b>Title of Study:</b> A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Enzalutamide in Subjects with Advanced Hepatocellular Carcinoma	
<b>Planned Study Period:</b> 4Q2015 – 1Q2018	
<b>Double-Blind Period:</b> The double-blind period is the study period when investigators and subjects are blinded to the study drug they receive. The double-blind period will conclude following the results of the primary analysis.	
<b>Open-Label Period:</b> The open-label period will begin following the results of the primary analysis. At the time of unblinding, open-label enzalutamide will be provided for subjects who meet eligibility criteria. The complete details for the conduct of the open-label period are provided in Appendix <a href="#">12.9</a> Open-Label Period.	
<b>Study Objective(s):</b> <u>Primary Objectives:</u> <ul style="list-style-type: none"> <li>To evaluate the efficacy of enzalutamide in subjects with advanced hepatocellular carcinoma (HCC) as measured by overall survival (OS)</li> </ul> <u>Secondary Objective:</u> <ul style="list-style-type: none"> <li>To evaluate the safety of enzalutamide in subjects with advanced HCC</li> <li>To evaluate the pharmacokinetics of enzalutamide and the active metabolite N-desmethyl enzalutamide in subjects with advanced HCC</li> <li>To evaluate the Progression Free Survival (PFS) of enzalutamide as compared to placebo in subjects with advanced HCC</li> </ul> <u>Exploratory Objectives:</u> <ul style="list-style-type: none"> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> </ul>	
<b>Planned Total Number of Study Centers and Location(s):</b> Approximately 40 centers in Europe, Asia and North America	

**Study Population:**

Male and female subjects with advanced (unresectable and/or metastatic) HCC with Barcelona Clinic Liver Cancer [BCLC] stage B or C of any etiology who have progressed on or were intolerant to sorafenib or other anti-vascular endothelial growth factor (VEGF) therapy in the advanced setting and are not amenable to local therapies or any curative treatments. Subjects may have received 1 line of systemic therapy before or after sorafenib/anti-VEGF treatment.

**Number of Subjects to be Enrolled/Randomized:**

Approximately 144 subjects were planned to be enrolled. 165 subjects were actually enrolled.

**Study Design Overview:**

This is a multicenter, randomized, double-blind, placebo-controlled phase 2 study evaluating the efficacy, safety, and tolerability of enzalutamide monotherapy in 165 subjects in Europe, Asia, and North America with HCC of any etiology who have progressed on or were intolerant to sorafenib or any other anti-VEGF therapy in the advanced setting. Each region will have no more than 70% of overall subjects enrolled. Enrollment may be limited by the sponsor in any region or country in order to have representation of the patient population from all 3 regions as there may be a difference in responses to treatment or tolerability.

The study will consist of a Screening Period, Treatment Period and a Follow-up Period. Eligible subjects will be stratified by geographic region (Asia versus others) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1) and randomized in a 2:1 ratio to receive enzalutamide 160 mg/day or placebo until disease progression, unacceptable toxicity, or any other discontinuation criterion is met. Best supportive care will also be given to all subjects in addition to study drug. Best supportive care may include medications and supportive measures deemed necessary per Investigator's discretion to palliate disease-related symptoms and improve quality of life. Study evaluations will occur as specified in the Schedule of Assessments.

An end of treatment visit will be performed within 7 days of the last dose of study drug. Upon discontinuation of treatment for any reason, subjects will enter the follow-up period. A follow-up visit will be performed approximately 30 days after the last dose of study drug. All adverse events (AEs) that occur during the safety reporting period (from first dose through 30 days after the last dose or initiation of new treatment, whichever comes first) 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. This may be performed by telephone if applicable. Long-term follow-up visits will be conducted every 30 days for up to 2 years to collect information on survival and subsequent therapies.

During the study, study drug treatment may be interrupted for individual subjects who experience a National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) Grade  $\geq 3$  AE (except Liver Function Test AEs) that is attributed to the study drug and cannot be ameliorated with appropriate medical intervention. Study drug may be resumed at the original dose (160 mg/day) or at a reduced dose (120 mg/day or 80 mg/day), after discussion with and approval by the Medical Monitor. Treatment interruption for  $> 14$  days must also be discussed with the Medical Monitor.

For LFT changes, study drug dosing should be interrupted if a subject experiences clinically significant liver toxicity related to study drug ( $\geq$  Baseline + 4 x ULN to  $< 20$  x ULN for AST and ALT; grade 3 total bilirubin [TBL]). Testing should be repeated at Investigator's discretion but at a minimum weekly to ensure that the subject's LFT's are returning to acceptable levels. If the subject's toxicity resolves within 14 days to either  $\leq$  grade 1 (if normal at baseline) or no more than 1 grade above baseline (but no higher than grade 2), study drug may be reintroduced at a dose of 120 mg/day in consultation with the Medical Monitor. If the toxicity has not resolved within 14 days (as defined by either  $\leq$  grade 1 or no more than 1 grade above screening but no higher than grade 2), then the Medical Monitor must be consulted to determine if further interruption is permitted.

If any drug-related liver toxicity requiring dose interruption recurs or develops despite the initial dose reduction to 120 mg/day, the LFT monitoring instructions above should be followed and the study drug may be reintroduced at a dose of 80 mg/day. If any drug-related liver toxicity recurs at the reduced dose of 80 mg/day, the study drug should be discontinued.

Study drug must be discontinued for subjects with study drug related grade 4 LFTs (AST, ALT and TBL).

There will be an initial safety review of the first 21 subjects. After the 21<sup>st</sup> randomized subject has been treated for 28 days or discontinued from the study (whichever occurs first), unblinded safety data will be evaluated by an independent Data Safety Monitoring Board (DSMB). Emerging safety issues may lead to a decision to change the dose, implement additional safety steps or assessments or terminate the study. Further safety review and details on the process and methods of the safety data review will be provided in the DSMB Charter.

**Inclusion/Exclusion Criteria:**

Waivers to the inclusion and exclusion criteria will NOT be allowed.

*Inclusion:*

1. Subject has consented and signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] for U.S. sites) prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is  $\geq 18$  years of age or is considered an adult according to local regulation at the time of signing informed consent.
3. Subject has a documented diagnosis of advanced HCC of any etiology.
4. Subject has BCLC stage B or C.
5. Subject's lesions are not amenable to local therapies which may be beneficial, such as transarterial chemoembolization (TACE), radiofrequency ablation, radiotherapy, etc., and the subject is not a candidate for any curative treatments such as resection or liver transplant.
6. Subject has hepatic function status of Child Pugh Class A at Screening.
7. Subject received prior systemic treatment for HCC with sorafenib or other anti-VEGF therapy and had confirmed disease progression or discontinued treatment due to a drug-related toxicity. Subject may have received 1 line of systemic therapy before or after sorafenib/anti-VEGF treatment.
8. Subject has adequately recovered from toxicities due to prior HCC therapy to  $\leq$  grade 1.
9. Subject has an ECOG performance status  $\leq 1$  at Screening and on Day 1.
10. Subject has available formalin-fixed, paraffin-embedded tumor specimen with adequate viable tumor cells in a tissue block or unstained serial slides accompanied by an associated pathology report prior to enrollment. Archival or fresh biopsy tissue is required.
11. Subject has an estimated life expectancy of at least 3 months on Day 1, in the opinion of the Investigator.
12. Female subject is either:
  - Not of childbearing potential:
    - postmenopausal (defined as no spontaneous menses for at least 12 consecutive months prior to Screening with follicle-stimulating hormone [FSH]  $> 40$  IU/L for women  $< 55$  years of age at Screening), or
    - documented to be surgically sterile or status posthysterectomy (at least 1 month prior



- to Screening).
- Or, if of childbearing potential:
    - must have a negative urine pregnancy test at Screening and on Day 1 before the first dose of study drug is administered, and
    - must use 2 acceptable methods of birth control\* if sexually active from Screening through 3 months after the last dose of study drug.
13. Sexually active male subject and his female partner who is of childbearing potential must use 2 acceptable methods of birth control\* from Screening through 3 months after the last dose of study drug.
- \*Two acceptable methods of birth control are as follows:
- Condom (barrier method of contraception);  
AND
  - One of the following is required:
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS) by the female subject or female partner of a male subject;
    - Additional barrier method: contraceptive sponge or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female subject or female partner of a male subject.
    - For male subject or male partner of female subject, vasectomy or other procedure resulting in infertility (e.g., bilateral orchiectomy) performed at least 6 months before Screening.
    - Tubal ligation in the female partner of a male subject performed at least 6 months before Screening.
    - Established and ongoing use of oral, injected, or implanted hormonal contraceptive by female partner of a male subject.
14. Female subject must not be breastfeeding at Screening or during the study period and for 3 months after final study drug administration.
15. Subject must agree not to donate sperm or ova from first dose of study drug through 3 months after the last dose of study drug.
16. Throughout the study, male subject must use a condom if having sex with a pregnant woman.
17. Subject must be able to swallow study drug and comply with study requirements.
18. Subject agrees not to participate in another interventional study while on treatment.

*Exclusion:*

1. Subject has a severe concurrent disease, infection or comorbidity that, in the judgment of the Investigator, would make the subject inappropriate for enrollment.
2. Subject has fibrolamellar variant of HCC.
3. Subject has status of Child-Pugh Class B or C at Screening.
4. Subject has a history of organ allograft including liver transplant.
5. Subject has uncontrolled symptomatic ascites.
6. Subject has known or suspected brain metastasis or active leptomeningeal disease.
7. Subject has a history of a non-HCC malignancy with the following exceptions:
  - The subject with a previous history of a noninvasive carcinoma is eligible if in the opinion of the Investigator he/she has had successful curative treatment any time prior to Screening and requires no further therapy for the malignancy.

- For all other malignancies, the subject is eligible if he/she has undergone potentially curative therapy and has been considered disease free for at least 3 years prior to Screening.
8. Subject has inadequate marrow, hepatic, and/or renal function at the Screening Visit defined as:
- Absolute neutrophil count  $< 1.5 \times 10^9/L$  ( $< 1500$  cells/mm<sup>3</sup>)
  - Platelet count  $< 50 \times 10^9/L$  ( $< 50,000$  cells/mm<sup>3</sup>)
  - Hemoglobin  $< 8.5$  g/dL ( $< 5.3$  mmol/L)
  - International normalized ratio  $> 1.7$
  - Albumin  $< 2.8$  g/dL ( $< 28$  g/L)
  - TBL  $> 2 \times$  ULN
  - AST or ALT  $> 5 \times$  ULN
  - Creatinine  $> 1.5 \times$  ULN
- Note: Transfusions/infusions to meet eligibility criteria are not allowed but if in the opinion of the Principal Investigator, it is beneficial, the patient may be rescreened after receiving one of these procedures.
9. Subject has a history of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke, significant brain trauma, encephalopathy within 3 months of Day 1).
10. Subject has a history of bleeding esophageal varices within 3 months before the Day 1 visit.
11. Subject has a history of loss of consciousness or transient ischemic attack within 12 months before the Day 1 visit.
12. Subject has clinically significant cardiovascular disease including:
- Myocardial infarction within 6 months before the Day 1 visit.
  - Uncontrolled angina within 6 months before the Day 1 visit.
  - Congestive heart failure New York Heart Association (NYHA) Class III or IV or history of congestive heart failure NYHA Class III or IV in the past, UNLESS a Screening echocardiogram or multi-gated acquisition scan performed within 3 months before the Day 1 visit reveals a left ventricular ejection fraction that is  $\geq 45\%$ .
  - History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, Torsade de Pointes).
  - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
  - Hypotension as indicated by systolic blood pressure  $< 86$  mmHg on 2 consecutive measurements at the Screening visit.
  - Bradycardia (in the presence of known cardiovascular disease) as indicated by a heart rate of  $< 50$  beats per minute on the Screening electrocardiogram (ECG) recording.
  - Uncontrolled hypertension as indicated by systolic blood pressure  $> 170$  mmHg or diastolic blood pressure  $> 105$  mmHg on 2 consecutive measurements at the Screening visit.
13. Subject has a gastrointestinal disorder affecting absorption.
14. Subject had previous local therapy (e.g., surgery, radiation therapy, hepatic arterial therapy, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation) within 14 days prior to Day 1, has not recovered from toxicities from prior local therapy or may require major surgical procedure during the course of the study.
15. Subject has received chemotherapy, immunotherapy or any other systemic anticancer therapy (including sorafenib) or any other investigational drug within 14 days prior to the Day 1 visit.
16. Subject has received an agent that either blocks androgen synthesis or targets the AR (e.g., abiraterone acetate, bicalutamide, enzalutamide, ARN-509 or other investigational AR signaling

<p>inhibitors). The exception of spironolactone is allowed after Medical Monitor consultation.</p> <p>17. Subject has used any of the following within 28 days before the Day 1 visit:</p> <ul style="list-style-type: none"> <li>• 5-<math>\alpha</math> reductase inhibitors</li> <li>• Systemic androgens and estrogens (vaginal estrogen creams are allowed)</li> <li>• Herbal therapies with an antitumor effect.</li> </ul> <p>18. Subject has a known history of positive test for Human Immunodeficiency Virus.</p> <p>19. Subject has shown a hypersensitivity reaction to the active pharmaceutical ingredient or any of the enzalutamide capsule components, including caprylocaproyl polyoxylglycerides (Labrasol), butylated hydroxyanisole and butylated hydroxytoluene.</p> <p>20. Subject has addictive/substance abuse problems.</p> <p>21. Subject has any other condition or reason that, in the opinion of the Investigator, interferes with the ability of the subject to participate in the trial, places the subject at undue risk or complicates the interpretation of safety data.</p>
<p><b>Investigational Product(s):</b>  Enzalutamide 40 mg gelatin capsules</p> <p><b>Dose(s):</b>  Enzalutamide 160 mg once daily (4 capsules once daily)</p> <p><b>Mode of Administration:</b>  Enzalutamide is an oral capsule.</p>
<p><b>Comparative Drug(s):</b>  Placebo.</p> <p><b>Dose(s):</b>  4 placebo capsules to match enzalutamide.</p> <p><b>Mode of Administration:</b>  Oral.</p>
<p><b>Concomitant Medication Restrictions or Requirements:</b>  Medications taken within 14 days before the Screening visit and up to the 30-Day Follow-up visit will be documented on the appropriate case report form. Prior and concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications. Subject with viral etiology (hepatitis B virus [HBV], hepatitis C virus [HCV]) should be on stable doses of antiviral therapy at the time of study entry, if the Investigator feels these are of benefit to the subject. The Investigator should consult with Medical Monitor if initiation of antiviral therapy is deemed necessary during the study.</p> <p>Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by cytochrome P450 (CYP) 3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional international normalization ratio (INR) monitoring should be conducted.</p> <p>Coadministration of enzalutamide with strong CYP2C8 inhibitors should be avoided. If coadministration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, the enzalutamide dose should be reduced to 80 mg/day. If coadministration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used before initiation of the strong CYP2C8 inhibitor</p>

Subject should avoid use of any herbal medications or dietary supplements including products containing *Hypericum perforatum* (e.g., St. John's wort).

The following medications or therapies are prohibited during the receipt of study drug:

- Medications, including herbal therapies, with an antitumor effect
- Any investigational agent
- AR antagonists (e.g., bicalutamide, flutamide, nilutamide), however, spironolactone initiation during the study is allowed after Medical Monitor consultation
- 5- $\alpha$  reductase inhibitors (e.g., finasteride, dutasteride)
- Systemic androgens and estrogens (vaginal estrogen creams are allowed)

**Duration of Treatment:**

From the first dose date of study drug to disease progression, unacceptable toxicity, or any other discontinuation criteria are met, whichever comes first.

**Formal Stopping Rules:**

Study Discontinuation

The study may be terminated by the Sponsor at any time. A DSMB will be used to monitor safety during the study. Emerging safety issues may lead to a decision to terminate the study.

**Endpoints for Evaluation:**

Primary

Overall Survival is defined as the time from the date of randomization until date of death from any cause.

Secondary

*Safety Endpoints:*

The safety of enzalutamide will be assessed on an ongoing basis by evaluation of AEs/serious adverse events, clinical safety laboratory tests, vital signs, and other safety measures.

*Pharmacokinetic Endpoints:*

Predose plasma concentrations of enzalutamide and N-desmethyl enzalutamide will be analyzed.

*Efficacy Endpoints:*

- PFS, defined as the time from the date of randomization until the date of documented radiographic disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or death from any cause on study, whichever occurs first as assessed by the Investigator.

Exploratory

[REDACTED]

## Statistical Methods:

### Sample Size Considerations:

This sample size was primarily determined to provide sufficient clinical experience to support the design of later-stage clinical development, such as phase 3 studies.

Sample size calculations were performed using EAST 5 software based on the following assumptions:

- 2:1 randomization for enzalutamide vs placebo.
- Median OS for placebo and enzalutamide are 7.0 months and 10.77 months (HR=0.65), respectively.
- A study enrollment period of 18 months and a total study duration of 27 months.

With 109 death events, the study can achieve 80% power to detect a statistically significant difference using 1-sided log-rank test with 10% level of significance. Assuming no loss to follow-up, approximately 144 subjects were originally planned to reach this number of events.

### Efficacy:

Efficacy analyses will be conducted using the Full Analysis Set (FAS). The FAS will consist of all randomized subjects. The primary endpoint, OS, will be defined as the time from the date of randomization until the documented date of death from any cause. Subjects who are still alive at the time of the data cutoff date will be censored on the last date known to be alive. The null hypothesis is that OS distributions of the two treatments are equivalent. The alternative hypothesis is that OS is prolonged in the enzalutamide arm. The null hypothesis will be tested using a stratified one-sided log-rank test at the 0.10 level (stratified by geographic region and ECOG performance status). The hazard ratio of the treatment effect and the two-sided 95% CI will also be calculated using a Cox proportional hazard model. Additional sensitivity analysis will be done using the unstratified test. Similar analyses will be conducted for the secondary efficacy endpoint PFS. The subgroup of AR+ (defined as  $\geq 10\%$  of tumor cells with nuclear expression) patients will be used to repeat the analyses described above.

### Safety:

Safety analyses will be conducted using the Safety Analysis Set (SAF). The SAF is defined as all subjects who have taken at least 1 dose of study drug. The treatment-emergent period will be defined as the period of time from the first dose date of study drug to 30 days after the last dose date of study drug or initiation of a new antineoplastic or new investigational agent (whichever is first). Safety will be assessed through descriptive statistics for the frequency of TEAEs by system organ class, preferred term, and the NCI CTCAE grade, the frequency of treatment discontinuations due to AEs, vital signs, ECG and laboratory evaluations.

The severity of all AEs is to be evaluated by the Investigator based on the NCI CTCAE, version 4.03. All AEs will be coded to preferred term and system organ class using MedDRA. The number and percentage of subjects with AEs will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and NCI CTCAE grade. A subject reporting the same AE more than once is counted once at the maximum severity or strongest relationship to study drug treatment, when calculating incidence.

Laboratory data consist of hematology, chemistry, coagulation, viral load (if applicable), pregnancy and urinalysis test results. Where applicable, NCI CTCAE version 4.03 will be used to categorize toxicity grades for the laboratory parameters. Laboratory shift tables compared to baseline results for each subsequent visit will be produced. For each laboratory parameter, the baseline laboratory value is defined as the last laboratory value collected on or prior to the first dose date of study drug.

Changes in body weight and vital signs will be described with similar methods.

Pharmacokinetics:

Pharmacokinetic analysis will be conducted using the pharmacokinetic analysis set (PKAS). The PKAS is defined as the subset of the SAF population for which at least one quantifiable enzalutamide and N-desmethyl enzalutamide concentration value based on a predose sample is available. The enzalutamide and N-desmethyl enzalutamide concentration-time data will be summarized by descriptive statistics at each visit. Additional model-based analyses may be performed but will be reported separately.

Interim Analysis:

There is no planned interim analysis; however, there will be periodic safety reviews throughout the study. After the 21<sup>st</sup> randomized subject has been treated for 28 days or has discontinued from the study (whichever occurs first), unblinded safety data will be evaluated by an independent DSMB. Further safety review and details on the process and methods of the safety data review will be provided in the DSMB Charter.

## V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

### Flow Chart

Informed Consent	→	Screening Period (Days -21 to -1)	→	Day 1 Predose  Confirmation of eligibility criteria and enrollment	Treatment Period (Day 1 - until a discontinuation criterion is met)  Visits at Weeks 3, 5, then every 4 weeks Tumor Assessment will be done every 8 weeks (+/- 7 days) and measurement of HBV viral load (for subjects with HBV) to be done per Institution SOC	End of Treatment  Visit (within 7 days after last dose)	Follow-up Period  (Approx. 30 days after last dose of study drug, then q30 days to collect information on survival and subsequent therapies)
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Abbreviations: HBV= hepatitis B virus, q = every, SOC = standard of care

**Table 1 Schedule of Assessments**

Assessments	Screen	Treatment Period						Unscheduled Visit	Follow-up Period		
Study Week/Visit	-3 to -1	1	3	5	9	13	17 + Q4 Weeks		EOT	30D FU <sup>1</sup>	Long-term FU <sup>1</sup>
Study Day	-21 to -1	1	15	29	57	85	113+	N/A	≤ 7D after last dose	30D after last dose	Q30 days
Window (days)	N/A	0	+/-3	+/-3	+/-3	+/-3	+/-3	N/A	N/A	+10	+10
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Return and/or dispense study drug		X	X	X	X	X	X	X [OPT]	X		
Concomitant medications <sup>2</sup>	X	X	X	X	X	X	X	X	X	X	
Demographics, medical and disease history	X										
BCLC staging	X										
Child-Pugh classification	X										
HBV/HCV status <sup>3</sup>	X										
Tumor assessment <sup>4</sup>	X	To be performed Q8Weeks (+/- 7 D) from Day 1						X [OPT]			
Height	X										
Weight	X	X		X	X	X	X	X [OPT]	X		
Vital signs	X	X	X	X	X	X	X	X [OPT]	X		
Adverse events <sup>5</sup>	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests <sup>6</sup>	X <sup>7</sup>	X <sup>8</sup>	X	X	X	X	X	X [OPT]	X		
Urine pregnancy test <sup>9</sup>	X	X		X	X	X	X	X [OPT]	X		
Physical examination	X	X	X	X	X	X	X	X [OPT]	X		
12-lead ECG	X					X		X [OPT]	X		
ECOG PS	X	X	X	X	X	X	X	X [OPT]	X		
Alpha-fetoprotein	X	X <sup>8</sup>	X	X	X	X	X	X [OPT]	X		
HBV viral load (if applicable)	X	To be done per SOC or as clinically indicated									
Pharmacokinetic sample <sup>10</sup>				X	X	X		X [OPT]			
██████████ ██████████		X				X					
Tumor tissue collection <sup>12</sup>	X										
Blood samples for PGx biobanking (optional)		X									
Survival and subsequent treatment										X	X
██████████ ██████████		X		X	X	X	X				

Footnotes appear on next page



Abbreviations: BCLC: Barcelona Clinic Liver Cancer, D: day(s), ECG: electrocardiogram, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EOT: end of treatment, FSH: follicle-stimulating hormone, FU: follow-up, HBV: hepatitis B virus, HCV: hepatitis C virus, N/A: not applicable, OPT: optional, PGx: pharmacogenomics, Q: every, SOC: standard of care

1. Phone call may be conducted if subject is unable to travel. Long-term follow-up will occur for up to 2 years, until death or subject withdraws consent or final analysis.
2. Medications taken within 14 days before the Screening visit and up to the 30-day Follow-up Visit will be collected.
3. HBV/HCV status will be assessed at Screening. HBV should be assessed using an assay for hepatitis B surface antigen. HCV testing should be performed using an antiHCV antibody assay (enzyme immunoassay [EIA] or enhanced chemiluminescence immunoassay [CIA]).
4. Computed tomography (CT)/magnetic resonance imaging (MRI) of the chest/abdomen/pelvis, as well as any other anatomical region appropriate for the subject's disease must be performed within 28 days prior to day 1. Results from CT/MRI assessments performed prior to consent and within 28 days of day 1 may be used for Screening if available. Subsequent scans will be done every 8 weeks (+/- 7 days) from Day 1 until treatment discontinuation criterion is met. To ensure comparability, the Screening and subsequent assessment should be performed using identical techniques.
5. Adverse events will be collected from the time of informed consent through the 30-day Follow-up Visit or through the day prior to the initiation of new antineoplastic treatment or investigational agent, or whichever comes first.
6. Clinical laboratory assessments include hematology, chemistry, coagulation, viral load (if applicable), pregnancy and urinalysis (urine dipstick). Lab parameters to be analyzed are listed under Appendix 12.8 Laboratory Assessments.
7. FSH testing is also required for postmenopausal women who are < 55 years of age at Screening.
8. Day 1 clinical laboratory tests do not need to be repeated if Screening labs were performed within 7 days prior to Day 1.
9. Urine pregnancy test will be performed in women of childbearing potential. Testing at treatment visits must occur prior to study drug administration.
10. Pharmacokinetic samples will be collected prior to dosing. Subjects will be instructed to record on a diary the date and time that study drug was taken on the 2 days before the visit and not to take study drug until after the pharmacokinetic sample is collected. The date and time that the subject took the previous 2 doses of study drug should be recorded, even if the most recent dose was inadvertently taken earlier the same day.
11. [REDACTED]
12. Subject has available formalin-fixed, paraffin-embedded tumor specimen with adequate viable tumor cells in a tissue block or unstained serial slides accompanied by an associated pathology report prior to enrollment. Archival or fresh biopsy tissue is required. Ensure that subject meets all other study entry criteria prior to performing a biopsy (as applicable).
13. [REDACTED]

# 1 INTRODUCTION

## 1.1 Background

Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and remains a major global health problem. Globally, HCC is the 6th most common cancer and the 3rd leading cause of cancer-related mortality, with approximately 750,000 new cases world-wide annually. HCC has a strong male prevalence with a male to female ratio estimated to be 2.4. Worldwide, the mean age at diagnosis is between 50 and 60 years, and the incidence and mortality is increasing.

High incidence areas include East Asia, sub-Saharan Africa and Melanesia. In most European countries and the United States, the incidence is lower with the exception of Southern Europe, where the occurrence of HCC in men is significantly higher than in other developed regions.

Approximately 90% of HCCs are associated with a known underlying risk factor, including chronic viral hepatitis (types B and C), alcohol intake, aflatoxin exposure and nonalcoholic steatohepatitis (NASH). In Africa and East Asia, the most common etiology is hepatitis B (60%) whereas in the developed Western world, chronic hepatitis C appears to be the major risk factor [European Association for the Study of the Liver (EASL)- European Organisation for Research and Treatment of Cancer (EORTC) Clinical Practice Guidelines, 2012].

HCC characteristically occurs in the background of a cirrhotic liver, and usually secondary to hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection. Up to 80% of patients with HCC have cirrhosis which restricts therapeutic options. In addition, HCC is most often diagnosed at an advanced stage, when potentially curative therapies (e.g., resection, transplantation, percutaneous radiofrequency ablation) are of limited utility. Only about 30% to 40% of the patients are diagnosed at an early stage with only approximately 20% of patients being candidates for surgery. About 20% of patients are diagnosed at an intermediate stage and can benefit from transarterial chemoembolization (TACE). Other locoregional therapies being used includes liver transplantation, cryoablation, chemoembolization, radioembolization, bland embolization, percutaneous ethanol injection and hepatic arterial infusion chemotherapy with doxorubicin. However, after an initial therapeutic benefit, up to 70% of patients who undergo these procedures will have recurrent disease within 5 years and reach a more advanced tumor stage [Bruix et al., 2012]. Many patients are nonsymptomatic in the early stages of liver cancer. When symptoms appear, HCC typically presents with jaundice, anorexia, weight loss, abdominal swelling and upper abdominal pain. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography are commonly used to then identify whether a tumor is present [NCCN Guidelines 2013]. The level of alpha-fetoprotein is elevated in 60% to 70% of HCC patients [Arrieta et al., 2007].

Sorafenib is a multi-targeted tyrosine kinase inhibitor that blocks the activity of Raf serine/threonine kinase isoforms, as well as the receptor tyrosine kinases vascular endothelial growth factor receptor (VEGFR)-2 and -3, platelet-derived growth factor receptor  $\beta$ , c-KIT, FLT-3, and RET, to inhibit tumor angiogenesis and tumor cell proliferation. The SHARP trial demonstrated that sorafenib significantly improved overall survival (OS) in patients with

advanced HCC and well-preserved liver function (>95% Child–Pugh A), and that drug-related adverse events (AEs) were manageable. Median OS in the sorafenib and placebo groups was 10.7 and 7.9 months, respectively (hazard ratio [HR] 0.69, 95% CI 0.55–0.87,  $p < 0.001$ ); median time to radiologic progression was 5.5 and 2.8 months, respectively (HR 0.58, 95% CI 0.45–0.74;  $p < 0.001$ ); and disease control rate (DCR) was 43% and 32%, respectively ( $p = 0.002$ ) [Llovet et al., 2008]. This positive impact of sorafenib in improving survival and delaying tumor progression was confirmed in the phase 3 sorafenib Asia-Pacific trial, performed in China, South Korea and Taiwan [Cheng et al., 2009].

Despite these data supporting the effectiveness of sorafenib leading to its approval as first-line systemic therapy for patients with advanced HCC, the outcome for patients with advanced HCC remains dismal and new treatment approaches are urgently needed. Literature review suggests androgen and androgen receptor (AR) signaling may play an important role in HCC. In patients with HBV-related HCC, the incidence is higher in males and postmenopausal females compared to other females. The high levels of serum testosterone in males with an HBV infection have been reported to be associated with their development of HCC and their active AR gene alleles [Liu and Liu, 2014; Yu et al., 2001; Wang et al., 2009]. AR regulates the production of HBV X viral protein in a transgenic mouse model, which is implicated in HBV-mediated HCC [Chui et al., 2007]. In addition to high androgen levels, overexpression of the AR has been demonstrated in 60–80% of human HCCs [Nagasue et al., 1989]. AR overexpression is correlated with cell cycle-related kinase (CCRK), an AR signaling mediator that drives hepatocarcinogenesis via a signaling pathway dependent on  $\beta$ -catenin and T cell factor [Feng et al., 2011].

Recent genetic studies have further established the pivotal role of AR in hepatocarcinogenesis. Liver-specific knockout of AR significantly reduced tumorigenicity in carcinogen- and HBV-induced HCC mouse models [Ma et al., 2008; Wu et al., 2010]. Jiang et al. [2014] reported that apoptosis in HepG2 cells, human HCC cell line, was induced via inhibition of AR signaling. These findings suggested that the activation of the AR signaling pathway might be involved in HCC. Although the molecular mechanisms of AR-induced hepatocarcinogenesis have not been clarified, these data warrant further clinical investigation into AR as a potential therapeutic target for the treatment of HCC. As enzalutamide is an inhibitor of the AR signaling pathway, the present study seeks to assess the efficacy and safety of enzalutamide in subjects with advanced HCC.

## **1.2 Nonclinical and Clinical Data**

### **1.2.1 Nonclinical Data**

#### **1.2.1.1 Pharmacology**

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

pharmacodynamics of enzalutamide show that it is an AR inhibitor, and further that it is distinct from other antiandrogens in affecting multiple steps in the AR signaling pathway in the setting of AR overexpression. A major human metabolite of enzalutamide, N-desmethyl enzalutamide, demonstrated key primary pharmacodynamics with similar potency to the parent molecule. [Refer to the current Investigator's Brochure].

In vitro and in vivo efficacy studies of enzalutamide have been conducted using a limited number of AR-positive HCC cell lines and the importance of AR signaling inhibition in HCC has not been demonstrated yet.

While enzalutamide did not have acute neurobehavioral effects (as assessed by functional observational battery endpoints) in the rat, convulsions were observed with this compound after a single dose in mice.

Because enzalutamide was demonstrated to bind to and inhibit the gamma aminobutyric acid-gated chloride channel, an in vivo study in mice to investigate convulsion potential was conducted. Convulsions occurred in mice given 400 mg/kg enzalutamide as a single dose or 200 mg/kg per day enzalutamide for 7 days. Based on the totality of the data, enzalutamide is associated with dose-dependent convulsions in mice.

Enzalutamide had no effect on any other clinical observations or respiratory function assessments at doses up to and including 200 mg/kg.

The nonclinical and clinical data suggest that enzalutamide is not associated with an increased risk of QT prolongation, ischemic heart disease, heart failure or arrhythmias [Refer to the current Investigator's Brochure].

#### **1.2.1.2 Pharmacokinetics**

Following oral administration in animals, enzalutamide is eliminated slowly from plasma with a long  $t_{1/2}$  across species. In vitro studies show that enzalutamide is metabolized by human recombinant cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4/5.

Enzalutamide and/or its major human metabolites caused direct in vitro inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. In vitro, enzalutamide caused time-dependent inhibition of CYP1A2. Based on in vitro data, enzalutamide is an inducer of CYP3A4 but is not expected to induce CYP1A2 at therapeutically relevant concentrations.

In vitro data show that enzalutamide and its active metabolite N-desmethyl enzalutamide are potential inhibitors, but not substrates, of the efflux transporter P-glycoprotein (P-gp) [Refer to the current Investigator's Brochure].

#### **1.2.1.3 Toxicology**

Overall, enzalutamide was generally well tolerated in nonclinical species with the most prominent effects occurring in reproductive and hormone-sensitive tissues. In studies in rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), changes in the reproductive organs associated with enzalutamide were decreases in organ weight with atrophy of the prostate and

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

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

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

Enzalutamide was non mutagenic in bacteria, nonclastogenic in mammalian cells and non genotoxic in vivo in mice. The 2 major human metabolites (N-desmethyl enzalutamide and an inactive carboxylic acid derivative) were negative for mutagenicity in the bacterial reverse mutation assay (Ames) [Refer to the current Investigator's Brochure].

### **1.2.2 Clinical Data**

As of the data cutoff date of 28 February 2016, over 5500 patients with prostate cancer, over 400 women with breast cancer, and over 300 subjects with no known cancer including healthy male subjects and subjects with hepatic impairment have received at least 1 dose of enzalutamide in completed and ongoing clinical studies (not including the expanded access program or 2 compassionate use programs).

The safety profile of enzalutamide in patients with castration-resistant prostate cancer (CRPC) is derived primarily from two phase 3 studies. Study CRPC2 (AFFIRM) was a randomized, double-blind, placebo-controlled, efficacy and safety clinical study of enzalutamide (160 mg daily) in 1199 patients with progressive metastatic CRPC (mCRPC) previously treated with docetaxel-based chemotherapy. MDV3100-03 (PREVAIL) was a multinational, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in 1717 chemotherapy-naïve patients with mCRPC who have failed androgen deprivation therapy.

Findings from the two phase 3 CRPC studies, study showed that AEs occurring in at least 5% of the patients treated with 160 mg/day enzalutamide (n = 1671) and at an incidence of at least 2% greater than in placebo patients were: asthenia, fatigue, back pain, diarrhea, constipation, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, muscular weakness, dizziness, insomnia, spinal cord compression, dysgeusia, hematuria, anxiety, hypertension, fall, decreased appetite, and weight decreased. The proportion of

patients with AEs associated with discontinuation of study drug in the combined controlled population was 17.7% in the enzalutamide group and 23.5% in the placebo group.

Seizures occurred in 7 (0.9%) of the enzalutamide treated patients and none (0%) of the placebo-treated patients in the blinded CRPC2 study. A lower seizure rate was observed in MDV3100-03 study (1 enzalutamide-treated patient [0.1%]).

There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving enzalutamide. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension [refer to the current Investigator's Brochure].

### 1.2.2.1 Pharmacokinetics

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

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

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. Steady state plasma levels of the active metabolite are similar to those of enzalutamide.

A mass balance and biotransformation study in healthy male volunteers showed that enzalutamide is primarily eliminated by hepatic metabolism.

A food-effect study showed that food does not have a clinically relevant effect on the AUC of enzalutamide or *N*-desmethyl enzalutamide; therefore, enzalutamide can be taken with or without food.

Based on population pharmacokinetics modeling, age, weight and renal function (creatinine clearance [ $CL_{CR} \geq 30$  mL/min]) do not have clinically meaningful effects on enzalutamide exposures, therefore, no dose adjustments are indicated for these covariates. Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Caucasian patients. Clinical

data are insufficient to assess the potential effect of severe renal impairment ( $CL_{CR} < 30$  mL/min) and end-stage renal disease on enzalutamide pharmacokinetics.

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

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

The pharmacokinetics of oral enzalutamide is being investigated in women with advanced breast cancer (MDV3100-08). Preliminary data demonstrate similar pharmacokinetics of enzalutamide and N-desmethyl enzalutamide in women relative to men with CRPC.

Refer to the current Investigator's Brochure for more information.

### **1.3 Summary of Key Safety Information for Study Drugs**

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

## 1.4 Benefit-Risk Assessment

The approval of sorafenib (Nexavar®) in 2007 changed the understanding of HCC and brought in a new era in the management of liver cancer. Sorafenib, a multi-target kinase inhibitor, was found to improve survival of patients with advanced-stage HCC (median OS 10.7 months vs 7.9 months for placebo, HR 0.69,  $P < 0.0006$ ) [Llovet et al., 2008] in Western patients. A phase 3 trial [Cheng et al., 2009] demonstrated a similar magnitude of benefit in Asian-Pacific patients (HR 0.68  $P = 0.014$ ), although overall survival values were lower (6.5 months for sorafenib vs 4.2 months for placebo). Sorafenib, where approved, is now considered the standard systemic therapy for HCC patients with advanced disease [Llovet et al., 2008].

However, despite this advancement in treatment of HCC, the outcome for patients remains poor and there is an unmet need for patients who have progressed after or were unable to tolerate first-line sorafenib treatment. Additional efforts in understanding the molecular regulation and the identification of new molecular targets are needed.

Hepatocellular carcinoma ranks among the top 5 oncology conditions in terms of unmet need after pancreatic and lung cancer (Zitter Managed Care Oncology Index 2013) primarily due to a lack of targeted treatment options and high mortality rates. Major unmet needs include new therapies for second-line advanced HCC patients who progress on sorafenib and tailored therapy (stratification according to biomarkers).

The high AR expression in HCC combined with data in the literature suggesting a potential role of AR signaling in HCC progression as well as growth and the lack of therapeutic options, support the development of enzalutamide in this indication.

Enzalutamide given at 160 mg/day is the FDA and EMA approved dose for use in men with mCRPC. This dose has been evaluated and found to be well tolerated in subjects with impaired hepatic function and is also being evaluated in women with breast cancer. Placebo was selected as the comparative drug because there are no approved treatments for advanced HCC in patients who have progressed on or were intolerant of sorafenib or other antivascular endothelial growth factor (VEGF) inhibitors.

The above provides significant rationale for proceeding with this trial in the advanced HCC patient population.

## 2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

### 2.1 Study Objectives

#### 2.1.1 Primary Objective

The primary objective of this study is:

- To evaluate the efficacy of enzalutamide in subjects with advanced HCC, as measured by OS



### 2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety of enzalutamide in subjects with advanced HCC
- To evaluate the pharmacokinetics of enzalutamide and the active metabolite N-desmethyl enzalutamide in subjects with advanced HCC
- To evaluate Progression Free Survival (PFS) of enzalutamide as compared to placebo in subjects with advanced HCC

### 2.1.3 Exploratory Objectives

The exploratory objectives of this study are:

- [REDACTED]
- [REDACTED]
- [REDACTED]

## 2.2 Study Design and Dose Rationale

### 2.2.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled phase 2 study evaluating the efficacy, safety, and tolerability of enzalutamide monotherapy in 165 subjects in Europe, Asia and North America with HCC of any etiology who have progressed on or were intolerant to sorafenib or other anti-VEGF therapy in the advanced setting. Each region will have no more than 70% of overall subjects enrolled. Enrollment may be limited by the sponsor in any region or country in order to have representation of the patient populations from all 3 regions as there may be a difference in responses to treatment or tolerability.

The study will consist of a Screening Period, Treatment Period and a Follow-up Period. Eligible subjects will be stratified by geographic region (Asia versus others) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1) and randomized in a 2:1 ratio to receive enzalutamide 160 mg/day or placebo until disease progression, unacceptable toxicity, or any other discontinuation criterion is met. Study evaluations will occur as specified in the Schedule of Assessments.

An end of treatment visit will be performed within 7 days of the last dose of study drug. Upon discontinuation of treatment for any reason, subjects will enter the follow-up period. A follow-up visit will be performed approximately 30 days after the last dose of study drug. All AEs that occur during the safety reporting period (from the first dose of study drug through 30 days after the last dose of study drug or initiation of a new antineoplastic or new investigational agent, whichever occurs first) 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. This may be performed by telephone if applicable. Long-term follow-up visits will be conducted every 30 days for up to 2 years to collect information on survival and subsequent therapies.

During the study, study drug treatment may be interrupted for individual subjects who experience a National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade  $\geq 3$  AE that is attributed to the study drug and cannot be ameliorated with appropriate medical intervention. Study drug may be resumed at the original dose (160 mg/day) or at a reduced dose (120 mg/day or 80 mg/day), after discussion with and approval by the Medical Monitor. Treatment interruption for  $> 2$  weeks must also be discussed with the Medical Monitor.

There will be an initial safety review of the first 21 subjects. After the 21<sup>st</sup> randomized subject has been treated for 28 days or discontinued from the study (whichever occurs first), unblinded safety data will be evaluated by an independent Data Safety Monitoring Board (DSMB). Emerging safety issues may lead to a decision to change the dose, implement additional safety steps or assessments or terminate the study. Further safety review and details on the process and methods of the safety data review will be provided in the DSMB Charter.

### **2.2.2 Dose Rationale**

Enzalutamide given at 160 mg/day has been approved by the FDA and EMA for use in men with mCRPC. Pharmacokinetics and tolerability of enzalutamide in men and women are similar and there is no clinically meaningful difference in pharmacokinetics between subjects with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B and C, respectively) versus healthy volunteers after a single 160 mg dose of enzalutamide. Safety will be monitored on an ongoing basis. The first review of unblinded data will occur after 21 randomized subjects have been treated for 28 days or discontinued from the study (whichever occurs first). If warranted, a dose adjustment can be made based on the safety data review.

## **2.3 Endpoints**

### **2.3.1 Primary Endpoints**

The primary efficacy variable is OS. OS is defined as the time from the date of randomization until date of death from any cause.

### **2.3.2 Secondary Endpoints**

#### *Safety Endpoints:*

The safety of enzalutamide will be assessed on an ongoing basis by evaluation of AEs/serious AEs (SAEs), clinical safety laboratory tests, vital signs and other safety measures.

#### *Pharmacokinetic Endpoints:*

Predose plasma concentrations of enzalutamide and N-desmethyl enzalutamide will be analyzed.

*Efficacy Endpoints:*

- PFS, defined as the time from the date of randomization until the date of documented radiographic disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or death from any cause on study, whichever occurs first as assessed by the Investigator.

### 2.3.3 Exploratory Endpoints

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 3 STUDY POPULATION

### 3.1 Selection of Study Population

The study population will include male and female subjects with advanced (unresectable and/or metastatic) HCC with Barcelona Clinic Liver Cancer [BCLC] stage B or C of any etiology who have progressed on or were intolerant to sorafenib or other anti-VEGF therapy in the advanced setting and are not amenable to local therapies or any curative treatments. Subjects may have received 1 line of systemic therapy before or after sorafenib/anti-VEGF treatment.

### 3.2 Inclusion Criteria

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

1. Subject has consented and signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] for U.S. sites) prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).

2. Subject is  $\geq 18$  years of age or is considered an adult according to local regulation at the time of signing informed consent.
3. Subject has a documented diagnosis of advanced HCC of any etiology.
4. Subject has BCLC stage B or C.
5. Subject's lesions are not amenable to local therapies which may be beneficial, such as TACE, radiofrequency ablation, radiotherapy, etc., and the subject is not a candidate for any curative treatments such as resection or liver transplant.
6. Subject has hepatic function status of Child-Pugh Class A at Screening.
7. Subject has received prior systemic treatment for HCC with sorafenib or other anti-VEGF therapy and had confirmed disease progression or had discontinued treatment due to a drug-related toxicity. Subjects may have received 1 line of systemic therapy before or after sorafenib/anti-VEGF treatment
8. Subject has adequately recovered from toxicities due to prior HCC therapy to  $\leq$  grade 1.
9. Subject has an ECOG performance status  $\leq 1$  at Screening and on Day 1.
10. Subject has available formalin-fixed, paraffin-embedded tumor specimen with adequate viable tumor cells in a tissue block or unstained serial slides accompanied by an associated pathology report prior to enrollment. Archival or fresh biopsy tissue is required.
11. Subject has an estimated life expectancy of at least 3 months on Day 1, in the opinion of the Investigator.
12. Female subject is either:
  - Not of childbearing potential:
    - postmenopausal (defined as no spontaneous menses for at least 12 consecutive months prior to Screening with FSH  $> 40$  IU/L for women  $< 55$  years of age at Screening), or
    - documented surgically sterile or status posthysterectomy (at least 1 month prior to Screening).
  - Or, if of childbearing potential:
    - must have a negative urine pregnancy test at Screening and on Day 1 before the first dose of study drug is administered, and
    - must use 2 acceptable methods of birth control\* if sexually active from Screening through 3 months after the last dose of study drug.
13. Sexually active male subject and his female partner who is of childbearing potential must use 2 acceptable methods of birth control\* from Screening through 3 months after the last dose of study drug.

\*Two acceptable methods of birth control are as follows:

- Condom (barrier method of contraception);  
AND
- One of the following is required:
  - Placement of an intrauterine device (IUD) or intrauterine system (IUS) by the female subject or female partner of a male subject;
  - Additional barrier method: contraceptive sponge or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female subject or female partner of a male subject.
  - For male subject or male partner of female subject, vasectomy or other procedure resulting in infertility (e.g., bilateral orchiectomy) performed at least 6 months before Screening.
  - Tubal ligation in the female partner of a male subject performed at least 6 months before Screening.
  - Established and ongoing use of oral, injected, or implanted hormonal contraceptive by female partner of a male subject.

14. Female subject must not be breastfeeding at Screening or during the study period and for 3 months after final study drug administration.
15. Subject must agree not to donate sperm or ova from first dose of study drug through 3 months after the last dose of study drug.
16. Throughout the study, male subject must use a condom if having sex with a pregnant woman.
17. Subject must be able to swallow study drug and comply with study requirements.
18. 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. Subject has a severe concurrent disease, infection or comorbidity that, in the judgment of the Investigator, would make the subject inappropriate for enrollment.
2. Subject has fibrolamellar variant of HCC.
3. Subject has status of Child-Pugh Class B or C at Screening.
4. Subject has a history of organ allograft including liver transplant.
5. Subject has uncontrolled symptomatic ascites.
6. Subject has known or suspected brain metastasis or active leptomeningeal disease.

7. Subject has a history of a non-HCC malignancy with the following exceptions:
  - The subject with a previous history of a noninvasive carcinoma is eligible if in the opinion of the Investigator he/she has had successful curative treatment any time prior to Screening and requires no further therapy for the malignancy.
  - For all other malignancies, the subject is eligible if he/she has undergone potentially curative therapy and has been considered disease free for at least 3 years prior to Screening.
8. Subject has inadequate marrow, hepatic, and/or renal function at the Screening Visit defined as:
  - Absolute neutrophil count  $< 1.5 \times 10^9/L$  ( $< 1500$  cells/mm<sup>3</sup>)
  - Platelet count  $< 50 \times 10^9/L$  ( $< 50,000$  cells/mm<sup>3</sup>)
  - Hemoglobin  $< 8.5$  g/dL ( $< 5.3$  mmol/L)
  - INR  $> 1.7$
  - Albumin  $< 2.8$  g/dL ( $< 28$  g/L)
  - Total Bilirubin (TBL)  $> 2 \times$  ULN
  - AST or ALT  $> 5 \times$  ULN
  - Creatinine  $> 1.5 \times$  ULN

Note: Transfusions/infusions to meet eligibility criteria are not allowed but if in the opinion of the Principal Investigator, it is beneficial, the patient may be rescreened after receiving one of these procedures.
9. Subject has a history of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke, significant brain trauma, encephalopathy within 3 months of Day 1).
10. Subject has a history of bleeding esophageal varices within 3 months before the Day 1 visit.
11. Subject has a history of loss of consciousness or transient ischemic attack within 12 months before the Day 1 visit.
12. Subject has clinically significant cardiovascular disease including:
  - Myocardial infarction within 6 months before the Day 1 visit.
  - Uncontrolled angina within 6 months before the Day 1 visit.
  - Congestive heart failure New York Heart Association (NYHA) Class III or IV or history of congestive heart failure NYHA Class III or IV in the past, **UNLESS** a Screening echocardiogram or multi-gated acquisition scan performed within 3 months before the Day 1 visit reveals a left ventricular ejection fraction that is  $\geq 45\%$ .
  - History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, Torsade de Pointes).
  - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
  - Hypotension as indicated by systolic blood pressure  $< 86$  mmHg on 2 consecutive measurements at the Screening visit.

- Bradycardia (in the presence of known cardiovascular disease) as indicated by a heart rate of < 50 beats per minute on the Screening ECG recording.
  - Uncontrolled hypertension as indicated by systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg on 2 consecutive measurements at the Screening visit.
13. Subject has a gastrointestinal disorder affecting absorption.
  14. Subject had previous local therapy (e.g., surgery, radiation therapy, hepatic arterial therapy, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation) within 14 days prior to Day 1, has not recovered from toxicities from prior local therapy or may require major surgical procedure during the course of the study.
  15. Subject has received chemotherapy, immunotherapy or any other systemic anticancer therapy (including sorafenib) or any investigational drug within 14 days prior to the Day 1 visit.
  16. Subject has received an agent that either blocks androgen synthesis or targets the AR (e.g., abiraterone acetate, bicalutamide, enzalutamide, ARN-509 or other investigational AR signaling modulator). The exception of spironolactone is allowed after Medical Monitor consultation.
  17. Subject has used any of the following within 28 days before the Day 1 visit:
    - 5- $\alpha$  reductase inhibitors
    - Systemic androgens and estrogens (vaginal estrogen creams are allowed)
    - Herbal therapies, with an antitumor effect
  18. Subject has a known history of positive test for Human Immunodeficiency Virus.
  19. Subject has shown a hypersensitivity reaction to the active pharmaceutical ingredient or any of the enzalutamide capsule components, including caprylocaproyl polyoxylglycerides (Labrasol), butylated hydroxyanisole and butylated hydroxytoluene.
  20. Subject has addictive/substance abuse problems.
  21. Subject has any other condition or reason that, in the opinion of the Investigator interferes with the ability of the subject to participate in the trial, places the subject at undue risk or complicates the interpretation of safety data.

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

## **4 TREATMENT(S)**

### **4.1 Identification of Investigational Product(s)**

#### **4.1.1 Enzalutamide**

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

#### **4.1.2 Placebo**

The corresponding placebo is an opaque white to off-white oblong liquid-filled soft gelatin capsule for oral administration.

### **4.2 Packaging and Labeling**

Both enzalutamide and the corresponding placebo are supplied by APGD. Enzalutamide and placebo will be packaged in high-density polyethylene bottles with child-resistant induction seal closure. There are 124 capsules per bottle. All medication used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at APGD- Astellas United States Technologies (AUST) or Sponsor's designee in accordance with APGD-AUST or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

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

A qualified person of Astellas Pharma Europe B.V. (APEBV) or Sponsor's designee will perform the final release of the medication according to Directive 2003/94/EC annex 13.

### **4.3 Study Drug Handling**

Enzalutamide and the corresponding placebo will be stored in a secure 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 (e.g., pharmacist), and:

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

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



- The Investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The Investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the Investigator to dispense these test drugs.
- A study drug inventory will be maintained by the Investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the Investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return study drug to the Sponsor or designee at the end of the study or upon expiration.

#### **4.4 Blinding**

This is a double-blind study. Subjects will be randomized to receive enzalutamide or placebo in a double-blind fashion such that the Investigator, Sponsor's study management team, clinical staff nor the subject will know which agent is being administered. The randomization number will be assigned based on information obtained from the Interactive Response Technology (IRT).

##### **4.4.1 Confirmation of the Indistinguishability of the Study Drugs**

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

##### **4.4.2 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking**

The randomization list and study medication blind will be maintained by the IRT system. The DSMB will be provided access to the treatment assignment for periodic review of the unblinded data as documented in the DSMB Charter.

##### **4.4.3 Breaking the Treatment Code for Emergency**

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file. They must only be requested by the Investigator or other persons designated as sub-Investigators. No subjects or other study personnel will be

made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure.

Unblinding of the study medication should only be considered for subject safety or when critical therapeutic decisions are contingent upon knowing the blinded study drug assignment. Any unblinding by the investigational staff must be reported immediately to the Sponsor and must include an explanation of why the study medication was unblinded. If possible, the Sponsor should be contacted prior to unblinding of the study medication.

#### **4.4.4 Breaking the Treatment Code by the Sponsor**

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

### **4.5 Assignment and Allocation**

Subjects will be entered into the IRT system at Screening and assigned a number. Subjects who meet inclusion/exclusion criteria will be stratified by geographic region (Asia versus other) and ECOG performance status (0 versus 1) and randomized in a 2:1 ratio to receive enzalutamide 160 mg/day or placebo on Day 1. Randomization will be performed via 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 IRT procedures manual.

## **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**

Eligible subjects will receive enzalutamide 160 mg/day (4 x 40 mg capsules) or placebo until disease progression, unacceptable toxicity, or any other discontinuation criteria are met. Best supportive care will be given to all subjects in addition to study drug. Best supportive care may include medications and supportive measures deemed necessary per Investigator's discretion to palliate disease-related symptoms and improve quality of life. Subjects on strong CYP2C8 (e.g., gemfibrozil) inhibitor should start study drug at 80mg/day after consultation with the Medical Monitor, if coadministration cannot be avoided.

Study drug will be self-administered at home by the subject, except for visit days where pharmacokinetic samples are collected. On visit days with pharmacokinetic sampling, study drug will be administered in clinic after the pharmacokinetic sample is collected. Subjects will keep a diary to record the date and time of study drug dose on the 2 days before pharmacokinetic visit days.

Subjects should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed. For the purposes of this study, a “missed dose” is considered a dose not administered within 4 hours of the regular dosing time.

Subjects may take study drug with or without food. Subjects must swallow capsules whole. Study drug may not be chewed, dissolved or capsules opened.

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

During the study, study drug treatment may be interrupted for individual subjects who experience a NCI CTCAE Grade  $\geq 3$  AE (except LFT AEs) that is attributed to the study drug and cannot be ameliorated with appropriate medical intervention. Study drug may be resumed at the original dose (160 mg/day) or at a reduced dose (120 mg/day or 80 mg/day), after discussion with and approval by the Medical Monitor. Treatment interruption for  $> 2$  weeks must also be discussed with the Medical Monitor. The Sponsor may make a decision to change the dose based on recommendation from the DSMB’s safety review.

#### **5.1.2.1 Dose Modification Plan for LFT Changes**

Study drug dosing should be interrupted if a subject experiences clinically significant liver toxicity related to study drug ( $\geq$  Baseline + 4 x ULN to  $< 20$  x ULN for AST and ALT; grade 3 TBL). Testing should be repeated at Investigator’s discretion but at a minimum weekly to ensure that the subject’s LFT’s are returning to acceptable levels. If the subject’s toxicity resolves within 14 days to either  $\leq$  grade 1 (if normal at baseline) or no more than 1 grade above baseline (but no higher than grade 2), study drug may be reintroduced at a dose of 120 mg/day in consultation with the Medical Monitor. If the toxicity has not resolved within 14 days (as defined by either  $\leq$  grade 1 or no more than 1 grade above screening but no higher than grade 2), then the Medical Monitor must be consulted to determine if further interruption is permitted.

If any drug-related liver toxicity requiring dose interruption recurs or develops despite the initial dose reduction to 120 mg/day, the LFT monitoring instructions above should be followed and the study drug may be reintroduced at a dose of 80 mg/day. If any drug-related liver toxicity recurs at the reduced dose of 80 mg/day, the study drug should be discontinued.

Study drug must be discontinued for subjects with study drug related grade 4 LFTs (AST, ALT and TBL).

**Table 2 Dose Modification Table for Drug-Related Liver Toxicities**

NCI CTCAE V4.03	Dose Interruption	Dose Reduction
<b>Grade 1 (AST, ALT, TBL)</b>	No Change	No Change
<b>Grade 2 to &lt; Baseline + 4 x ULN (AST and ALT)</b>	No Change	No Change
<b>Grade 2 (TBL)</b>	No Change	No Change
<b>≥ Baseline + 4 x ULN and below 20 x ULN (AST and ALT)</b>	Hold until grade 1 or, if event was grade 1 or 2 at screening, until returns to grade 2 or lower. If it takes over 14 days to reduce toxicity to acceptable levels then the MM should be consulted	1st episode – reduce to 120 mg/ day 2nd episode – reduce to 80 mg/day 3rd episode – Discontinue treatment
<b>Grade 3 (TBL)</b>	Hold until grade 1 or, if event was grade 2 at screening, until returns to grade 2 or lower. If it takes over 14 days to reduce toxicity to acceptable levels then the MM should be consulted	1st episode – reduce to 120 mg/day 2nd episode – reduce to 80 mg/day 3rd episode – Discontinue treatment
<b>Grade 4 (AST, ALT, TBL)</b>	Discontinue Treatment	Discontinue Treatment

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; NCI CTCAE: National Cancer Institute Common Toxicity Criteria for Adverse Events; TBL: total bilirubin; ULN: upper limit or normal

Note: For any Grade 3 or 4 hepatic toxicity that does not resolve within 14 days to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 if liver infiltration with tumor present), an abdominal CT scan should be performed to assess if the event is related to disease progression. Subjects with a history of viral hepatitis and an ALT or AST ≥ Baseline + 4 x ULN while on treatment should have a hepatitis B and C viral loads performed per institutional guidelines to check for possible reactivation.

For Grade 4 LFTs (AST, ALT, TBL), increases related to the underlying disease or other nonstudy drug related causes, the Investigator in consultation with the Medical Monitor may consider holding study drug until values return to baseline or lower.

### 5.1.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

Medications taken within 14 days before the Screening visit and up to the 30-Day Follow-up visit will be documented on the appropriate case report form.

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

Subject with viral etiology (HCV, HBV) should be on stable doses of antiviral therapy at the time of study entry, if the Investigator feels these are of benefit to the subject. The Investigator should consult with Medical Monitor if initiation of antiviral therapy is deemed necessary during the study.

Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided if possible as enzalutamide may

decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted.

Coadministration of enzalutamide with strong CYP2C8 inhibitors should be avoided. If coadministration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, the enzalutamide dose should be reduced to 80 mg/day. If coadministration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used before initiation of the strong CYP2C8 inhibitor.

Subject should avoid use of any herbal medications or dietary supplements including products containing *Hypericum perforatum* (e.g., St. John's wort).

The following medications or therapies are prohibited during the receipt of study drug:

- Medications, including herbal therapies, with an antitumor effect
- Any investigational agent
- AR antagonists (e.g., bicalutamide, flutamide, nilutamide), however, spironolactone initiation during the study is allowed after Medical Monitor consultation
- 5- $\alpha$  reductase inhibitors (e.g., finasteride, dutasteride)
- Systemic androgens and estrogens (vaginal estrogen creams are allowed)

#### **5.1.4 Treatment Compliance**

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

Treatment compliance should be monitored closely as sites will perform accountability of study drug doses dispensed and returned and deviation in overall compliance < 80% should be reported to the Sponsor.

## **5.2 Demographics and Baseline Characteristics**

### **5.2.1 Demographics**

Demographic information will be collected at Screening for all subjects and will include age or date of birth, sex, race, ethnicity (as local regulations allow) and history of smoking and alcohol use.

### **5.2.2 Medical History**

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

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

Diagnosis of advanced HCC will be captured including dates of diagnosis, etiology and the presence/absence of cirrhosis. Prior systemic treatment for advance HCC with sorafenib or other anti-VEGF therapy and confirmed disease progression or discontinuation of sorafenib

due to intolerance will also be collected. BCLC stage (Appendix 12.4) and the Child-Pugh class status (Appendix 12.5) will be documented during Screening.

## 5.3 Efficacy and Pharmacodynamics Assessments

### 5.3.1 Efficacy Assessment

#### 5.3.1.1 Survival Status and Subsequent Therapies

Subjects who are alive after the completion of the 30-day Follow-up Visit will continue to be contacted by site personnel for long-term survival follow-up every 30 days. This assessment may be conducted by telephone if the subject is unable to travel. Information on survival status and subsequent therapies will be obtained. Follow-up will continue for up to 2 years after the 30-day Follow-up Visit or until the final analysis.

#### 5.3.1.2 Radiographic Assessment

Disease response and progression will be evaluated in this study using the RECIST criteria (version 1.1, 2009) and assessed by the Investigator. Radiographic imaging technique will be performed using either diagnostic CT scan or MRI with contrast.

Imaging may be performed at any time to confirm suspected progression of disease. Assessment will include tumor measurements for target lesions, nontarget lesions and assessment for any new lesions. An overall assessment will be characterized for each time point evaluation. At the end of study for that subject, the overall best response to the study regimen will be characterized. Refer to Appendix 12.7 RECIST v1.1 for additional details.

Baseline imaging performed prior to informed consent may be used so long as it is performed within 28 days prior to Day 1. Subsequent scans including chest/abdominal/pelvic imaging will be done every 8 weeks ( $\pm$  7 days) from Day 1 until disease progression or other discontinuation criterion is met. Scans should be done every 8 weeks regardless of treatment interruption or delays. To ensure comparability, the radiology/scans throughout the study should be performed using identical techniques (e.g., scans performed immediately following bolus contrast administration should be made with a standard volume of contrast, the identical contrast agent and preferably the same scanner). The same method should be employed and assessed by the same individual on each occasion, when possible.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 5.3.2.3 [REDACTED]

[REDACTED]

### 5.4 Safety Assessment

#### 5.4.1 Height and Weight

Height and weight will be measured using standard institution practice and equipment.

#### 5.4.2 Vital Signs

Vital signs will include systolic and diastolic blood pressure (mmHg), radial pulse (beats/min) and temperature. All vital signs will be measured with the subject in the sitting or supine position.

#### 5.4.3 Adverse Events

All observed or spontaneously reported AEs will be documented within the source. The Investigator will avoid asking leading questions to influence the reporting of AEs.

AE collection will begin at the time the informed consent form (ICF) is signed and continue through to 30 days after the last dose date of study drug or initiation of a new antineoplastic or new investigational agent, whichever comes first.

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

#### **5.4.4 Laboratory Assessments**

Routine laboratory samples for hematology, chemistry, coagulation, viral load (if applicable), pregnancy and urinalysis will be collected and analyzed at the Institution's local laboratory. The local laboratory must be accredited to perform the protocol required tests and a certificate of accreditation and laboratory normal ranges must be provided to the Sponsor. Please refer to Appendix 12.8 Laboratory Assessments for a listing of analytes to be assessed.

#### **5.4.5 Physical Examination**

Standard, full physical examinations will be performed at Screening and Day 1 to assess general appearance, skin, eyes, ears, nose, throat neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status, and lymphatic systems. Genitourinary and rectal system examinations are to be performed only if clinically indicated. After Day 1, a brief symptom directed physical examination may be performed.

New or worsening clinically significant findings on physical exam will be recorded as AEs if they meet the criteria in Section 5.5.1 Definition of Adverse Events.

#### **5.4.6 Electrocardiogram (ECG)**

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

ECG should be obtained after the subject has rested quietly and is awake in a fully supine position or semi-recumbent, if supine not tolerated) for 10 minutes.

All on-treatment ECGs will be obtained prior to drug administration. Whenever a study procedure coincides with the scheduled time point for an ECG, the study activities are ideally undertaken in a fixed sequence: ECG first, vital signs.

### **5.5 Adverse Events and Other Safety Aspects**

#### **5.5.1 Definition of Adverse Events (AEs)**

AEs will be collected from the time of consent until 30 days after the last dose of study drug or initiation of a new antineoplastic or new investigational agent, whichever comes first. An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the



Investigator's responsibility to ensure that these AEs or other reporting requirements are followed and the information is appropriately recorded in the source data accordingly.

Adverse events are events that begin or worsen from the time of informed consent through the 30-day Follow-up Period or initiation of a new antineoplastic or new investigational agent, whichever comes first. Treatment-emergent AEs (TEAEs) are events that begin or worsen from the date of first study drug administration through the 30-day Follow-up Period or initiation of new treatment, whichever comes first.

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 AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

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

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

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

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

All of the events of interest noted above should be documented within the source. Any situation involving these events of interest that also meets the criteria for an SAE should be handled as described in Section 5.5.5 Reporting of Serious Adverse Events.

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

### 5.5.3 Criteria for Causal Relationship to the Study Drug

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

Causal relationship to the study drug	Criteria for causal relationship
Not related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on readministration (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 NCI CTCAE guidelines (Version 4.03). The items that are not stipulated in the NCI CTCAE Version 4.03 will be assessed according to the criteria below and will be documented within the source:

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 SAE, which will be collected from signing of the ICF until 30 days after last study drug administration, the Investigator must contact the Sponsor by telephone, fax or email immediately (within 24 hours of awareness).

The Investigator should complete and submit an SAE Worksheet containing all information that is required by the regulatory authorities to the Sponsor by fax or email immediately (within 24 hours of awareness). If the faxing or emailing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact shown in Section II Contact Details of Key Sponsor's Personnel should be informed by telephone.

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

Astellas Pharma Global Development – United States  
Pharmacovigilance  
Fax number: +1 847 317 1241  
Email: [safety-us@astellas.com](mailto: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 electronic case report form (eCRF).

The following minimum information is required:

- International Study Number (ISN)/Clinical 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., Investigational New Drug [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 IRB/IEC within timelines set by regional regulations (i.e., EU, eCTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The Sponsor will notify all Investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements (IRB/IEC / head of the study site).

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

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

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

#### **5.5.6 Follow-up of Adverse Events**

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

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

#### **5.5.7 Monitoring of Common Serious Adverse Events**

Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in Appendix 12.2 Common Serious Adverse Events. The list does NOT change the Investigator's 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 the Investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs" as specified in Appendix 12.2 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 female subject or partner of a male subject becomes pregnant during treatment, this should be reported as if it was an SAE (refer to Section 5.5.8 Procedure in Case of Pregnancy). Administration of study drug must be discontinued in case evidence of pregnancy is obtained during the treatment period. 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. Should the partner of the male subject become pregnant, a separate ICF will be submitted for IRB/IEC review and approval that, upon signing by the pregnant female, will allow medical supervision during the pregnancy and allow follow-up after the birth of the infant.

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

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

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

### **5.5.9 Emergency Procedures and Management of Overdose**

If an overdose of enzalutamide occurs, the Medical Monitor must be contacted. An overdose is defined as any dose greater than the protocol-specified dose of enzalutamide 160 mg once daily. In the event of an overdose, stop treatment with study drug and initiate general supportive measures taking into consideration the enzalutamide  $t_{1/2}$  of 5.8 days.

Neither the effects of overdose of enzalutamide nor an antidote to overdose are known. Subjects may be at increased risk of seizures following an overdose of enzalutamide.

All overdose events are to be reported within 24 hours of awareness by the study site per Section 5.5.2, whether or not the event meets AE criteria.

### **5.5.10 Supply of New Information Affecting the Conduct of the Clinical Study**

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

The Investigator will also inform the subjects, who will be required to sign an updated ICF in order to continue in the clinical study.

## **5.6 Test Drug Concentration**

### **5.6.1 Pharmacokinetic Assessments**

Plasma samples will be analyzed to determine enzalutamide and N-desmethyl enzalutamide concentrations in all subjects treated in the study. In addition, inactive metabolite (M1) of enzalutamide may be analyzed. Pharmacokinetic samples will be obtained before study drug dosing. Blood samples will be collected from a vein or port that is not used for drug infusions. Blood sampling, processing, storage and shipment instructions are provided in a lab manual. Samples will be shipped to and analyzed by a Sponsor designated analytical laboratory.

## **5.7 Other Measurements, Assessments or Methods**

### **5.7.1 Blood Sample for Future Pharmacogenomics (PGx) Analysis (Retrospective PGx Analysis)**

A PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues. After randomization (see schedule of assessments), approximately 5 mL sample of whole blood for possible retrospective PGx analysis will be collected using a vacutainer tube containing ethylenediaminetetraacetic acid. After collection, gently invert the blood sample 8 to 10 times. The blood collection tube may either be stored upright at 4°C for up to 5 days prior to shipment or stored frozen at -20°C or below at the site for extended storage. Samples will be shipped to a Sponsor designated banking contract research organization (CRO).

Labels should uniquely identify each sample and contain at least:

- Protocol number (9785-CL-3021),
- Subject number, and
- Purpose and biological matrix (i.e., “biobanking”, “whole blood”).

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See Appendix [12.3](#) Retrospective PGx Sub-study for further details on the banking procedures.

## **5.8 Total Amount of Blood**

The total amount of blood for each subject will vary depending on the course of their disease, duration on treatment, and local laboratory requirements. At any time during the study, if any laboratory abnormalities are found for a subject, additional blood may be drawn for monitoring.

The maximum amount of blood estimated over any approximate 3 month period is from Day 1 through Week 13 where approximately 89.5 mL may be drawn.

## **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 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 or for reasons of gross noncompliance.

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.

Discontinuation Criteria from Treatment for Individual Subjects:

- Evidence of symptomatic and radiographic disease progression per Investigator's assessment.
- Subject develops an unacceptable drug-related AE, based on the opinion of the Investigator and in consultation with the Medical Monitor
- Seizure of any grade.
- Subject's disease becomes amenable to local or curative treatments.
- Subject is lost to follow up despite reasonable efforts by the Investigator to locate the subject
- There is a significant protocol violation or non-compliance that occurs with a subject that compromises study objectives or subject safety.
- Female subject becomes pregnant
- Subject's death
- Increased liver function tests per discontinuation criteria in Section 5.1.2.1 Dose Modification Plan for LFT Changes

Discontinuation Criteria from Post-Treatment Follow Up for Individual Subjects:

- Subject withdraws consent for further study participation
- Subject is lost to follow up despite reasonable efforts by the Investigator to locate the subject
- Subject's death

### **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.

A DSMB will be used to monitor safety during the study. Emerging safety issues may lead to a decision to terminate the study.

## **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 drafted before first subject enrolled and finalized before the database soft lock. Any changes from the analyses planned in SAP will be justified in the clinical study report.

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

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

### **7.1 Sample Size**

This sample size was primarily determined to provide sufficient clinical experience to support the design of later-stage clinical development, such as phase 3 studies.

Sample size calculations were performed using EAST 5 software based on the following assumptions:

- 2:1 randomization for enzalutamide vs placebo.
- Median OS for placebo and enzalutamide are 7.0 months and 10.77 months (HR=0.65), respectively.
- A study enrollment period of 18 months and a total study duration of 27 months.

With 109 death events, the study can achieve 80% power to detect a statistically significant difference using 1-sided log-rank test with 10% level of significance. Assuming no loss to follow-up, approximately 144 subjects were originally planned to reach this number of events.

### **7.2 Analysis Set**

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



### **7.2.1 Full Analysis Set (FAS)**

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

### **7.2.2 Safety Analysis Set (SAF)**

For the statistical summary of the safety data, the SAF will be used. The SAF consists of all subjects who took at least one capsule of study medication, and will be used for safety analyses using the actual treatment received.

### **7.2.3 Pharmacokinetic Analysis Set (PKAS)**

The PKAS is defined as the subset of the SAF population for which at least one quantifiable enzalutamide and N-desmethyl enzalutamide concentration value from the same predose sample is available.

### **7.2.4 Pharmacodynamic Analysis Set (PDAS)**

The pharmacodynamic analysis set (PDAS) will include the subjects from the SAF population for whom sufficient pharmacodynamic measurements (a baseline and at least one post baseline value) were collected. The PDAS will be used for all analyses of pharmacodynamic data.

Any formal definitions for exclusion of subjects from the PDAS will be documented in the Classification Specifications.

## **7.3 Demographics and Other Baseline Characteristics**

Demographics and other baseline characteristics will be summarized by treatment group for the FAS and if different for the SAF. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

## **7.4 Analysis of Efficacy**

Efficacy analysis will be conducted on the FAS.

### **7.4.1 Analysis of Primary Endpoint**

#### **7.4.1.1 Primary Analysis**

The primary endpoint, OS will be defined as the time from the date of randomization until the documented date of death from any cause. Subjects who are still alive at the time of the data cutoff date will be censored on the last date known to be alive or at the data cutoff date, whichever occurs first. The null hypothesis is that OS distributions of the 2 arms are equivalent. The alternative hypothesis is that OS is prolonged in enzalutamide arm. The null hypothesis will be tested using a stratified one-sided log-rank test at the 0.10 level (stratified by geographic region and ECOG performance status). The hazard ratio of the treatment effect along with two-sided 95% CI will also be calculated using a Cox proportional hazard model.

#### **7.4.1.2 Secondary Analysis**

A sensitivity analysis of the primary endpoint will be performed using the unstratified test.

#### **7.4.1.3 Subgroup Analysis**

The same analysis of the primary endpoint as described in Section 7.4.1.1 will be conducted using the subgroup of AR+ (defined as  $\geq 10\%$  of tumor cells with nuclear expression) patients and other subgroups such as age, gender, geographic region, ECOG status and etiology. Results will be presented as forest plots.

#### **7.4.2 Analysis of Secondary Endpoints**

Similar analysis of the primary endpoint as described in Section 7.4.1.1 will also be conducted on the secondary endpoint PFS. Patients who have not progressed or died before the data cutoff date for analysis will be censored at the date of last disease assessment which is the date of last scan. Detailed rules for censoring will be provided in the SAP.

#### **7.4.3 Analysis of Exploratory Endpoints**

[REDACTED]

### **7.5 Analysis of Safety**

#### **7.5.1 Adverse Events**

Safety will be assessed through descriptive statistics for the frequency of TEAEs by system organ class, preferred term, and the NCI CTCAE grade, the frequency of treatment discontinuations due to AEs, vital signs, ECG and laboratory evaluations.

The severity of all AEs is to be evaluated by the Investigator based on the NCI CTCAE, version 4.03. All AEs will be coded to preferred term and system organ class using MedDRA. The number and percentage of subjects with TEAEs will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and NCI CTCAE grade. TEAE is defined as an AE observed during the treatment-emergent period, which is from the first dose date of study drug to 30 days after the last dose date of study drug or the start of subsequent treatment, whichever is first. A subject reporting the same AE more than once is counted once and at the maximum severity or strongest relationship to study drug treatment, when calculating incidence.

The number and percentage of TEAEs, serious TEAEs, AEs leading to discontinuation and TEAEs related to study drug will be summarized by system organ class, preferred term and treatment group. The number and percentage of TEAEs by severity will also be summarized. All AEs will be listed.

### 7.5.2 Laboratory Assessments

Laboratory data consist of hematology, chemistry, coagulation, viral load (if applicable), pregnancy and urinalysis test results. Where applicable, NCI CTCAE version 4.03 will be used to categorize toxicity grades for the laboratory parameters. Laboratory shift tables compared to baseline results for each subsequent visit will be produced. For each laboratory parameter, the baseline laboratory value is defined as the last laboratory value collected on or prior to the first dose date of study drug.

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment group and time point. Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings.

### 7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign and body weight results, including change from baseline, by treatment group and time. Categorical analysis will be done by means of frequency tables of relevant decrease or increase in the vital sign values. Vital signs and body weight data will be displayed in listings.

### 7.5.4 Physical Examination

Physical examination will be listed by treatment group.

### 7.5.5 ECGs

The 12-lead ECG results will be summarized by treatment group and time point. Abnormalities and clinical significance as judged by the Investigator will be reported as well.

## 7.6 Analysis of Pharmacokinetics

Pharmacokinetic analysis will be conducted using the pharmacokinetic analysis set (PKAS). The PKAS is defined as the subset of the SAF population for which at least one quantifiable enzalutamide and N-desmethyl enzalutamide concentration value from the same predose sample is available. The enzalutamide and N-desmethyl enzalutamide concentration-time data will be summarized by descriptive statistics at each visit. Additional model-based analyses may be performed but will be reported separately.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 7.7.2

## 7.8 Protocol Deviations and Other Analyses

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

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

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

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

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

## 7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)

There is no planned interim analysis; however, there will be periodic safety reviews throughout the study. After the 21<sup>st</sup> randomized subject has been treated for 28 days or has discontinued from the study (whichever occurs first), unblinded safety data will be evaluated by an independent DSMB. Further safety reviews and details on the process and methods of the safety data review will be provided in the DSMB Charter.

## 7.10 Handling of Missing Data, Outliers, Visit Windows and Other Information

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

Further details including the definitions for windows to be used for analyses by visit, will be described in the SAP.

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

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

Analytical laboratory tests for pharmacokinetic and pharmacodynamic measures will be collected and managed by Sponsor designated vendors during the study. Laboratory data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

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

#### **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 within the source records:

- Demographic data (age, sex, race, ethnicity, height and body weight, history of smoking and alcohol use)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated 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 medications
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- 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 CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the Investigator/sub-Investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

### **8.1.4 Direct Access to Source Data/Documents**

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

### **8.1.5 Data Management**

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

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)**

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

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

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

### **8.2.2 Ethical Conduct of the Study**

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

### **8.2.3 Informed Consent of Subjects**

#### **8.2.3.1 Subject Information and Consent**

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

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

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

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



#### **8.2.4 Subject Confidentiality**

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

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

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number 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 obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., Health Insurance Portability and Accountability Act).

### **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 New Drug Application (NDA) or discontinuation of the IND application. The Sponsor will notify the site/Investigator if the NDA/Marketing Authorisation Application/Japanese NDA is approved or if the IND/Investigational Medical Product Dossier/Clinical Trial Notification (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 and/or nonsubstantial). Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the Investigator, the regulatory authority and the IRB/IEC (if applicable). Amendments to this protocol must be signed by the Sponsor and the Investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

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

### **8.3.4 Insurance of Subjects and Others**

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

### **8.3.5 Signatory Investigator for Clinical Study Report**

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

## **9 QUALITY ASSURANCE**

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

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

## **10 STUDY ORGANIZATION**

### **10.1 Data and Safety Monitoring Board (DSMB)**

A DSMB will evaluate the unblinded safety data of the first 21 patients enrolled and then on periodic basis during the study. After the 21<sup>st</sup> randomized subject has been treated for 28 days or discontinued from the study (whichever occurs first). DSMB members will be clinicians (who are not Investigators for this trial and not an APGD employee) with expertise in HCC oncology trials. A separate DSMB charter will outline safety review details, processes and methods to be followed.

### **10.2 Other Study Organization**

Not applicable.

## 11 REFERENCES

- Arreita O, Cacho B, Morales-Espinosa D, Ruelas-Villavicencio A, Flores-Estrada D, Hernández-Pedro N. The progressive elevation of alpha fetoprotein for the diagnosis of hepatocellular carcinoma in patients with liver cirrhosis. *BMC Cancer*. 2007;7:28.
- Brahm J, Brahm M, Segovia R, Latorre R, Zapata R, Poniachik J, et al. Acute and fulminant hepatitis induced by flutamide: case series report and review of the literature. *Ann Hepatol*. 2011;10:93-8.
- Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol*. 2012;57:821-9.
- Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10:25-34.
- Chui CM, Yeh SH, Chen PJ, Kuo TJ, Chang CJ, Chen PJ, et al. Hepatitis B virus X protein enhances androgen receptor-responsive gene expression depending on androgen level. *Proc Natl Acad Sci USA*. 2007;104:2571-8.
- EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*. 2012;56:908-43.
- Feng H, Cheng ASL, Tsang DP, Li MS, Go MY, Cheung YS, et al. Cell cycle-related kinase is a direct androgen receptor-regulated gene that drives  $\beta$ -catenin/T cell factor-dependent hepatocarcinogenesis. *J Clin Invest*. 2011;121:3159-75.
- Gomez JL, Dupont A, Cusan L, Tremblay M, Suburu R, Lemay M, et al. Incidence of liver toxicity associated with the use of flutamide in prostate cancer patients. *Am J Med*. 1992;92:465-70.
- Investigator's Brochure. Enzalutamide (MDV3100) for the treatment of cancer.
- Jiang X, Kanda T, Nakamoto S, Miyamura T, Wu S, Yokosuka O. Involvement of androgen receptor and glucose-regulated protein 78 kDa in human hepatocarcinogenesis. *Exp Cell Res*. 2014;323:326-36.
- Liu WC, Liu QY. Molecular mechanisms of gender disparity in hepatitis B virus-associated hepatocellular carcinoma. *World J Gastroenterol*. 2014;20:6252-61.
- Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378-90.
- Ma WL, Hsu CL, Wu MH, Wu CT, Wu CC, Lai JJ, et al. Androgen receptor is a new potential therapeutic target for the treatment of hepatocellular carcinoma. *Gastroenterology*. 2008;135:947-55.
- Nagasue N, Chang YC, Hayashi T, Galizia G, Kohno H, Nakamura T, et al. Androgen receptor in hepatocellular carcinoma as a prognostic factor after hepatic resection. *Ann Surg*. 1989;209:424-27.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines<sup>®</sup>) hepatobiliary cancers: version 1. 2013. 94 pp.

Wang SH, Yeh SH, Lin WH, Wang HY, Chen DS, Chen PJ. Identification of androgen response elements in the enhancer I of hepatitis B virus: a mechanism for sex disparity in chronic hepatitis B. *Hepatology*. 2009;50:1392-402.

Wu MH, Ma WL, Hsu CL, Chen YL, Ou JH, Ryan CK, et al. Androgen receptor promotes hepatitis B virus-induced hepatocarcinogenesis through modulation of hepatitis B virus RNA transcription. *Sci Transl Med*. 2010;2:32ra35.

Yu MW, Yang YC, Yang SY, Cheng SW, Liaw YF, Lin SM, et al. Hormonal markers and hepatitis B virus-related hepatocellular carcinoma risk: a nested case-control study among men. *J Natl Cancer Inst*. 2001;93:1644-51.

Zitter Health Insights. The managed care oncology index: Winter 2013. 147 pp.

## 12 APPENDICES

### 12.1 List of Excluded Concomitant Medications

The following medications or therapies are prohibited during the receipt of study drug:

- Medications, including herbal therapies, with an antitumor effect (Use of luteinizing hormone-releasing hormone agonist used to induce menopause in women of childbearing potential is permitted).
- Any investigational agent
- AR antagonists (e.g., bicalutamide, flutamide, nilutamide) however, spironolactone initiation during the study is allowed after Medical Monitor consultation
- 5- $\alpha$  reductase inhibitors (e.g., finasteride, dutasteride)
- Systemic androgens and estrogens (vaginal estrogen creams are allowed)
- Megestrol acetate for appetite stimulation may be used at Investigator discretion.

Subject should avoid use of any herbal medications or dietary supplements including products containing *Hypericum perforatum* (e.g., St. John's wort).

Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted.

Coadministration of enzalutamide with strong CYP2C8 inhibitors should be avoided. If coadministration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, the enzalutamide dose should be reduced to 80 mg/day. If coadministration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used before initiation of the strong CYP2C8 inhibitor.

Refer to the following website for a complete list:

<http://medicine.iupui.edu/clinpharm/ddis/main-table>

## 12.2 Common Serious Adverse Events

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

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

- Weight loss
- Decreased appetite/Anorexia
- Asthenia / Fatigue/general weakness
- Nausea
- Vomiting
- Jaundice
- Abdominal pain
- Ascites
- Cancer pain
- Hepatomegaly
- Metastatic liver cancer
- Metastases to lung
- Metastases to peritoneum
- Metastases to abdominal lymph nodes
- Metastases to bone
- Bone pain

## **12.3 Retrospective PGx Sub-Study**

### **INTRODUCTION**

PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by one or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

### **OBJECTIVES**

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

### **SUBJECT PARTICIPATION**

Subjects who have consented to participate in this study may participate in this PGx sub-study. As part of this sub-study, subjects must provide separate written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

### **SAMPLE COLLECTION AND STORAGE**

Subjects who consent to participate in this sub-study will provide one approximately 5 mL tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

### **PGx ANALYSIS**

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis in case evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety.

### **DISPOSAL OF PGx SAMPLES / DATA**

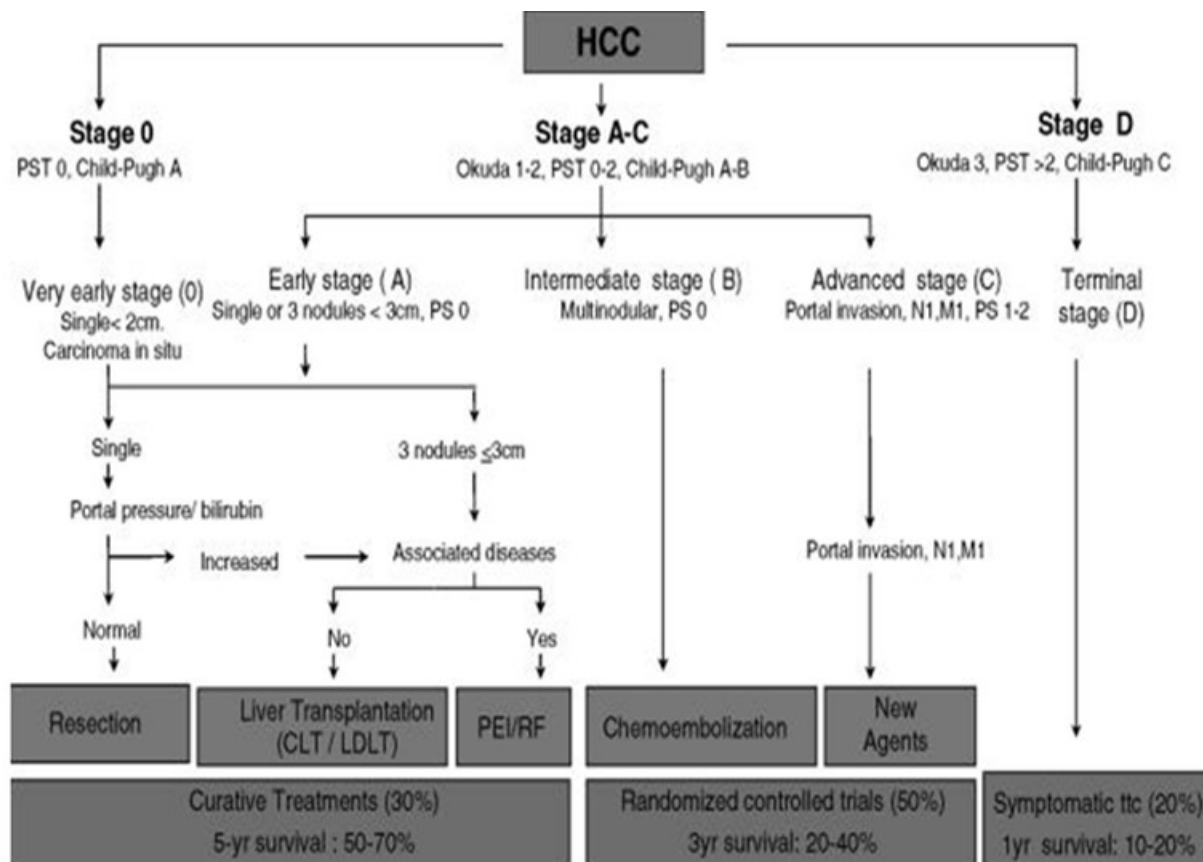
All PGx samples collected will be stored for a period of up to 15 years following study database hard lock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.



## **INFORMATION DISCLOSURE TO THE SUBJECTS**

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any Investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

## 12.4 Barcelona Clinic Liver Cancer Staging System



### Reference

Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362:1907-17.

## 12.5 Child-Pugh Classification of Severity of Liver Disease

A total score of 5-6 is considered Class A (well-compensated disease), 7-9 is Class B (significant functional compromise) and 10-15 is Class C (decompensated disease).

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

Measure	1 point	2 points	3 points
Total bilirubin, $\mu\text{mol/L}$ (mg/dL)	< 34 (< 2)	34-50 (2-3)	> 50 (> 3)
Serum albumin, g/L	> 35	28-35	< 28
Prothrombin time/International normalized ratio	< 1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

## 12.6 ECOG Performance Status Scale

### GRADE

- 0 Fully active, able to carry on all predisease performance without restriction.
- 1 Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, (e.g., light housework, office work).
- 2 Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

## 12.7 RECIST v1.1

### Objective Response Criteria (RECIST)

All patients will have their BEST RESPONSE on study classified as outlined below:

**Complete Response (CR):** Disappearance of all target and nontarget lesions including normalization of elevated tumor marker level. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm. All nontarget lymph nodes must be nonpathological in size (< 10 mm short axis).

**Partial Response (PR):** At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD.

**Stable Disease (SD):** Steady state of disease; neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameters of target lesions while on study. There may be no appearance of new lesions for this category.

**Progressive Disease (PD):** At least a 20% increase (and an absolute increase of at least 5 mm) in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute PD. In exceptional circumstances, unequivocal progression of nontarget lesions may be accepted as evidence of disease progression.

**NonCR/NonPD:** Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

### *Summary of RECIST v1.1 Response Criteria*

Target Lesions	Nontarget Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
CR	CR	No	CR	
CR	NonCR/NonPD	No	PR	
CR	Not evaluated	No	PR	
PR	NonPD or not all evaluated	No	PR	
SD	NonPD or not all evaluated	No	SD	Documented at least once $\geq$ 4 weeks from baseline
Not All Evaluated	NonPD	No	NE	NE
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD <sup>a</sup>	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, SD = stable disease

<sup>a</sup> In exceptional circumstances, unequivocal progression in nontarget lesions may be accepted as disease progression.

***Time Point Response: Patients with Nontarget Disease Only***

<b>Nontarget Lesions</b>	<b>New Lesions</b>	<b>Overall Response</b>
CR	No	CR
NonCR/NonPD	No	NonCR/NonPD <sup>a</sup>
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response, NE = not evaluable, PD = progressive disease

a 'NonCR/nonPD' is preferred over 'stable disease' for nontarget disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

**Reference**

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

## 12.8 Safety Laboratory Assessments

Test	Parameters to be analyzed
Hematology	Red blood cell count Hemoglobin Hematocrit White blood cell count Platelet count White blood cell count differentials/absolute neutrophil count will be recorded
Biochemistry	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Blood urea nitrogen/Blood urea Serum creatinine Calcium Chloride Glucose Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Total bilirubin (including direct and indirect if available) Total protein Follicle-stimulating hormone (required for postmenopausal women < 55 years of age at Screening)
Urinalysis (standard urine dipstick)	Color Appearance Specific gravity pH Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite Protein Urobilinogen
Coagulation	International normalized ratio (with prothrombin time/prothrombin time percent if reported, or partial thromboplastin time ratio if reported) Activated partial thromboplastin time or partial thromboplastin time
Pregnancy Test -Urine	Human chorionic gonadotropin (hCG)
Hepatitis Virus	Hepatitis C virus Antibody Hepatitis B virus Surface Antigen Hepatitis B viral load
Biomarker	Alpha-fetoprotein

## 12.9 Open-Label Period

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

Following the results of the primary analysis, which demonstrated no statistically significant advantage of enzalutamide compared to placebo as assessed by the primary endpoint, all ongoing enzalutamide treated subjects will be offered open-label enzalutamide at the discretion of the subject and study investigators after approval of the amendment at the local institution. Subjects continuing to the Open-Label Period must not have met any discontinuation criteria as outlined in Section 6 of the main protocol and must meet the eligibility requirements of the Open-Label Period. Subjects who do not participate in the Open-Label Period or withdraw consent for further treatment will have a 30-day safety follow-up visit as per protocol. Following the 30-day safety follow-up visit their participation in the study will end.

The sponsor has the right to terminate the study at any time. However, the sponsor will ensure that enzalutamide will be available to subjects who participate in the Open-Label Period and have not met discontinuation criteria for as long as they are deriving clinical benefit as assessed by the investigator.

### Schedule and Assessments for the Open-Label Period:

Subjects who meet eligibility requirements for the Open-Label Period will sign the informed consent on Open-Label day 1 (or their next regularly scheduled visit following the approval of the protocol at the study site). Subjects participating in the Open-Label period will have clinic visits every 8 weeks.

Study assessments will include the collection and review of adverse events and concomitant medications. Assessment of laboratory tests, physical examination, weight, and vital signs will also be conducted.

Vital signs include blood pressure and pulse rate.

Routine laboratory assessment for hematology and chemistry will be collected and analyzed at the local laboratory. Laboratory assessments will be assessed at every clinic visit.

Hematology assessments required for the Open-Label Period include red blood cell count (RBC), hemoglobin (Hgb), hematocrit (HCT), white blood cell count (WBC), platelets, and WBC differential/absolute neutrophil count.

Chemistry analytes required for the Open-Label Period include sodium, potassium, calcium, chloride, magnesium, phosphorus, glucose, creatinine, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, albumin, bicarbonate (CO<sub>2</sub>), blood urea nitrogen (BUN), lactate dehydrogenase.

Subjects will have a safety follow-up visit 30 days after the date of last dose of Open-Label enzalutamide or prior to initiation of a new antineoplastic or new investigational agent



(whichever is first). If a new cytotoxic or investigational anticancer treatment is initiated before 30 days after the last dose, then safety follow-up should occur immediately before starting the new treatment.

Refer to Section [5.5](#) Adverse Events and Other Safety Aspects during the Open-Label Period of the study.

#### Flow Chart

Eligible for Open-Label Period Participation	→	Day 1 - Obtain Informed Consent Administer Open-Label Enzalutamide	→	Treatment Period Every 8 weeks until discontinuation criteria are met	End of Treatment Visit (within 7 days after last dose)	Follow-up Period (Approx. 30 days after last dose of study drug)
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#### Open-Label Period Inclusion Criteria:

Subjects must continue to meet inclusion criteria 1, 12, 13, 14, 15, 16, 18 and meet the new criterion 19.

19. Received double-blind enzalutamide study treatment during the main study.

#### Open-Label Period Exclusion Criteria:

22. Received double-blind placebo during the main study.
23. Subject has met discontinuation criteria during the main study.
24. Subject has any other condition or reason that, in the opinion of the Investigator, interferes with the ability of the subject to participate in the trial or places the subject at undue risk.

## Schedule of Assessments

Assessments	Open Label Day 1	Treatment Period	Unscheduled Visit	Follow-up Period	
Study Week/Visit	1 <sup>1</sup>	Q8 Weeks	N/A	EOT	30D FU <sup>2</sup>
Window (days)	N/A	+/-3	N/A	+7	+10
Informed consent	X				
Inclusion/exclusion criteria	X				
Return and/or dispense study drug		X	X [OPT]	X	
Concomitant medications <sup>3</sup>	X	X	X	X	X
Tumor assessment <sup>4</sup>	X		X [OPT]		
Vital signs	X	X	X [OPT]	X	
Adverse events <sup>5</sup>	X	X	X	X	X
Clinical laboratory tests <sup>6</sup>	X	X	X [OPT]	X	
Urine pregnancy test <sup>7</sup>	X	X	X [OPT]	X	
12-lead ECG	X		X [OPT]	X	
ECOG PS	X	X	X [OPT]	X	

Abbreviations: D: day(s), ECG: electrocardiogram, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EOT: end of treatment, FSH: follicle-stimulating hormone, FU: follow-up, N/A: not applicable, OPT: optional, Q: every, SOC: standard of care

1. The D1 visit of the open label period will continue from the visit numbering of the main study schedule.
2. Phone call may be conducted if subject is unable to travel. Visit to be conducted 30 days after last dose or prior to initiating a new antineoplastic treatment, whichever comes first.
3. Medications taken up to the 30-day Follow-up Visit will be collected.
4. Computed tomography (CT)/magnetic resonance imaging (MRI) of the chest/abdomen/pelvis will be done every 8 weeks (+/- 7 days) from D1 until treatment discontinuation criterion is met. To ensure comparability, the Screening and subsequent assessment should be performed using identical techniques.
5. Adverse events will be collected through the 30-day Follow-up Visit or through the day prior to the initiation of new antineoplastic treatment or investigational agent, whichever comes first.
6. Clinical laboratory assessments include hematology: red blood cell count (RBC), hemoglobin (Hgb), hematocrit (HCT), white blood cell count (WBC), platelets, and WBC differential/absolute neutrophil count, Chemistry: sodium, potassium, calcium, chloride, magnesium, phosphorus, glucose, creatinine, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, albumin, bicarbonate (CO<sub>2</sub>), blood urea nitrogen (BUN), lactate dehydrogenase, and pregnancy.
7. Urine pregnancy test will be performed in women of childbearing potential. Testing at treatment visits must occur prior to study drug administration.

### Enzalutamide Administration, Storage, Packaging and Accountability:

Refer to Section [5.1](#) Dosing and Administration of Study Drug(s) and Other Medication(s) for dose modification guidance.

After signing Open-Label Period informed consent, subjects will be assigned Open-Label enzalutamide through the Interactive Response System (IRT).

Enzalutamide will be supplied in bottles and labeled in compliance with local regulations. Enzalutamide will be stored in a secure location with limited access at 20°C to 25°C (68°F to 77°F).

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.

All subjects will self-administer 4, 40 mg soft gelatin enzalutamide capsules (160 mg/day) by mouth once daily with or without food, unless they were receiving a reduced dose during double-blind treatment (treatment will continue at the reduced dose). Subjects should return all study drug bottles to the site at each visit. Study site personnel must make reasonable efforts to obtain all bottles and unused study drug from subjects.

Concomitant and Prohibited Medications:

Refer to Section [5.1.3](#) and Appendix [12.1](#) for Concomitant and Prohibited Medications. Medications taken up to the 30-day Follow-up visit will be documented on the appropriate case report form.

Duration of Treatment and Criteria for Discontinuation:

Refer to Section [6](#) for Criteria for Discontinuation.

Statistical Methods:

Data from the open-label period will be listed by patient. Listings will focus on adverse events, safety laboratory parameters, and tumor assessment data.

## 13 SUBSTANTIAL AMENDMENT 4

### I. The purpose of this amendment is:

Substantial Changes
<b>1. Add an Open-Label Period</b>
DESCRIPTION OF CHANGE:
Add open-label period to allow subjects to continue on enzalutamide after the double-blind period.
RATIONALE:
An open label extension period is added to ensure continuing treatment of enzalutamide treated subjects receiving clinical benefit from study participation after unblinding as a result of the primary analysis.

Non-Substantial Changes
<b>1. Update Contact Details of Key Sponsor's Personnel</b>
DESCRIPTION OF CHANGE:
Update Clinical Research Contact details.
RATIONALE:
Sponsor personnel details are updated based on changes to study team members.

### II. Amendment Summary of Changes:

#### A. Substantial Changes

IV Synopsis
ADDED:
<b>Double-Blind Period:</b> The double-blind period is the study period when investigators and subjects are blinded to the study drug they receive. The double-blind period will conclude following the results of the primary analysis.
<b>Open-Label Period:</b> The open-label period will begin following the results of the primary analysis. At the time of unblinding, open-label enzalutamide will be provided for subjects who meet eligibility criteria. The complete details for the conduct of the open-label period are provided in Appendix 12.9 Open-Label Period.

## **12.9 Open-Label Period**

### **ADDED:**

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

Following the results of the primary analysis, which demonstrated no statistically significant advantage of enzalutamide compared to placebo as assessed by the primary endpoint, all ongoing enzalutamide treated subjects will be offered open-label enzalutamide at the discretion of the subject and study investigators after approval of the amendment at the local institution. Subjects continuing to the Open-Label Period must not have met any discontinuation criteria as outlined in Section 6 of the main protocol and must meet the eligibility requirements of the Open-Label Period. Subjects who do not participate in the Open-Label Period or withdraw consent for further treatment will have a 30-day safety follow-up visit as per the main protocol. Following the 30-day safety follow-up visit their participation in the study will end.

The sponsor has the right to terminate the study at any time. However, the sponsor will ensure that enzalutamide will continue to be available to subjects who participate in the Open-Label Period and have not met discontinuation criteria for as long as they are deriving clinical benefit as assessed by the investigator.

### **Schedule and Assessments for the Open-Label Period:**

Subjects who meet eligibility requirements for the Open-Label Period will sign the informed consent on Open-Label day 1 (or their next regularly scheduled visit following the approval of the protocol at the study site). Subjects participating in the Open-Label period will have clinic visits every 8 weeks.

Study assessments will include the collection and review of adverse events and concomitant medications. Assessment of laboratory tests, physical examination, weight, and vital signs will also be conducted.

Vital signs include blood pressure and pulse rate.

Routine laboratory assessment for hematology and chemistry will be collected and analyzed at the local laboratory. Laboratory assessments will be assessed at every clinic visit.

Hematology assessments required for the Open-Label Period include red blood cell count (RBC), hemoglobin (Hgb), hematocrit (HCT), white blood cell count (WBC), platelets, and WBC differential/absolute neutrophil count.

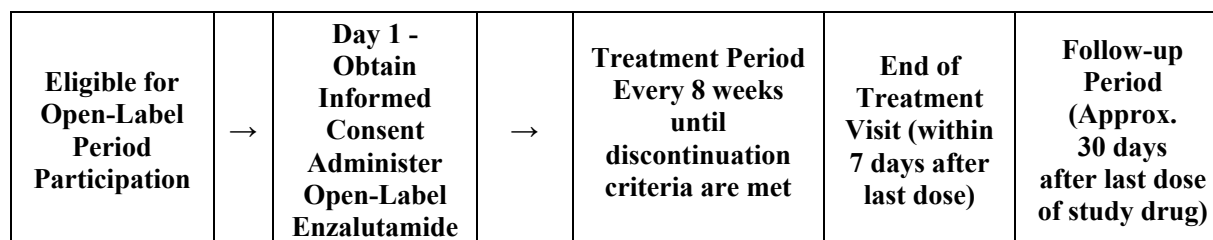
Chemistry analytes required for the Open-Label Period include sodium, potassium, calcium, chloride, magnesium, phosphorus, glucose, creatinine, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, albumin, bicarbonate (CO<sub>2</sub>), blood urea nitrogen (BUN), lactate dehydrogenase.

Subjects will have a safety follow-up visit 30 days after the date of last dose of Open-Label enzalutamide or prior to initiation of a new antineoplastic or new investigational agent (whichever is first). If a new cytotoxic or investigational anticancer treatment is initiated before 30 days after the last dose, then safety follow-up should occur

**immediately before starting the new treatment.**

**Refer to Section 5.5, Adverse Events and Other Safety Aspects during the Open-Label Period of the study.**

#### Flow Chart



#### Open-Label Period Inclusion Criteria:

Subjects must continue to meet inclusion criteria 1, 12, 13, 14, 15, 16, 18 and meet the new criterion 19.

**19. Received double-blind enzalutamide study treatment during the main study.**

#### Open-Label Period Exclusion Criteria:

**22. Received double-blind placebo during the main study.**

**23. Subject has met discontinuation criteria during the main study.**

**24. Subject has any other condition or reason that, in the opinion of the investigator, interferes with the ability of the subject to participate in the trial or places the subject at undue risk.**

#### Schedule of Assessments

Assessments	Open Label Day 1	Treatment Period	Unscheduled Visit	Follow-up Period	
Study Week/Visit	1 <sup>1</sup>	Q8 Weeks	N/A	EOT	30D FU <sup>2</sup>
Window (days)	N/A	±3	N/A	+7	+10
Informed consent	X				
Inclusion/exclusion criteria	X				
Return and/or dispense study drug		X	X [OPT]	X	
Concomitant medications <sup>3</sup>	X	X	X	X	X
Tumor assessment <sup>4</sup>	X		X [OPT]		
Vital signs	X	X	X [OPT]	X	
Adverse events <sup>5</sup>	X	X	X	X	X
Clinical laboratory tests <sup>6</sup>	X <sup>7</sup>	X	X [OPT]	X	
Urine pregnancy test <sup>7</sup>	X	X	X [OPT]	X	
12-lead ECG	X		X [OPT]	X	
ECOG PS	X	X	X [OPT]	X	

**Abbreviations:** D: day(s), ECG: electrocardiogram, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EOT: end of treatment, FSH: follicle-stimulating hormone, FU: follow-up, N/A: not applicable, OPT: optional, Q: every, SOC: standard of care

- 1. The D1 visit of the open label period will continue from the visit numbering of the main study schedule.**
- 2. Phone call may be conducted if subject is unable to travel. Visit to be conducted 30 days after last dose or prior to initiating a new antineoplastic treatment, whichever comes first.**

3. Medications taken up to the 30-day Follow-up Visit will be collected.
4. Computed tomography (CT)/magnetic resonance imaging (MRI) of the chest/abdomen/pelvis will be done every 8 weeks ( $\pm 7$  days) from D1 until treatment discontinuation criterion is met. To ensure comparability, the Screening and subsequent assessment should be performed using identical techniques.
5. Adverse events will be collected through the 30-day Follow-up Visit or through the day prior to the initiation of new antineoplastic treatment or investigational agent, whichever comes first.
6. Clinical laboratory assessments include hematology: red blood cell count (RBC), hemoglobin (Hgb), hematocrit (HCT), white blood cell count (WBC), platelets, and WBC differential/absolute neutrophil count, chemistry: sodium, potassium, calcium, chloride, magnesium, phosphorus, glucose, creatinine, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, albumin, bicarbonate (CO<sub>2</sub>), blood urea nitrogen (BUN), lactate dehydrogenase,, and pregnancy. .
7. Urine pregnancy test will be performed in women of childbearing potential. Testing at treatment visits must occur prior to study drug administration.

**Enzalutamide Administration, Storage, Packaging and Accountability:**

Refer to Section 5.1 Dosing and Administration of Study Drug(s) and Other Medication(s) for dose modification guidance.

After signing Open-Label Period informed consent, subjects will be assigned Open-Label enzalutamide through the Interactive Response System (IRT).

Enzalutamide will be supplied in bottles and labeled in compliance with local regulations. Enzalutamide will be stored in a secure 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.

All subjects will self-administer 4, 40 mg soft gelatin enzalutamide capsules (160 mg/day) by mouth once daily with or without food, unless they were receiving a reduced dose during double-blind treatment (treatment will continue at the reduced dose). Subjects should return all study drug bottles to the site at each visit. Study site personnel must make reasonable efforts to obtain all bottles and unused study drug from subjects.

**Concomitant and Prohibited Medications:**

Refer to Section 5.1.3 and Appendix 12.1 for Concomitant and Prohibited Medications. Medications taken up to the 30-day Follow-up visit will be documented on the appropriate case report form.

**Duration of Treatment and Criteria for Discontinuation:**

Refer to Section 6 for Criteria for Discontinuation.

**Statistical Methods:**

Data from the open-label period will be listed by patient. Listings will focus on adverse events, safety laboratory parameters, and tumor assessment data.

**B. Non-Substantial Changes**

**II Contact Details of Key Sponsor's Personnel**

**WAS:**

Clinical Research Contact:

[REDACTED]  
Astellas Pharma Global Development, Inc.  
Telephone: [REDACTED]  
Mobile: [REDACTED]  
Email: [REDACTED]

**IS AMENDED TO:**

Clinical Research Contact:

[REDACTED]  
**Phone:** [REDACTED]  
**Mobile:** [REDACTED]  
**Email:** [REDACTED]  
[REDACTED]  
~~Astellas Pharma Global Development, Inc.~~  
[REDACTED]



## **14 SPONSOR'S SIGNATURES**