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

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STATISTICAL ANALYSIS PLAN

Final Version 2.0, dated 07-September-2017

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Northbrook, IL 60062

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALT	Alanine Aminotransferase (GPT)
APGD	Astellas Pharma Global Development, Inc.
AR	Androgen Receptor
AST	Aspartate Aminotransferase (GOT)
BCLC	Barcelona Clinic Liver Cancer
BLOQ	Below the Lower Limit of Quantification
CR	Complete Response
CRF	Case Report Form
CS	Classification Specifications
CSR	Clinical Study Report
CT	Computer Tomography
[redacted]	[redacted]
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
FU	Follow-Up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
ICH	International Conference on Harmonization
IRT	Interactive Response System
ISN	International Study Number
LFT	Liver Function Tests
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
OPT	Optional
[redacted]	[redacted]
OS	Overall Survival
PD	Progressive Disease
PD	Protocol Deviation
PDAS	Pharmacodynamic Analysis Set
PFS	Progression Free Survival
PGx	Pharmacogenomics
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set

Abbreviations	Description of abbreviations
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Stable Disease
SD	Standard Deviation
SOC	Standard of Care
SOC	System Organ Class
TBL	Total Bilirubin
TEAE	Treatment-emergent Adverse Event
TLF	Table, Listings, and Figures
[redacted]	[redacted]
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor

List of Key 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 study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet one or more criteria required for participation in a trial.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP will be drafted before first subject enrolled and finalized before the database soft lock. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

This statistical analysis plan is coordinated by the responsible biostatistician of APGD-US. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and Table, Listings, and Figures (TLFs) meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

2 FLOW CHART AND VISIT SCHEDULE

Informed Consent	→	Screening Period (Days –21 to –1)	→	Day 1 Pre-dose 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 levels (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)

Abbreviations: HBV= hepatitis B virus, q = every, SOC = standard of care

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[1]**	**Long Term FU[1]**
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 of study drug		X	X	X	X	X	X	X [OPT]	X		
Concomitant Medications[2]	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[3]	X										
Tumor Assessment[4]	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[5]	X	X	X	X	X	X	X	X	X	X	
Clinical Laboratory Tests[6]	X[6]	X[7]	X	X	X	X	X	X [OPT]	X		
Urine Pregnancy Test[9]	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[6]	X	X	X	X	X	X [OPT]	X		
HBV Viral Levels (if applicable)	X	To be done per SOC or as clinically indicated									
Pharmacokinetic Sample[10]				X	X	X		X [OPT]			
[redacted]		X				X					
Tumor Tissue Collection[12]	X										
Blood Samples for PGx Biobanking (optional)		X									
Survival and Subsequent Treatment										X	X
[redacted]		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 (+/- 7days) 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]

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

3.1.1 Primary Objective

To evaluate the efficacy of enzalutamide as compared to placebo in subjects with advanced hepatocellular carcinoma (HCC), as measured by overall survival (OS).

3.1.2 Secondary Objectives

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

3.1.3 Exploratory Objectives

- [redacted]

3.2 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled phase 2 study evaluating the efficacy, safety, and tolerability of enzalutamide monotherapy in approximately 144 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 other) 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 Adverse Events (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 ≥ 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 21st 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.

3.3 Randomization

Subjects who meet the inclusion/exclusion criteria will be randomly assigned to receive enzalutamide or placebo using a 2:1 randomization schedule, with two-third of the subjects being randomized to the enzalutamide treatment group and the other one-third of the subjects being randomized to the placebo group. Subjects randomization will be stratified by two primary regions (Asia versus Other), and ECOG performace status (0 versus 1).

Randomization will be performed via an Interactive Response Technology (IRT).

4 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 (Hazard Ratio=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 are needed to reach this number of events.

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

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

5.1 Full Analysis Set (FAS)

The full analysis set will consist of all randomized subjects, regardless of whether or not subjects received study drug. This will be the primary analysis set for efficacy analyses.

5.2 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all subjects who have received at least 1 or partial capsule of study drug.

The SAF will be used for the statistical summary of the safety data.

5.3 Pharmacokinetics Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) consists of the subset of the SAF population for which at least one quantifiable enzalutamide or N-desmethyl enzalutamide concentration value is available. Any formal definitions for exclusion of subjects or time-points from the PKAS will be documented in the Classification Specifications. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Details will be reported in the CSR.

The PKAS is used for all tables and graphical summaries of the PK data.

5.4 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 sample) were collected.

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

The PDAS will be used for all analyses of pharmacodynamic data.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint(s)

6.1.1.1 Primary Analysis

The primary endpoint, overall survival (OS) will be defined as the time from the date of randomization until the documented date of death from any cause. For detailed information for definition, please refer to Appendix 10.1

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 regions [Asia versus Other] and ECOG performance status [0 versus 1]). The hazard ratio of the treatment effect along with two-sided 95% confidence interval will also be calculated using a Cox proportional hazard model, stratified by geographic regions and ECOG performance status. In addition, an 80% two-sided confidence interval will also be provided to correspond to the 0.1 one-sided alpha level for the primary analysis.

Time to death for a given subject will be defined as the number of days from the date that the subject was randomized to the date of the subject's death. The primary analysis is triggered by the occurrence of the 109th event. All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has not died, then the data will be censored at the date when the subject was last known to be alive or at the data cutoff date, whichever occurs first.

6.1.1.2 Secondary Analysis

Sensitivity analysis on OS will be done using the unstratified analysis.

6.1.1.3 Subgroup Analysis

The same analysis of the primary endpoint as described in 6.1.1.1 will be conducted using the subgroups of AR (defined as Ventana Total AR Nuclear) patients and other subgroups such as age, gender, geographic region, ECOG status, hepatitis medical history, HepB surface antigen and HCV antibody. Please refer to section 7.8 for details of subgroups of interest.

6.1.2 Secondary Efficacy Endpoints

The Secondary efficacy analyses comparing the effects of Enzalutamide versus placebo will also be performed on progression-free survival (PFS). PFS is defined as the time from the date of randomization until the date of disease progression per RECIST 1.1 or death from any cause on study, whichever occurs first. For detailed information for censoring rules, please refer to Appendix 10.1

6.1.3 Other Efficacy Variables

[redacted]

- [redacted]

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs); frequency of TEAEs by system organ class, preferred term, NCI CTCAE grade, frequency of treatment discontinuations due to AEs, severity, and relationship to study drug.
- Clinical laboratory variables (hematology, biochemistry including liver function tests, coagulation parameters and urinalysis, viral load, and pregnancy test).
- Vital signs (systolic and diastolic blood pressure and pulse rate) and body weight.
- 12-lead electrocardiogram (ECG).

6.2.1 Adverse Events

TEAE is defined as an adverse event observed during the treatment emergent period, which is from the first dose date of enzalutamide to 30 days after the last dose date of enzalutamide or the start of subsequent treatment, whichever is first. If the adverse event occurs on Day 1 and the onset check box is marked “Onset after first dose of study drug” or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked “Onset before first dose of study drug”, then the adverse event will not be considered treatment emergent.

A drug-related TEAE is defined as any TEAE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

6.2.2 Laboratory Assessments

Routine laboratory samples for hematology, biochemistry, 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.

6.2.3 Vital Signs

Vital signs will include systolic and diastolic blood pressure (mmHg), radial pulse (beats/min) and temperature.

Change from baseline, defined as the post-baseline value minus the baseline value will be calculated for each assessment.

6.2.4 Electrocardiogram (ECG)

A 12-lead ECG will be performed and 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.

6.2.5 Other Safety-Related Observations

6.2.5.1 ECOG

ECOG performance status data are collected according to Schedule of Assessment.

6.3 Pharmacokinetic Variables

Pharmacokinetic variables include pre-dose plasma concentrations of enzalutamide, its active metabolite N-desmethyl enzalutamide, and sum of enzalutamide plus N-desmethyl enzalutamide.

6.4 [redacted]

[redacted]

6.5 Other Variables

6.5.1 Previous and Concomitant Treatment

Previous medication is defined as a medication with at least one dose taken before the date of first dose of study drug. Concomitant medication is defined as a medication with at least one dose taken after the date of first dose (inclusive). According to the protocol, concomitant medications were to be recorded up to the 30-Day Follow-up visit.

6.5.2 [redacted]

[redacted]

7 STATISTICAL METHODOLOGY

7.1 General Considerations

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

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g.10%, 25%, 75% and 90%) will be mentioned in the relevant section. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%.

For time to events variables (OS, PFS and [redacted]), descriptive statistics will include the number of subjects (n), the number of events, the number of censored subjects, median time and 95% CI. Kaplan-Meier plots will also be generated.

Summaries based on FAS (e.g. baseline and efficacy data) will be presented, unless specifically stated otherwise. Safety analysis and other summaries based on SAF will be presented.

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 or higher on Unix. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

7.2 Study Population

7.2.1 Disposition of Subjects

Number and percentage of subjects with informed consent, enrolled, discontinued before enrollment will be presented for all subjects.

The following subject data will be presented for the All Randomized Subjects:

- Number and percentage of subjects in each analysis set;
- Number and percentage of subjects discontinued treatment, by primary reason for treatment discontinuation;
- Number and percentage of subjects discontinued study, by primary reason for study discontinuation;
- Number and percentage of subjects completed the study.

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 7.8 Protocol Deviations and Other Analyses) will be assessed for the FAS. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation (PD) 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.

7.2.3 Demographic and Other Baseline Characteristics

Number and percentage of subjects enrolled in each country and site will be presented for the FAS.

For demographics table, descriptive statistics for age, sex, race, ethinicity, weight, body mass index (BMI), height, and history of smoking and alcohol use at study entry will be presented by treatment group. Frequency tabulations for ethnicity, age group and race will be presented by treatment group. This will be done for the SAF and FAS populations. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

For disease history table, descriptive statistics for time from initial diagnostic will be presented by treatment group. Frequency tabulations for histopathology at diagnosis, histologic grade, anatomic staging/prognostic category at initial diagnosis, primary tumor stage, regional lymph node stage, distant metastasis, Barcelona Clinic Liver Cancer (BCLC) stage at screening will be presented by treatment group. Disease history will be summarized by descriptive statistics for the FAS.

HCC etiology factors, presence/absence of cirrhosis, prior systemic treatment for HCC with sorahenib or other anti-VEGF therapy, confirmed disease progression or discontinuation of sorafenib due to intolerance, child-pugh scoring, and HBV/HCV status will be summarized by treatment group for the FAS.

Medical history is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, for the SAF.

7.2.4 Previous and Concomitant Medications

Previous medications are coded with WHO-DD, and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Prior HCC treatment will also be summarized for the FAS.

As with previous medication, concomitant medication are coded with WHO-DD, and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

7.3 Study Drugs

7.3.1 Exposure

The following information on drug exposure will be presented for the SAF:

- Descriptive statistics for cumulative amount of the drug a subject was exposed to and average daily dose; and
- Number and percent of subjects with dose increase, decreases or interruptions.

Duration of exposure (defined in days as the date of last dosing - the date of first dosing + 1) will be summarized in two ways.

- Descriptive statistics will be presented.
- Exposure time will be categorized according to the following categories by study drug:
    - less than 3 months
    - at least 3 months and less than 6 months
    - at least 6 months

Counts and percentages of subjects in each of these categories will be summarized for the SAF.

7.3.2 Treatment Compliance

Overall compliance with the dosing schedule will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance (defined as the percentage of the total study drug taken over total planned study drug doses) for Enzalutamide and placebo will be summarized in two ways for the SAF:

- Descriptive statistics will be presented by study drug.
- Percent compliance will be categorized according to the following categories by study drug:
    - less than 80%
    - at least 80%, less or equal to 90%
    - at least 90%, less or equal to 100%
    - greater than 100%

7.4 Analysis of Efficacy

All efficacy analysis will be performed using the FAS unless otherwise stated.

7.4.1 Analysis of Primary Endpoint(s)

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, stratified by geographic region and ECOG performance status. In addition, an 80% two-sided confidence interval will also be provided to correspond to the 0.1 one-sided alpha level for the primary analysis. Unstratified analysis will be performed too as sensitivity analysis.

A sensitivity analysis same as primary analysis but for subjects randomized and treated will be performed if needed, depending on number of patients randomized and not treated, this analysis will be decided at the Final Data Review meeting if needed.

7.4.2 Analysis of Secondary Endpoints

Similar analysis of the primary endpoint as described in Section 7.4.1 will also be conducted on the secondary endpoint PFS.

PFS is defined as the time from the date of randomization until the date of disease progression (radiographic progression) per RECIST 1.1, or death from any cause on study, whichever occurs first.

The following subjects will be censored at the date of the last radiological assessment showing no progression:

1) subjects who initiated another anti-tumor therapy before documented PD or death,
2) subjects who progressed or died after missing two or more consecutive radiological assessments.

Subjects are considered to have missed two or more consecutive radiological assessments if duration between two consecutive imaging scans are more than 20 weeks while on treatment. Subjects who have no valid post-baseline tumor assessment will be censored at day 1.

The distribution of PFS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the Enzalutamide and placebo treatment groups using the stratified log-rank test. Stratification will be done by the regions (Asia versus Other) and ECOG performance status (0 versus 1). Additionally, unstratified analysis will be performed as well.

A sensitivity analysis for subjects randomized and treated will be performed if needed, depending on number of patients randomized and not treated, this will be decided at the Final Data Review if this analysis is needed or not.

A sensitivity analysis will be done if needed with similar PFS definition, and the initiation of another anti-tumor therapy will be considered as an event, and evidence of progression could come from two sources: radiographical or clinical. This sensitivity analysis will be performed only if further investigation is needed.

7.4.3 Analysis of Exploratory Endpoints

[redacted]

[redacted]

[redacted]

7.5 Analysis of Safety

Safety will be assessed on an ongoing basis by physical examination, measurement of vital signs, laboratory assessments, 12-lead ECGs, and evaluation of TEAEs/serious TEAEs.

Safety analyses will be conducted using the SAF. The SAF is defined as all subjects who have initiated at least 1 or partial capsule 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 the start of subsequent treatment (whichever is first). Only data within this period will be summarized in safety analysis. Safety will be assessed through descriptive statistics for the frequency of adverse events by system organ class (SOC), preferred term (PT), and NCI CTCAE grade, the frequency of treatment discontinuations due to adverse events, vital signs, ECG, and laboratory evaluations.

All safety summaries will be provided using the SAF population.

7.5.1 Adverse Events

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

The coding dictionary for this study will be MedDRA. It will be used to summarize AEs by SOC and PT.

An overview table will include the following details:

- Number of TEAEs,
- Number and percentage of subjects with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of subjects with drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number of TEAEs leading to withdrawl of treatment,
- Number and percentage of subjects with TEAEs leading to withdrawl of treatment,
- Number of drug related TEAEs leading to withdrawl of treatment,

- Number and percentage of subjects with drug related TEAEs leading to withdrawl of treatment,
- Number of TEAEs leading to death,
- Number and percentage of subjects with TEAEs leading to death,
- Number of drug related TEAEs leading to death,
- Number and percentage of subjects with drug related TEAEs leading to death, and
- Number and percentage of subjects with death.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized. Summaries will be provided for:

- TEAEs
- drug related TEAEs,
- serious TEAEs,
- grade 3 or higher TEAEs.
- drug related serious TEAEs,
- TEAEs leading to withdrawl of treatment,
- drug related TEAEs leading to withdrawal of treatment,

TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by grade and by relationship to study drug. If an adverse event changes in grade or relationship, then the subject will be counted only once with the maximum grade and highest degree of relationship. The adverse event however will be presented in each category they were classified to. If a subject has an event more than once with missing grade/relationship and with non-missing grade/relationship, then the subject will be counted as missing grade/relationship. Drug related TEAEs will be presented in a similar way by grade only.

The Always Serious Terms List is a list of AEs that a Sponsor determines regardless of Investigator assessment are to be captured as serious. Serious TEAEs table will include both investigator reported and Astellas upgraded ones according to Always Serious Terms List. In the listing they will be presented with different flag.

7.5.2 Clinical Laboratory Evaluation

For each quantitative laboratory parameter, summary statistics of change from baseline value by visit will be presented. The baseline laboratory value is defined as the last laboratory value collected on or prior to the first dose date of study drug.

Using the definitions provided in the NCI CTCAE, lab values will be classified as Grade 0 through 4, where possible. For each lab parameter at each scheduled collection time point, the number and percentage of subjects who have lab values within the categories defined by each of the grades will be displayed. If a subject has multiple lab values that fall into more than one NCI CTCAE grade, the highest NCI CTCAE grade will be displayed for that subject. In the event the NCI CTCAE grade is listed as > ULN or < LLN, standard laboratory normal values will be used for the purposes of comparison. These values are maintained by

the Data Management group using the New England Journal of Medicine SI Unit Conversion Guide as a reference.

It is acknowledged that data summaries based upon the standard normal laboratories may result in observations falling into different NCI CTCAE/normal/abnormal categories than those that the treating physician reports.

Shift tables will be created for each of the lab parameters after classifying by NCI CTCAE criteria. Shift from baseline to the highest NCI CTCAE grade will be presented.

Lab abnormalities will also be summarized by CTCAE Grade with number and percent, by visit and overall during the study.

Shift table for highest CTCAE grade urinalysis and urinalysis by CTCAE will not be provided.

Summary shifts of reference range changes from baseline to each treatment visit will be presented.

7.5.2.1 Liver Function Tests

The number and percentage of subjects with potentially clinically significant values in liver function tests will be presented.

For LFT changes, study drug dosing should be interrupted if a subject experiences clinically significant liver toxicity related to study drug (≥ Baseline + 4 x ULN to < 20 x ULN for AST and ALT; grade 3 total bilirubin [TBL]). Clinically significant values in liver function tests leading to interrup dosing will be summarized.

7.5.3 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, body temperature, weight and pulse rate) will be summarized using n, mean, standard deviation, minimum, maximum and median by visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized by visit.

The number and proportion fo patiensts experiencing potentially clinically significant abnormalities during the treatment-emergent period will be summarized. The definition of potentially clinically significant abnormalities are provided in the Table below.

Parameter	Criteria for Potentially Clinically Significant Abnormalities
Systolic blood pressure	Absolute result > 180 mm Hg and increase from baseline > 40 mm Hg
	Absolute result < 90 mm Hg and decrease from baseline > 30 mm Hg
	Final visit or 2 consecutive visits results ≥ 20 mm Hg change from baseline
	Most extreme postbaseline result ≥ 140 mm Hg
	Most extreme postbaseline result ≥ 180 mm Hg
	Most extreme result ≥ 180 mm Hg and ≥ 20 mm Hg change from baseline
	Most extreme result ≥ 140 mm Hg and ≥ 20 mm Hg change from baseline
Diastolic blood pressure	Absolute result > 105 mm Hg and increase from baseline >30 mm Hg
	Absolute result < 50 mm Hg and decrease from baseline >20 mm Hg
	Final visit or 2 consecutive visits results ≥ 15 mm Hg change from baseline
	Most extreme post-baseline result ≥ 90 mm Hg
	Most extreme post-baseline result ≥ 105 mm Hg
	Most extreme result ≥ 105 mm Hg and ≥ 15 mm Hg change from baseline
	Most extreme result ≥ 90 mm Hg and ≥ 15 mm Hg change from baseline
Heart Rate	Absolute result >120 bpm and increase from baseline >30 bpm
	Absolute result < 50 bpm and decrease from baseline >20 bpm

bpm, beats per minute; mm Hg, millimeters of mercury.

7.5.4 Electrocardiograms (ECGs)

Number and percent of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results for the 12-lead ECG will be summarized by treatment group and time point.

Continuous ECG parameters, such as heart rate, PR, QRS, QT and RR, will be summarized by treatment group and time point.

7.5.5 Other Safety-Related Observations

7.5.5.1 ECOG

Summary statistics and the shift table for ECOG from baseline to post-baseline visits will be provided by treatment group.

7.6 Analysis of Pharmacokinetics

Pharmacokinetic analyses will be conducted using the PKAS.

Individual and summary tables of plasma concentration of enzalutamide and N-desmethyl enzalutamide and a listing of blood collection times and concentrations will be provided. Summary statistics will be provided including n, mean, standard deviation (SD), geometric mean, minimum, median, maximum, and %CV. Values below the lower limit of quantification (BLOQ) will be set to not be calculated if all values are BLOQ. In cases where

more than half of the individual data in a group are BLOQ, SD and %CV will not be calculated. If one or more values are BLOQ, the geometric mean will not be calculated. Additional model-based analyses may be performed and will be described in a separate population PK analysis plan.

For analysis of PK data, only samples for which the time of sampling relative to the dose and the exact dose is known will be included.

7.7 [redacted]

7.8 Subgroups of Interest

The same analysis of the primary endpoint as described in Section 7.4.1 will be conducted separately, using the following subgroups:

- Region (Asia vs Other)
- Baseline ECOG status (0 vs 1)
- AR, defined as Ventana Total AR Nuclear %, (<10% ; AR>=10% ; AR>=30% ; AR>=50%; AR>=80%)
- Age (<65 vs >=65)
- Gender (Male vs Female)
- Number of prior lines (1; >=2)
- Alpha fetoprotein (<= 400 ug/L ; >400 ug/L) at baseline
- Medical history (HBV, HCV, or non-viral)

- HepB surface antigen (positive, negative)
- HCV antibody (positive, negative)
- Patients with medical history of HBV (HBV positive) , examine AR <10% and >=10%
- Patients with medical history of HCV (HCV positive) , examine AR <10% and >=10%

Results will be presented as forest plots.

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

There is no planned interim analysis; however, 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 period, 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.

7.10.1 Missing Data

Subjects who do not satisfy the criteria to be counted as responders or have insufficient data to determine or confirm a response per the RECIST 1.1 Criteria will be considered as non-responders in the primary final analysis of response rates. No imputation of data will be done to determine individual subject response.

For continuous variables (e.g., clinical laboratory measurement, vital signs), subjects with missing baseline variable will be excluded from the analysis of change from baseline.

Visit-by-visit analyses of data will exclude subjects who did not provide data at the visit in question. For visit by visit summary of ECOG, no imputation will be made.

Adverse events with missing grade will be displayed as “Missing”, no imputation will be made.

For all analyses other than PK analysis, all values will be included in the analyses.

7.10.2 Missing Dates

As a general rule, the worst case scenario imputation rule is used. Completely missing dates will not be imputed.

To calculate Time from initial diagnosis, 1st day of the Month will be used when Month and Year are available; and 1st of January will be used if only Year is available, as defined below.

Reported Date (from the eCRF)	Analysis Date (Derived)
--/MM/YYYY	01/MM/YYYY
--/--/YYYY	01/01/YYYY
DD/--/----, or --/MM/----, or --/--/----	No imputation

7.10.3 Outliers

All values will be included in the analyses.

7.10.4 Visit Windows

Labs, vital signs, weight, PE, urine preganancy test and ECG will be analyzed based on the following visit window.

Visit (study day)	Lab, Vital signs, PE	Weight, Urine Pregnancy Test	ECG
Baseline (1)	<= 1	<= 1	<= 1
Week 3 (15)	>=2 – <22	NA	NA
Week 5 (29)	>=22 – < 43	>=22 – < 43	NA
Week 9 (57)	>=43 – <71	>=43 – <71	NA
Week 13 (85)	>=71 – <99	>=71 – <99	CRF visit
Week 17 (113)	>=99 – <127	>=99 – <127	NA
Week 21 (141)	>=127 – <155	>=127 – <155	NA
Week 25 (169)	>=155 – <183	>=155 – <183	NA
Week 29 (197)	>=183 – <211	>=183 – <211	NA
Week 33 (225)	>=211 – <239	>=211 – <239	NA
Week x (7*x -6) (x is every 4 weeks after week 5)	>=7*x-20 – <7*x+8	>=7*x-20 – <7*x+8	NA
Final	Last Value within 7 days of last dose of study drug	Last Value within 7 days of last dose of study drug	Last Value within 7 days of last dose of study drug

8 DOCUMENT REVISION HISTORY

Version	Change
1	Finalized before protocol amendment but never signed. Document was finalized after protocol amendment and fully approved on the 22OCT2015 as verion 2.0 when it should be version 1.0. Additional note to document this has been archived in the study TMF.
2	Updated section 7.10.3 visit window.
	Footnote of Schedule of Assessment table was updated based on protocol v3.0. Section 7.5.4 was removed. Added more analysis details to sections 7.6, 7.7 and 7.8. Updated section 7.10.1.
	[redacted] Added viral /non-viral medical history to subgroup analysis section 7.8 [redacted]
	Updated the list of Abbreviations. Added sections 6.2.1, 6.2.2, 6.2.3 and 6.2.4 to describe AE, labs, vital signs, and ECG respectively. Added section 6.2.5 for ECOG, and section 6.5 for previous and concomitant medications. Used the population “All Randomized Subjects” instead of “FAS” to summarize subject disposition (section 7.2.1). Added sensistivity analyses for efficacy endpoints when needed (section 7.4).

Version	Change
	[redacted] [redacted] [redacted] Specified the populations for efficacy and safety analyses. Changed to use standard term "withdrawl of treatment" instead of "permanent discontinuation of study drug" for AE analysis (section 7.5.1). Added summary shifts to replace shift tables for abnormalities by reference range, and updated analysis: Shift table for highest CTCAE grade urinalysis and urinalysis by CTCAE will not be provided (section 7.5.2). Added the details for LFT changes, study drug dosing should be interrupted (section 7.5.2.1). Added the descriptions for continuous ECG parameters (section 7.5.4). [redacted] More subgroups were added for subgroup analysis and updated the subgroups categories (section 7.8). Updated the definition for AR+ (section 7.8). Updated the description for interim analysis (section 7.9). Added section 7.10.2 for the imputation rule to calculate the time from initial diagnosis.

9 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

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(2):228-247.

10 APPENDICES

10.1 Appendix 1: Definition of Efficacy Endpoints

10.1.1 Overall Survival

Overall survival is 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.

10.1.2 Progression-Free Survival

Progression-free survival (PFS) is defined as the time interval from the date of randomization to the date of disease progression as determined by the investigator using RECIST 1.1 or the date of on-study death due to any cause, whichever occurs first. Please refer to section 7.4.2.

Patients who die after receiving the first dose of enzalutamide without postbaseline tumor assessments evaluable using RECIST 1.1, will be considered to have a PFS event on the date of death.

The censoring rules for the primary and sensitivity analyses of PFS are summarized in the following table. The earliest of the following censoring times will be used:

Analysis	Censoring Rules	Date of Censoring
Primary analysis of PFS	No evaluable post-baseline imaging assessments, nor death	Date of randomization
	No radiographical progression nor death before analysis cutoff date	Date of last radiological assessment before analysis cutoff date
	No radiographical progression nor death before new HCC treatment	Date of last radiological assessment before start of new HCC treatment

10.1.3 [redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

10.2 Appendix 2: Signatures

Prepared by: [redacted] Date: Date (DD Mmm YYYY)

Approved by: [redacted] Date: Date (DD Mmm YYYY)

Reviewed by: [redacted] Date: Date (DD Mmm YYYY)

[redacted] Date: Date (DD Mmm YYYY)

[redacted] Date: Date (DD Mmm YYYY)