STATISTICAL ANALYSIS PLAN

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

ISN: 9785-CL-0413

Astellas Pharma Inc. (API)

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
AESI	Adverse Event of Special Interest
Alb	Albumin.
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
API	Astellas Pharma Inc.
AST	Aspartate aminotransferase
BMI	Body Mass Index
BSA	Body Surface Area
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
Hb	Hemoglobin
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Council for Harmonisation
IHD	Ischemic Heart Disease
ISN	International Study Number
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NCI	National Cancer Institute
PD	Pharmacodynamics
PK	Pharmacokinetics
PRES	Posterior Reversible Encephalopathy Syndrome
PSA	Prostate-Specific Antigen
PT	Preferred Term
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCAR	Severe Cutaneous Adverse Reactions
SD	Standard Deviation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SPM	Second Primary Malignancies
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings, and Figures
ULN	Upper limit of normal
WHO	World Health Organization
WHODDE(B2)	WHO Drug Dictionary Enhanced (B-2 Format)

List of Key Terms

Terms	Definition of terms
Baseline	Assessments of subjects as they enter a trial before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a trial.
Enroll	To register or enter a subject into a clinical trial. NOTE: Once a subject has received the study drug or placebo, the clinical trial protocol applies to the subject.
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any entity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

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 is finalized and signed prior to database hard lock.

This statistical analysis is coordinated by the responsible biostatistician of Data Science, API. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

2 FLOW CHART AND VISIT SCHEDULE

Refer to Section V. FLOW CHART AND SCHEDULE OF ASSESSMENTS of the protocol.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

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

3.1.1 Primary Objective

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

3.1.2 Secondary Objective

To evaluate the effect of enzalutamide on PSA.

3.2 Study Design

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

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

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

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

3.3 Randomization

Randomization will be not performed as this is single-arm study.

4 SAMPLE SIZE

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

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 and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

5.1 Full Analysis Set (FAS)

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

5.2 Safety Analysis Set (SAF)

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

For the statistical summary of the safety data, the SAF will be used.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

Secondary endpoints

- Confirmed PSA response rate (≥ 50% decline in PSA from baseline to the lowest postbaseline PSA result, with a consecutive assessment conducted at least 3 weeks later to confirm the PSA response)

6.2 Safety Variables

Primary endpoints

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

Other endpoints

- Weight

TEAE (Treatment Emergent Adverse Event) is defined as an adverse event observed after starting administration of the study drug.

A drug-related TEAE is defined as any TEAE with a causal relationship of YES by the investigator or with missing assessment of the causal relationship.

AESI (Adverse Events of Special Interest) are defined as below.

AESI Category	Selection based on MedDRA 26.0
Convulsions (Seizure)	Narrow SMQ of 'Convulsions'.
Hypertension	Narrow SMQ 'Hypertension'.
Neutrophil Count Decreased	PTs of 'Neutrophil Count Decreased', 'Neutropenia', 'Agranulocytosis',' Granulocyte Count Decreased', 'Granulocytopenia', 'Febrile Neutropenia', 'Neutrophil Percentage Decreased', 'Band Neutrophil Count Decreased', 'Band Neutrophil Percentage Decreased', 'Neutropenic Sepsis', 'Neutropenic Infection' And 'Neutrophil Count Abnormal'.
Cognitive and Memory Impairment	All PTs under the MedDRA HGLT: 'Mental Impairment Disorders'.
Ischemic Heart Disease (IHD)	Narrow SMQs of 'Myocardial Infarction' And 'Other Ischemic Heart Disease'.
Other Selected Cardiovascular Events	Narrow SMQs of 'Haemorrhagic Central Nervous System Vascular Conditions', 'Ischemic Central Nervous System Vascular Conditions' And 'Cardiac Failure'.
Posterior Reversible Encephalopathy Syndrome (PRES)	PT of 'Posterior Reversible Encephalopathy Syndrome'.
Fatigue	PTs of 'Fatigue', 'Asthenia'.
Renal Disorder	Broad [1] SMQ of 'Acute Renal Failure'.
Second Primary Malignancies (SPM) [2]	Narrow SMQs of 'Malignant Or Unspecified Tumours' Customized To Exclude PTs of 'Congenital Fibrosarcoma', 'Congenital Malignant Neoplasm', 'Congenital Retinoblastoma', 'Metastases To···', 'Metastasis', 'Metastatic Neoplasm', 'Prostate Cancer···', 'Carcinoid Tumour of The Prostate', And 'Neoplasm Prostate' And (Inclusive of) Narrow SMQ of 'Myelodysplastic Syndrome', And (inclusive of) All PTs under HLT of 'Myeloproliferative Disorders (Excl Leukaemias)' Note: Non-Melanoma Skin Cancers Are Excluded (Preferred Terms Of 'Basal Cell Carcinoma', 'Basosquamous Carcinoma', 'Basosquamous Carcinoma Of Skin', 'Keratoacanthoma', 'Skin Cancer', 'Skin Cancer Metastatic', 'Squamous Cell Carcinoma', 'Squamous Cell Carcinoma Of Skin', 'Lip Squamous Cell Carcinoma', 'Bowen's disease').
Fall	PT of 'Fall'.
Fractures	All PTs under the MedDRA HGLT: 'Fractures' And 'Bone And Joint Injuries'.
Loss of Consciousness	PTs of 'Loss of Consciousness', 'Syncope', 'Presyncope'.
Thrombocytopenia	PTs of 'Thrombocytopenia', 'Platelet Count Decreased'.
Musculoskeletal Events	PTs of 'Back Pain', 'Arthralgia', 'Myalgia', 'Musculoskeletal Pain', 'Pain In Extremity', 'Musculoskeletal Stiffness', 'Muscular Weakness','Muscle Spasms'.
Severe Cutaneous Adverse Reactions (SCAR)	Narrow SMQ of 'Severe Cutaneous Adverse Reactions'.

Footnotes

AESI Category	Selection based on MedDRA 26.0
Angioedema	Narrow SMQ of 'Angioedema'.
Rash	PTs of 'Butterfly rash', 'Exfoliative rash', 'Eyelid rash', 'Genital rash', 'Heliotrope rash', 'Mucocutaneous rash', 'Nodular rash', 'Paraneoplastic rash', 'Penile rash', 'Perineal rash', 'Rash', 'Rash erythematous', 'Rash follicular', 'Rash macular', 'Rash maculo-papular', 'Rash maculovesicular', 'Rash morbiliform', 'Rash neonatal', Rash papular', 'Rash papulosquamus', 'Rash pruritic', 'Rash pustular', 'Rash rubelliform', 'Rash scarlataniniform',' Rash vesicular', 'Septic rash', 'Systemic lupus erythematosus rash', 'Vasculitic rash', 'Viral rash', 'Vulvovaginal rash'.
Hepatic Disorder	Narrow SMQ of 'Hepatic Failure, Fibrosis And Cirrhosis And Other Liver Damage Related Conditions', 'Hepatitis, Non-Infectious' And 'Liver Related Investigations, Signs And Symptoms'.

SMQ: Standardized MedDRA Query, HLT: High Level Term, HLGT: High Level Group Term.

[1] Broad includes either broad or narrow.

[2] AE terms identified as second primary malignancies according to the search criteria undergo review to confirm.

6.3 Other Variables

- Duration of exposure

  For each subject, the length of time on treatment will be calculated in days, using the following formula:
  - Last dose date of enzalutamide – First dose date of enzalutamide + 1, for patients who completed.
  - Discontinuation dose date of enzalutamide – First dose date of enzalutamide + 1, for patients who discontinued.
- Percent overall compliance
  - Percent compliance = Number of taken capsules of enzalutamide / Number of planned capsules of enzalutamide x 100 (%)
  - Number of taken capsules of enzalutamide = Sum of (Number of prescribed capsules of enzalutamide – Number of returned capsules of enzalutamide)
  - Number of planned capsules of enzalutamide = Sum of ((Stop Date – Start Date + 1) x Dose / 40).
- Duration of disease at screening (month)
  - Duration of disease at screening (month) = (Date of screening visit – Date of histological or cytological diagnosis of prostate cancer + 1) / 30.

  If the onset day and/or month of diagnosis is unknown, then the day and/or month will be imputed by 1st and January respectively.
- Duration of metastatic progression at screening (month)
  - Duration of metastatic progression at screening (month) = (Date of screening visit – First Date of Diagnosis of Metastatic Progression + 1) / 30.

  If the onset day and/or month of diagnosis is unknown, then the day and/or month will be imputed by 1st and January respectively.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

- All data processing, summarization, and analyses will be performed using SAS® Version 9.4 or higher on Red Hat Enterprise Linux.
- For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum.
- For categorical variables: number and percentages of subjects will be described.
- Specifications for table, figures, and data listing formats can be found in the TLFs specifications for this study.
- MedDRA will be used as the coding dictionary for adverse event and medical history.
- WHODDE(B2) will be used as the coding dictionary for previous and concomitant medications.
- Baseline is defined as last nonmissing value before the first dose of the study drug.
- Change from baseline to postbaseline will be calculated as: postbaseline value - baseline value. If the baseline value is missing, then that subject is not included in the calculation at any visit.

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be summarized and presented with regard to all subjects with Screening Failure Log and Case Report Form:

- Number of subjects with informed consent
- Number of subjects who discontinued before registration
- Number of subjects who registered

The following subject data will be summarized and presented with regard to subjects with informed consent:

- Number and percentage of subjects who prematurely discontinued during the screening period
- Number and percentage of subjects who prematurely discontinued during the screening period by primary reason for withdrawal

The following subject data will be summarized and presented with regard to all registered subjects:

- Number and percentage of subjects who prematurely discontinued during the study period
- Number and percentage of subjects who prematurely discontinued during the study period by primary reason for withdrawal
- Number and percentage of subjects who took study drug
- Number and percentage of subjects who were included/excluded in SAF and FAS

The following subject data will be summarized and presented with regard to subjects who took the study drug:

- Number and percentage of subjects who were excluded from SAF and FAS by reason

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all subjects allocated to treatment. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by total 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 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

Demographic and other baseline characteristics will be summarized by descriptive statistics or categorical analysis for SAF and FAS.

The following demographic variables will be summarized and presented.

Demographic Variables and Analysis Methods

Item	Classification	Analysis Methods
Age [at the time of informed consent] (years)	Measurement value <75, >=75 <65, 65 to <75, >=75	Descriptive statistics Categorical analysis
EudraCT Age Category	>=18 years to <=64 years, >=65 years to <=84 years, >=85 years	Categorical analysis
Sex	Male, Female	Categorical analysis
Self-Reported Race	White, Black or African American, American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Native Hawaiian, Guamanian or Chamorro, Samoan, Other Pacific Islander	Categorical analysis
Ethnicity	Not Hispanic or Latino, Hispanic or Latino	Categorical analysis
Height [Screening] (cm)	Measurement value	Descriptive statistics
Weight [Screening] (kg)	Measurement value	Descriptive statistics
Weight[Day 1] (kg)	Measurement value	Descriptive statistics

Item	Classification	Analysis Methods
BMI [Screening] (kg/m^2)	BMI (kg/m^2) = Weight (kg) / (Height (cm) / 100)^2	Descriptive statistics
BSA [Screening] (m^2)	BSA (m^2) = Weight (kg) ^ 0.425 x Height (cm) ^ 0.725 x 0.007184	Descriptive statistics
ECOG Performance Status	Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5	Categorical analysis
Previous Disease	No, Yes	Categorical analysis
Concomitant Disease	No, Yes	Categorical analysis
Duration of disease at screening (month)	Measurement value <60month, >=60month <=Median, >Median	Descriptive statistics Categorical analysis
Primary Gleason score initial histological/cytological diagnosis	1, 2, 3, 4, 5, Unknown	Categorical analysis
Secondary Gleason score initial histological/cytological diagnosis	1, 2, 3, 4, 5, Unknown	Categorical analysis
Total Gleason score initial histological/cytological diagnosis	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, Unknown Low: 1-4, Medium: 5-7, High: 8-10	Categorical analysis
Clinical Tumor Stage (T) initial histological/cytological diagnosis	TX, T0, T1, T2, T3, T4, Unknown	Categorical analysis
Pathologic Tumor Stage (pT) initial histological/cytological diagnosis	pT2, pT3, pT4, Unknown	Categorical analysis
Clinical Lymph Node (N) Stage initial histological/cytological diagnosis	NX, N0, N1, Unknown	Categorical analysis
Pathological Lymph Node (pN) Stage initial histological/cytological diagnosis	pNX, pN0, pN1, Unknown	Categorical analysis
Distant Metastasis (M) initial histological/cytological diagnosis	MX, M0, M1, Unknown	Categorical analysis
Duration of metastatic progression at screening (month)	Measurement value	Descriptive statistics
Location	Abdominal cavity, Adrenal gland, Anus, Bile duct, Bladder, Body, Bone, Bone marrow, Brain, Breast, Cervix uteri, Chest, Colon, Esophagus, Gallbladder, Head, Heart, Head and neck, Kidney, Liver, Lung, Lymph node, Mediastinum, Neck, Omentum, Oral cavity, Pancreas, Pelvis, Penis, Pericardium, Peritoneum, Pleura, Prostate gland, Rectum, Retroperitoneum, Skin, Small intestine, Spleen, Stomach, Testis, Other	Categorical analysis
Prostate Cancer Treatment History - Radiation	No, Yes	Categorical analysis

Item	Classification	Analysis Methods
Prostate Cancer Treatment History - Procedure	No, Yes	Categorical analysis
Prostate Cancer Treatment History - Drug Therapy	No, Yes	Categorical analysis
PSA at Baseline	Measurement value <2 ug/L, >=2 ug/L <=Median, >Median	Descriptive statistics Categorical statistics
Hb at Baseline	Measurement value <=Median, >Median	Descriptive statistics Categorical analysis
ALP at Baseline	Measurement value <=Median, >Median	Descriptive statistics Categorical analysis
Alb at Baseline	Measurement value <=Median, >Median	Descriptive statistics Categorical analysis

7.2.4 Previous and Concomitant Medications

Previous Medications/Non-Medication Therapy mean drugs and therapies undergone before entering the investigational period and Concomitant Medications/ Non-Medication Therapy refer to drugs and therapies used during the investigational period.

Previous and Concomitant Medications/Non-Medication Therapy will be summarized for SAF and FAS.

Previous and Concomitant Medications/Non-Medication Therapy and Analysis Methods

Item	Classification	Analysis Methods
Previous Medications	No, Yes	Categorical analysis
Previous Non-Medication Therapy	No, Yes	Categorical analysis
Concomitant Medications	No, Yes	Categorical analysis
Concomitant Non-Medication Therapy	No, Yes	Categorical analysis

7.3 Study Drugs

7.3.1 Exposure

Analysis set: FAS, SAF

Duration of exposure will be summarized using descriptive statistics.

7.3.2 Treatment Compliance

Analysis set: FAS, SAF

Percent overall compliance will be summarized using descriptive statistics.

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS.

PSA response rate (the proportion of patients with >= 50% decline in PSA from baseline) will be summarized at each visit (See Section 7.11.3).

Confirmed PSA response rate (the proportion of patients with >= 50% decline in PSA from baseline to the lowest postbaseline PSA result, with a consecutive assessment conducted at least 3 weeks later to confirm the PSA response) will be summarized.

Summary statistics of measured values and the percent changes from baseline will be calculated at each visit and mean ± standard deviation (SD) plots will be constructed.

7.5 Analysis of Safety

All analysis of safety will be presented for SAF, unless specified otherwise.

7.5.1 Adverse Events

Following definitions of AE will be used for analysis.

The definitions of TEAE and drug-related TEAE are provided in Section 6.2.

7.5.1.1 An Overview of Adverse Events

An overview table will include the following details:

- Number and percentage of subjects with TEAEs
- Number and percentage of subjects with drug-related TEAEs
- Number and percentage of subjects with serious TEAEs
- Number and percentage of subjects with drug-related serious TEAEs
- Number and percentage of subjects with TEAEs leading to death
- Number and percentage of subjects with drug-related TEAEs leading to death
- Number and percentage of subjects with TEAEs leading to withdrawal of treatment
- Number and percentage of subjects with drug-related TEAEs leading to withdrawal of treatment
- Number and percentage of subjects with grade 3 or higher TEAEs
- Number and percentage of subjects with drug-related grade 3 or higher TEAEs
- Number and percentage of subjects with deaths
- Number of TEAEss
- Number of drug-related TEAEs
- Number of serious TEAEs
- Number of drug-related serious TEAEs
- Number of TEAEs leading to death
- Number of drug-related TEAEs leading to death
- Number of TEAEs leading to withdrawal of treatment
- Number of drug-related TEAEs leading to withdrawal of treatment
- Number of grade 3 or higher TEAEs
- Number of drug-related grade 3 or higher TEAEs

7.5.1.2 Adverse Events by SOC and PT

The number and percentage of subjects with TEAEs and number of TEAEs, as classified by SOC and PT will be summarized. Subjects reporting more than one AE for a given MedDRA PT will be counted only once for that term. Subjects reporting more than one AE within a SOC will be counted only once for the SOC total. Subjects reporting more than one AE will be counted only once in the overall AE total.

For summaries by severity based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade (Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe or medically significant, Grade 4 = life threatening, Grade 5 = death related to AE), subjects reporting more than one AE for a given PT, SOC total and AE total will be counted only once for that term in the most severe category reported. If a subject has an AE which has a missing severity, then the subject will be counted in the severity category of "Missing" (i.e., missing severity will not be imputed).

Summaries will be provided for:

- TEAEs
- Drug-related TEAEs
- Serious TEAEs
- Drug-related serious TEAEs
- TEAEs leading to withdrawal of treatment
- Drug-related TEAEs leading to withdrawal of treatment
- TEAEs leading to death
- Drug-Related TEAEs leading to death
- Grade 3 or higher TEAEs
- Drug-related grade 3 or higher TEAEs
- Common (>=5%) TEAEs
- TEAEs by severity based on NCI-CTCAE grade
- Drug-related TEAEs by severity based on NCI-CTCAE grade
- Common (>=5%) TEAEs excluding serious adverse events

7.5.1.3 Adverse Events of Special Interest

An overview table of TEAE of Special Interest will describe the number and percentage of patients, as classified by AESI category and PT.

An overview table of TEAE of Special Interest with Grade 3 or above will describe the number and percentage of patients, as classified by AESI category and Severity.

7.5.2 Clinical Laboratory Evaluation

7.5.2.1 All Laboratory Tests

Descriptive statistics for quantitative clinical laboratory variables, i.e. hematology and biochemistry will be presented at each visit (See Section 7.11.3). Additionally, a within-subject change will be calculated as the postbaseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as

low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges. The number and percentage of subjects below and above reference range will be summarized using shift table (from baseline to postbaseline).

The following data will be presented for quantitative clinical laboratory variables graphically:

- Laboratory test results (actual values) using box plot
- Laboratory test results x study days (relative days from administration of the study drug) using spaghetti plot

7.5.2.2 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria for liver tests – defined as Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the study period will be used.

Parameter	Criteria
ALT	> 3xULN > 5xULN > 10xULN > 20xULN
AST	> 3xULN > 5xULN > 10xULN > 20xULN
ALT or AST	> 3xULN > 5xULN > 10xULN > 20xULN
Total Bilirubin	> 2xULN
Alkaline Phosphatase	> 1.5xULN
ALT and/or AST AND Total Bilirubin [1]	ALT and/or AST > 3xULN AND Total Bilirubin > 2xULN
ALT and/or AST AND Alkaline Phosphatase AND Total Bilirubin [1]	ALT and/or AST > 3xULN AND Alkaline Phosphatase < 2xULN AND Total Bilirubin > 2xULN

[1] Combination of values measured within same day or within 1 day apart

The number and percentage of subjects with potentially clinically significant values in liver enzyme and total bilirubin tests during the study period will be presented.

7.5.3 Vital Signs

Descriptive statistics for vital signs (systolic blood pressure, diastolic blood pressure, pulse and body temperature) and weight will be presented at each visit (See Section 7.11.3).

Additionally, a within-subject change will be calculated per visit as the postbaseline measurement minus the baseline measurement and summarized in the same way.

The following data will be presented graphically:

- Vital sign results (actual values) using box plot
- Vital sign results x study days (relative days from administration of the study drug) using spaghetti plot

7.6 Analysis of PK

Not Applicable.

7.7 Analysis of PD

Not Applicable.

7.8 Subgroups of Interest

Not Applicable.

7.9 Other Analyses

Not Applicable.

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

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

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

7.11.1 Missing Data

As a general principle, missing data will not be imputed, except for the following exceptions.

The partial missing start/end dates of AE (Adverse Events), CM (Prior and Concomitant Prostate Cancer Medications, Concomitant Medications, Non-Medication Therapy), MH (Medical History, Primary Diagnosis), and PR (Radiation for Prostate Cancer, Procedures for Prostate Cancer) will be imputed as below.

- If the start day and/or month is unknown, the day and/or month will be imputed by 1st and January, respectively. In case of AE with onset after first dose of study drug, use the imputed date or the first dose date of study drug, whichever is later.
- If the end day and/or month is unknown, the day and/or month will be imputed by the last day of the month and December, respectively.

The imputed dates will be used to determine duration of disease at screening (See Section 6.3).

7.11.2 Outliers

All values will be included in the analyses.

7.11.3 Visit Window for Vital Signs, Clinical Labs and PSA

Analysis visit	Specified day	Allowed time window
Baseline	Day0001	Last nonmissing value before the first dose.
Day0029(Week5)	Day0029	Specified day ± 7 days
Day0057(Week9)	Day0057	Specified day ± 7 days
Day0085(Week13)	Day0085	Specified day ± 7 days
Day0169(Week25)	Day0169	Specified day ± 7 days
Day0253(Week37)	Day0253	Specified day ± 7 days
Day0337(Week49)	Day0337	Specified day ± 7 days
Day0421(Week61)	Day0421	Specified day ± 7 days
Day0505(Week73)	Day0505	Specified day ± 7 days
Day0589(Week85)	Day0589	Specified day ± 7 days
Day0673(Week97)	Day0673	Specified day ± 7 days
Day0757(Week109)	Day0757	Specified day ± 7 days
Day0841(Week121)	Day0841	Specified day ± 7 days
Day0925(Week133)	Day0925	Specified day ± 7 days
Day1009(Week145)	Day1009	Specified day ± 7 days
Day1093(Week157)	Day1093	Specified day ± 7 days
Day1177(Week169)	Day1177	Specified day ± 7 days
Day1261(Week181)	Day1261	Specified day ± 7 days
Day1345(Week193)	Day1345	Specified day ± 7 days
Day1429(Week205)	Day1429	Specified day ± 7 days
…	…	…
Safety Follow-up	30 days after Last Dose	Specified day ± 7 days

As for the analysis visits of Day XXXX (Week XXX), the values measured on or before withdrawal day will be accepted for discontinued subjects. The value which assessment day is the closest to the defined specified day within this window is used. If two values are equally close, the latter is used in the analysis.

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.0	3-Jun-2019	NA	Document finalized
2.0	25-Jan-2021	**Protocol Deviations** Newly added the section.	To include the analysis of protocol deviations according to the change of quality documents.
3.0	26-Feb-2024	**General Considerations** Removed dictionary version of MedDRA and WHODDE.	To comply with the Statistical Analysis Plan template.
		Visit Window for Vital Signs, Clinical Labs and PSA Updated time windows for visit increase.	To address visit increase.
		Missing Data Updated imputation for partial missing start/end dates of AE, CM, MH, PR.	To address partial missing dates.
		FLOW CHART AND VISIT SCHEDULE Removed the flow chart and visit schedule and changed to refer to the protocol. **General Considerations** Updated SAS version. **Appendix 1: SIGNATURE** Removed the list of key contributors.	To follow the contents of latest Statistical Analysis Plan format.
		Safety Variables Added AESI definition . **Adverse Events of Special Interest** Added AESI analysis.	To add AESI analysis.

Version	Date	Changes	Comment/rationale for change
		An Overview of Adverse Events Removed AE subgroup analysis. **Adverse Events by SOC and PT** Removed AE subgroup analysis. **Subgroups of Interest** Changed to "Not Applicable".	To remove AE subgroup analysis, which is not necessary in CSR analysis.

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)

10 APPENDICES

10.1 Appendix 1: SIGNATURE

Author and Approver Signatories

(E-signatures are attached at end of document)

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