# STATISTICAL ANALYSIS PLAN FOR OPEN LABEL EXTENSION

Version 1.0, dated 18 July 2021

ARCHES: A Multinational, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients with Metastatic Hormone Sensitive Prostate Cancer

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# I. LIST OF ABBREVIATIONS AND KEY TERMS

## List of Abbreviations

| Abbreviations | Description of abbreviations |
|---|---|
| ADT | Androgen deprivation therapy |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BPI-SF | Brief pain inventory - Short form |
| COVID-19 | Coronavirus Disease 2019 |
| CRF | Case report form |
| CRPC | Castration-resistant prostate cancer |
| CT | Computed tomography |
| CTCAE | Common terminology criteria for adverse events |
| ECG | Electrocardiogram |
| ECOG | Eastern cooperative oncology group |
| eCRF | Electronic case report form |
| EQ-5D-5L | EuroQol group-5 dimension-5 level instrument |
| FACT-P | Functional assessment of cancer therapy - prostate |
| HR | Hazard ratio |
| ICF | Informed consent form |
| ICH | International conference on harmonization |
| ICR | Independent central review |
| IRT | Interactive response technology |
| ITT | Intent-to-treat |
| LHRH | Luteinizing hormone-releasing hormone |
| mHSPC | Metastatic hormone sensitive prostate cancer |
| M1 | metastatic disease |
| MRI | Magnetic resonance imaging |
| NCI | National cancer institute |
| ORR | Objective response rate |
| OS | Overall survival |
| PSADecR | Rate of PSA decline to <2ng/mL |
| PSA | Prostate-specific antigen |
| QLQ-PR25 | Quality of life prostate-specific questionnaire |
| QoL | Quality of life |
| RECIST | Response evaluation criteria in solid tumors |
| rPD | Radiographic disease progression (i.e. radiographic progression; radiographic progression of disease) |
| rPFS | Radiographic progression-free survival |
| SAP | Statistical analysis plan |
| SOC | System organ class |
| SMQ | Standardised MedDRA Queries |
| SSE | Symptomatic skeletal event |
| TTPP | Time to PSA progression |
| ULN | Upper limit of normal |
| WHO | World Health Organization |

## List of Key Terms

| Terms | Definition of terms |
|---|---|
| Adverse Event | An adverse event is any untoward medical occurrence in a patient administered a study drug or has undergone study procedure and which does not necessarily have a causal relationship with this treatment. |
| Data analysis cut-off date | A cut-off date will be set so that a minimum of 262 events for the primary variable, radiographic progression-free survival, occurred by that date. All data available for all visits occurring prior to or on the cut-off date will be reported. |
| Baseline | Observed values/findings that are considered as the value at the starting point. |
| Enroll | To register or enter into a clinical trial.<br>Note: once a patient has been enrolled, the clinical trial protocol applies to the patient. |
| Endpoint | A variable that pertains to the trial objectives |
| Intervention | The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics). |
| Investigational period | Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug is usually given to a patient 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. |
| Randomization | The process of assigning trial patients to treatment or control groups using an element of chance to determine assignments in order to reduce bias. |
| Screen failure | Potential patient who did not meet 1 or more criteria required for participation in a trial. |
| Screening | A process of active consideration of potential patients for enrollment in a trial. |
| Screening period | Period of time before entering the investigational period, usually from the time of starting a patient signing consent until just before the test drug or comparative drug is allocated to a patient (i.e. randomization). |
| 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

A 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. This SAP contains details related to analyses specific to the Open Label Extension Period (OLE), in addition to the SAP (version 3.0) used for the primary analysis.

The SAP is finalized and signed prior to database hard lock to ensure lack of bias. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

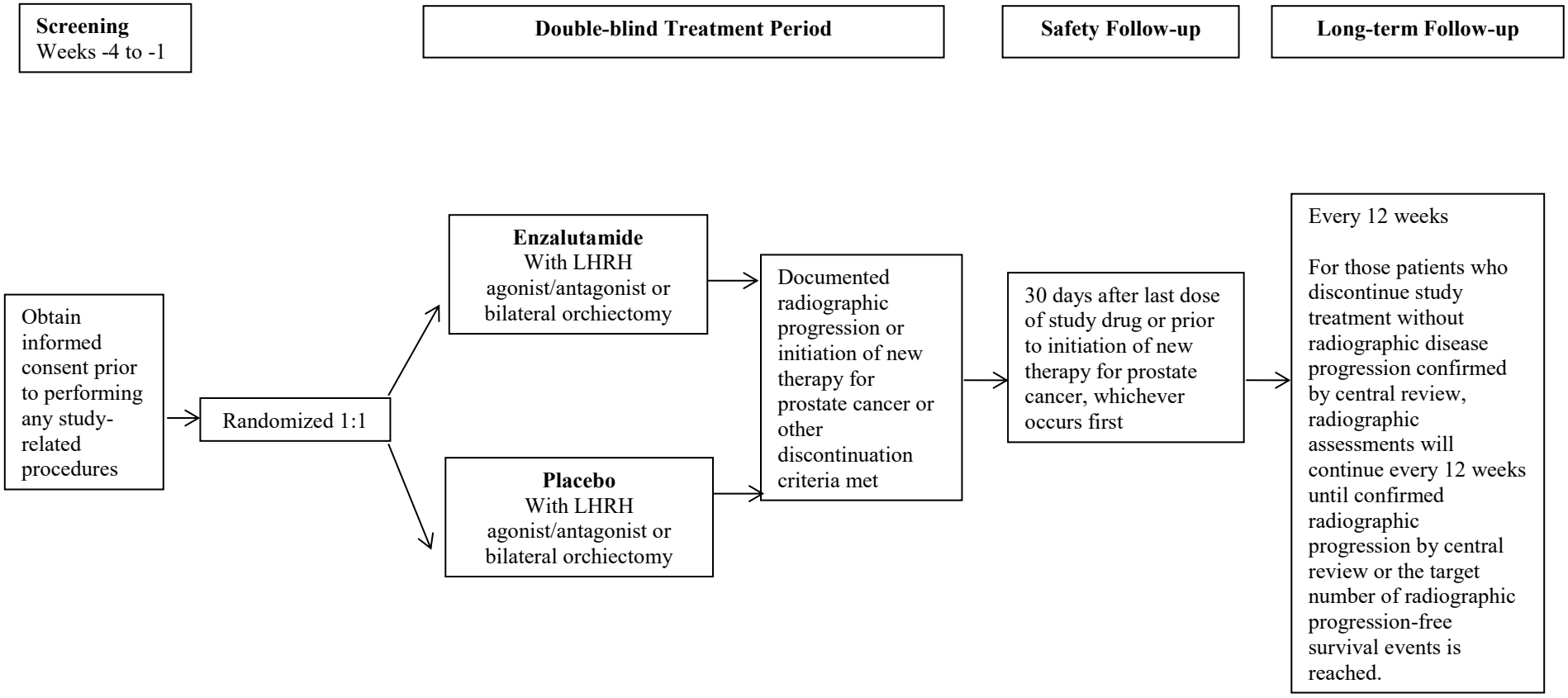
This statistical analysis is coordinated by the responsible biostatistician of Astellas Pharma. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report.

Prior to database hard lock, a final blinded review of data and TLFs meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for any new 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.

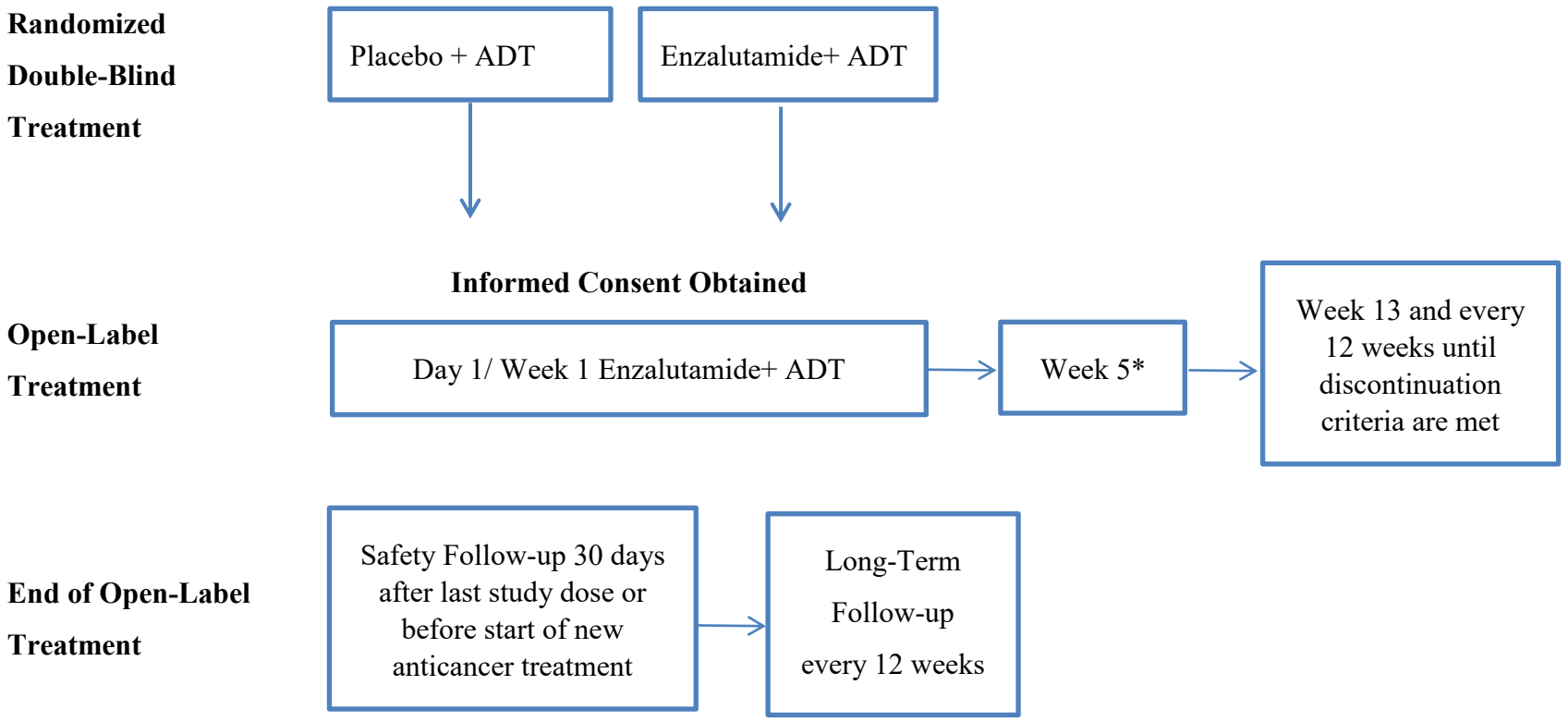
This SAP for the open-label extension is a supplement to the main study SAP which was completed prior to unblinding the study. The methods for the analysis of overall survival were established in the main study SAP. This SAP includes those methods and adds sensitivity and subgroup analyses for overall survival and an updated analysis for time to new antineoplastic. This SAP also describes the planned summaries for safety, disposition, and other data to incorporate the placebo patients who crossed over to open-label enzalutamide.

# 2 FLOW CHART AND VISIT SCHEDULE

## 2.1 Double blind Period



## 2.2 Open Label Extension




*Week 5 visit required only for subjects who received placebo + ADT during the double-blind period

**Table 1 Double-Blind Period Schedule of Assessments**

| Study Day | Screening Visit | 1 | 29 | 85 and Every Subsequent 84 Days | Safety Follow-up | Unscheduled Visit† | Long Term Follow-up‡ |
|---|---|---|---|---|---|---|---|
| Study Week | -4 to -1 (28 Days) | 1 | 5 | 13 and Every Subsequent 12 Weeks | 30 Days after Last Dose§ | | Every 12 Weeks |
| Window (Days) | | | ± 5 | ± 5 | ± 7 | NA | ± 7 |
| Informed Consent | X | | | | | | |
| Medical History | X | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | |
| Randomization (IRT) | | X | | | | | |
| Vital Signs | X | X | X | X | X | X | |
| Physical Examination including Weight¶ | X | X | X | X | X | X | |
| Height | X | | | | | | |
| 12-lead Electrocardiogram | X | X | | | X | | |
| Clinical Labs†† | X | X | X | X | X | X | |
| Prostate-specific antigen | X | X | X | X | X | | |
| Sample for Genotyping Analysis‡‡ | | X | | | | | |
| [redacted] CCI | | X | | X | | | |
| Testosterone | | | | X | | | |
| CT/MRI and Bone Scan§§, ¶¶ | X§§ | | | X¶¶ | | | X |
| Chest X-ray or Chest CT/MRI††† | X | | | X | | | X |
| ECOG Performance Status | X | X | X | X | X | X | |
| QoL Assessment (QLQ-PR25, EQ-5D-5L, FACT-P, BPI-SF) | | X | | X | X | | X‡ |
| Adverse Events§§§ | X | X | X | X | X | X | |
| Previous and Concomitant Medications | X | X | X | X | X | X | |
| Study Drug Dispensing | | X | X | X | | | |
| Study Drug Treatment | | X | X | X | | | |

CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L: EuroQol Group-5 Dimension-5 Level Instrument; IRT: Interactive Response Technology; MRI: magnetic resonance imaging; NA: not applicable; FACT-P: Functional Assessment of Cancer Therapy-Prostate; QLQ-PR25: Quality of Life Prostate-specific Questionnaire; QoL: quality of life; BPI-SF: Brief Pain Inventory-Short Form

† Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events at the patient's request or if deemed necessary by the Investigator. Procedures and assessments are to be performed as clinically indicated. Testosterone testing through central laboratory at unscheduled visit requires prior approval by sponsor.

*Footnotes continued on next page*

‡ After study drug discontinuation, all patients MUST undergo long term follow-up. Long term follow-up assessments will include monitoring for survival status, new antineoplastic therapies for prostate cancer, and symptomatic skeletal events. Follow-up may be conducted by telephone interview. Patients will continue to be scanned every 12 weeks until radiographic progression is confirmed by independent review or the number of radiographic progression-free survival events is reached. For patients continuing with radiographic assessments, if seen in clinic, QoL assessment will also be completed until the initiation of new antineoplastic therapy for prostate cancer or the number of progression events is reached. Additional follow-up contacts may be requested. Patients will be followed for overall survival until death, lost to follow up, overall survival final analysis or termination of the study by the sponsor.

§ Or prior to initiation of new antineoplastic therapy for prostate cancer, whichever occurs first.

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

†† Laboratory assessments include serum chemistries and hematology.

‡‡ Genotyping samples will only be collected from patients who agree to provide genotyping samples as documented by signing a separate genotyping informed consent form (ICF).

∫∫ [redacted] CCI

§§ The abdominal-pelvic CT scan or MRI, bone scan, chest x-ray or chest CT must occur within 6 weeks of day 1; otherwise the screening visit assessment must be repeated. Radiographic assessments performed prior to informed consent, as part of the routine care, may be used as the baseline assessment if performed within 6 weeks of day 1 and if digital format images are available for submission to the sponsor-designated independent central review facility.

¶¶ The window for all radiographic (CT/MRI) assessments is ± 7 days. For patients who discontinue study treatment without radiographic progression, confirmed by central review, patients will continue to be scanned every 12 weeks until radiographic progression is confirmed by independent review or the number of radiographic progression-free survival events is reached.

††† Chest CT is required at all imaging time points if screening chest x-ray demonstrates metastatic chest disease.

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

## Table 2 Open-Label Extension Schedule of Assessments

| Study Period or Visit | OL Treatment | | | Unscheduled Visit | OL Safety Follow-up | OL Long Term Follow-up |
|---|---|---|---|---|---|---|
| Study Week | OL 1[1] (Day 1) | OL 5[2] (Day 29) | OL 13 and every subsequent 12 weeks (Day 85 and every subsequent 84 days) | Varies[3] | 30 Days after Last Dose[4] | Every 12 Weeks |
| Window (Days) | NA | ± 3 | ± 5 | NA | ± 7 | ± 7 |
| Informed Consent[5] | X | | | | | |
| Inclusion/Exclusion Criteria for OLE | X | | | | | |
| Open-Label Enrollment (via IRT) | X | | | | | |
| Brief Physical Examination | X | | X | X | X | |
| Vital Signs including Weight | X | X | X | X | X | |
| ECOG Performance Status | X | X | X | X | X | X |
| 12-lead Electrocardiogram | X | | | | X | |
| Clinical Labs (including PSA) | X | X | X | X | X | |
| [redacted] CCI | X[7] | | X[6] | | | |
| Radiographic Assessments[7] | X | | X | | | X |
| QoL Assessment (QLQ-PR25, EQ-5D-5L, FACT-P, BPI-SF) | X | | X | | X | X |
| Adverse Events[8] | X | X | X | X | X | |
| Concomitant Medication Review | X | X | X | X | X | |
| Study Drug Dispensing (via IRT) | X | X | X | | | |
| Study Drug Accountability | X | X | X | | X | |
| Long-Term Follow-up Assessments[9] | | | | | | X |

ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L: Euro Qol Group-5 Dimension-5 Level Instrument; FACT-P: Functional Assessment of Cancer Therapy-Prostate; IRT: Interactive Response Technology; OL: Open-Label; OLE: Open-Label Extension; QLQ-PR25: Quality of Life Prostate-specific Questionnaire; QoL: Quality of Life.

1 For subjects previously receiving placebo, Open-Label (OL) Day 1/Week 1 should occur within approximately 16 weeks after the approval and activation of this protocol at the study site and no later than 6 weeks after screening. For subjects continuing treatment with enzalutamide, OL Day 1/Week 1 will be their next regular scheduled visit following approval and activation of this protocol at the study site.

2 Only for subjects starting new treatment with enzalutamide (previously received placebo).

3 As necessary to assess or follow up adverse events.

4 Prior to initiation of new antineoplastic therapy for prostate cancer, or 30 days after last dose of enzalutamide, whichever occurs first.

5 Informed consent must be obtained before performing any study-specific procedures on Day 1/Week 1 for all subjects participating in OL Period.

6 [redacted] CCI

7 For subjects who have not progressed radiographically, scans (CT/MRI and bone scan) will be performed every 12 weeks for the first year on enzalutamide and then every 24 weeks until the subject has progressed radiographically, as assessed by local read.

8 Adverse events will be collected from the time the subject signs the consent form until screen failure or through safety follow-up visit (prior to initiation of new antineoplastic therapy for prostate cancer, or 30 days after last dose of enzalutamide, whichever occurs first).

9 Long-term follow-up assessments include survival status, symptomatic skeletal events and new antineoplastic therapies for prostate cancer. May be obtained by telephone contact, chart review or clinic visit.

# 3 STUDY OBJECTIVE(S) AND DESIGN

## 3.1 Study Objective(s)

Refer to the study protocol for a full list of study objectives.

Efficacy objective in the open label extension period is to determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by overall survival (OS). Additionally, time to new antineoplastic therapy will be summarized descriptively as supportive information in the evaluation of the overall survival endpoint.

Safety objective is to determine the safety of enzalutamide plus ADT as compared to placebo plus ADT.

## 3.2 Study Design

This is a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of enzalutamide plus ADT versus placebo plus ADT in patients with mHSPC. After the double-blind period has completed, eligible patients were allowed to received open label enzalutamide in an open label extension period.

Approximately 1100 subjects were randomized centrally 1:1, and the randomization was stratified by volume of disease (low versus high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1-5 cycles, 6 cycles). High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Prior docetaxel therapy is defined as 1 or more cycles of docetaxel but no more than 6 cycles.

In this study, patients received 4 capsules of enzalutamide (40 mg each) or placebo per day orally in the double-blind period. After the double-blind period has completed, eligible patients received 4 capsules of enzalutamide (40 mg each) in the open label extension period. As long as the patient is tolerating the study drug, the treatment should be continued until radiographic disease progression (rPD) or starting an investigational agent or new therapy for treatment of prostate cancer. Patients who discontinue study drug without radiographic progression will continue to follow the radiographic assessment schedule until radiographic progression event or until the target number of deaths is reached for the final analysis of OS.

The following assessments of prostate cancer status will be collected during OLE: soft tissue disease on CT scan or on MRI, bone disease on radionuclide bone scans, survival status, EQ-5D-5L, QLQ-PR25, FACT-P for QoL and BPI-SF for pain symptom assessment. Throughout the study, safety and tolerability were assessed by the recording of adverse events (AE), vital signs, physical examinations, 12-lead electrocardiograms (ECG), and safety laboratory evaluations (including PSA).

Patients will have a safety follow-up visit 30 days after their last dose of study drug or prior to initiation of new antineoplastic therapy for prostate cancer, whichever occurs first. All

patients are to be followed for survival until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. All patients will be followed until the final OS analysis.

## 3.3 Randomization

Subjects were entered into the Interactive Response Technology system (IRT) at screening and assigned a subject number.

After the double-blind period, which included random assignment to enzalutamide or placebo (stratified by prior docetaxel use and disease volume), eligible patients were allowed to received open label enzalutamide, as recorded in the IRT system.

# 4 SAMPLE SIZE

For OS, 342 death events will be required to provide 80% power to detect a target HR of 0.73 with a target difference in Kaplan-Meier estimated median of approximately 15 months (40 months for placebo versus 55 months for enzalutamide) at the 4% significance level under the assumption of an exponential distribution. This significance level was chosen to apply a parallel testing strategy between OS and other key secondary endpoints (with allocated type I error rate of 1%) as described in section 7.4.1.

# 5 ANALYSIS SETS

## 5.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all subjects who were randomized in this study. The ITT population will be analyzed by treatment arm as randomized, (i.e., treatment arm by randomization assignment) regardless of whether or not study drug was administered. The ITT population will be used to conduct efficacy analyses, unless otherwise specified.

## 5.2 Safety Population

The safety (SAF) population is defined as all randomized subjects who received at least 1 dose of study drug. The safety population will be used to conduct safety analyses by treatment arm as treated (i.e., based on the actual study drug the subject mostly received, rather than the study drug to which the subject was randomized to).

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. This was done prior to unblinding.

# 6 ANALYSIS VARIABLES

Analysis variables are defined in the SAP for the primary analysis. This section further details those for which data derivation require to be modified.

## 6.1 Overall Survival

OS is defined as the time from randomization to death from any cause. All deaths on or before the data cut-off will be included.

For patients who are alive at the time of the cut-off date, OS time will be censored on the last date the patient is known to be alive or the cut-off date, whichever occurs first. The date the patient is last known alive by the cut-off date will be derived as follows:

- for patients on treatment by the cut-off date (i.e., patients who did not discontinue from treatment), the date last known alive will be the cut-off date.
- for patients who withdraw consent by the cut-off date, the date last known alive is the date of consent withdrawal.
- for patients lost to follow up, the date last known alive depends on the period the patient was lost to follow-up. It will be as follows:

| Period lost to follow-up | The date last known alive |
|---|---|
| Since randomization (i.e. without further post-randomization visit) | The date of randomization |
| During treatment period | The last assessment/visit date or the date of the last dose of study drug, whichever occurs later |
| Safety follow-up period | The date of the last dose of study drug or the last treatment visit date collected on the End of Treatment Case Report Form (CRF) page, whichever occurs last. |
| Long-term follow-up period | The last visit/contact date (collected either on the 30 Day Follow-Up Status CRF page, or the Patient Status - Survival CRF page or the Long-Term Follow-Up Status CRF page). |

- for other patients (i.e., not on treatment, not withdrawn and not lost to follow-up) who are alive by the cut-off date, the date last known alive is the date of last visit (collected either on the Patient Status - Survival CRF page or the Long-Term Follow-Up Status CRF page) or the date of randomization, whichever occurs last.

## 6.2 Time to Initiation of a New Antineoplastic Therapy

The initiation of a new antineoplastic therapy is based on the information collected in the (new) prostate cancer therapy CRF pages about all antineoplastic therapies, including cytotoxic and hormone therapies, initiated for prostate cancer subsequent to the study drug.

In patients with a new antineoplastic therapy initiated for prostate cancer, time to initiation of a new antineoplastic therapy (i.e., time to new antineoplastic therapy) is defined as the time interval from randomization to the date of first dose administration of the first antineoplastic therapy.

In patients with no new antineoplastic therapy initiated for prostate cancer, time to start of new antineoplastic therapy will be censored on the last visit date or the date of randomization, whichever occurs last.

## 6.3 Treatment Emergent Adverse Event (TEAE)

A TEAE is defined as an AE that occurs or worsen at any time during the treatment emergent period. The treatment emergent period is time interval encompassing the double-blind treatment emergent period and the OLE treatment emergent period.

The double-blind treatment emergent period is defined as the time interval from the first double-blind study drug intake up to 30 days after the date of the last dose of double-blind study drug, study discontinuation, the start of new antineoplastic therapy, or the first dose of OLE treatment, whichever occurs first.

If AE start date is the same date as the study start, then it will be considered as a TEAE if the box *'Onset after first dose of study'* is ticked in the Electronic case report form(eCRF). If a patient experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e. it is reported with a new start date).

The OLE treatment emergent period is defined as the time interval from the OLE study drug intake up to 30 days after the date of the last dose of OLE study drug, study discontinuation, or the start of new antineoplastic therapy, whichever occurs first.

AE with both a missing start and stop dates, and AEs with a missing start date but has a known stop date which is on or after the first dose of study drug will be considered treatment-emergent.

For each treatment group, the treatment emergent period is as follows;

- Enzalutamide group: from the first DBT study drug intake up to 30 days after the date of the last dose of study drug, study discontinuation, or the start of new antineoplastic therapy, whichever occurs first.
- Placebo group: from the first DBT study drug intake up to 30 days after the date of the last dose of placebo, start of open-label enzalutamide, study discontinuation, or the start of new antineoplastic therapy, whichever occurs first.
- Placebo crossover group: from the first OLE study drug intake up to 30 days after the date of the last dose of OLE study drug, study discontinuation, or the start of new antineoplastic therapy, whichever occurs first.

AEs will be coded to System Organ Class (SOC) and preferred term using MedDRA v23.0 and severity graded using National Cancer Institute's Common Terminology Criteria version 4.03 (NCI-CTCAE v4.03) for AEs.

# 7 STATISTICAL METHODOLOGY

## 7.1 General Considerations

For continuous variables, descriptive statistics will include the number of patients (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. Unless otherwise specified, percentages by categories will be based on the number of patients with no missing data, i.e. will add up to 100%.

All listings will be produced by site and patient id numbers in ascending order.

Disposition, demographics, other baseline characteristics and efficacy data will be summarized based on the ITT population, unless stated otherwise. Safety analysis summary and other summaries based on SAF are presented by actual treatment received, unless stated otherwise.

All statistical comparisons will be made using two sided tests. All null hypotheses will be of no treatment difference.

All data processing, summarization, and analyses will be performed using SAS® Version 9.4 or higher on Unix. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

For the definition of subgroups of interest, please refer to section 7.9.

A data analysis cut-off date for the database will be used. All data from visits or assessments done on or prior to the cut-off date will be reported.

## 7.2 Study Population

### 7.2.1 Disposition of Subjects

The following subject data will be presented for Enzalutamide, Placebo and Placebo crossover group:

- Number of patients randomized in DBP, received treatment in DBP, with ICF for OLE and received treatment in OLE (All Randomized Subjects).
- Treatment disposition in DBP (All Randomized Subjects) and OLE (All subjects on Enzalutamide)
- Number of patients who took study drug, patients who did not take study drug in DBP and OLE
- Number and percentage of patients by study visits completed in DBP and OLE, based on the SAF
- Number and percentage of patients who discontinued from the treatment in DBP and OLE by primary reason for discontinuation
- Number and percentage of patients who discontinued from the 30 day safety follow-up in DBP and OLE by primary reason for discontinuation
- Number and percentage of patients who discontinued from the long term follow-up in DBP, OLE and overall by primary reason for discontinuation
- Number of patients with protocol deviations in DBP and OLE
- Number of OLE patients by site and country

Treatment disposition, 30 day follow-up disposition, and long term follow-up disposition, randomization information will be listed. The protocol deviations, as well as the description of protocol deviation criteria will also be listed.

### 7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all randomized patients.

The protocol deviation criteria will be uniquely identified in the summary table by study period (DBP and OLE) and in 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.

Patients deviating from a criterion more than once will be counted once for the corresponding criterion. Any patients who have more than one protocol deviation will be counted once in the overall summary.

The number and percentage of patients meeting any criteria will be summarized for each criterion and in total, for Enzalutamide, Placebo and Placebo crossover group, as well as by country, study site and by study period. Inclusion and exclusion criteria will be summarized for each criterion for Placebo crossover group.

A data listing will be provided by site and patient, where each protocol deviation will be indicated according to the period in which it had occurred.

### 7.2.3 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics (at the time of randomization) will be summarized for Placebo crossover group on the ITT.

Descriptive statistics for age and height at study entry will be presented along with frequency tabulations for age group (< 65, 65- <75 and >= 75; and EudraCT age groups), ethnicity, race, Geographic region, at study entry. The weight, body mass index (BMI), ECOG status, PSA, and ALP at baseline will also be presented by descriptive statistics. The 10%, 25%, 75% and 90% percentiles will be provided for PSA, and ALP at baseline.

Disease History, Results of Metastasis at screening, Prostate Cancer Treatment History (Radiation and Procedures) and Non-Prostate Cancer Related Medical History will be summarized for Placebo cross-over group on the ITT.

Number and percentage of patients randomized in each country and site will also be summarized.

### 7.2.4 Concomitant Medications and New Antineoplastic Therapy

Concomitant medications will be summarized Enzalutamide, Placebo and Placebo crossover group and by study period on the SAF.

Those medications, including prostate cancer drug therapies, will be coded with World Health Organization Drug Reference List (WHO-DD), and will be summarized by presenting the number and percentage of patients by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name. It will be ordered alphabetically by ATC subgroup and decreasing order of frequency of preferred WHO name

within each ATC class. Patients taking the same medication multiple times will be counted once per medication and period.

Concomitant medications are those medications or therapies with at least one dose taken between the date of first dose (inclusive) of enzalutamide and the date of last dose (inclusive) of enzalutamide and up to 30 day safety follow-up visit. All concomitant medications will be summarized.

New antineoplastic prostate cancer therapy will be summarized for patients from the ITT population.

New antineoplastic prostate cancer therapy are therapies with at least one dose taken after the last dose of study drug (enzalutamide or placebo), including cytotoxic and hormone therapies. They are recorded as 'antineoplastic medication' in the eCRF (either prostate cancer concomitant eCRF page, with 'antineoplastic medication' ticked; or on the new prostate cancer drug therapy eCRF page with 'antineoplastic medication' ticked).

All concomitant prostate cancer related medications or therapies reported in the corresponding eCRF will be summarized separately. All (new) antineoplastic prostate cancer therapies (started on or after first dose of study drug date) will also be summarized separately, along with a summary table on the first new antineoplastic prostate cancer after study drug (after placebo or enza [in double blind or OLE]) ended.

All concomitant non prostate cancer related medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

All concomitant medications recorded in the eCRF will be listed, as well as all new prostate cancer therapies.

## 7.3 Study Drugs

### 7.3.1 Exposure

The following information on drug exposure will be presented for Enzalutamide, Placebo and Placebo crossover group on the SAF.

- The duration of exposure (number of months) to study medication will be summarized using descriptive statistics, including 10%, 25%, 75% and 90% percentiles.
- Number and percentage of patients on study drug at 6 months and at year 1, 2, 3, and 4 (that is with duration of exposure superior or equal to day 182, 365, 730, 1095, and 1461).
- Number and percent of patient with dose reductions or interruptions, the reasons for these, as well as the number of these per patient
- Descriptive statistics for the average daily dose of the drug patient was exposed to
- Time to study drug discontinuation will be analyzed using the same analysis methods as OS, but formal statistical test will not be conducted.

### 7.3.2 Compliance

Compliance data will be presented for the SAF, on subjects whose total study drug count and first and last days of treatment are known.

Overall compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented by treatment group.
- Percent compliance will be categorized according to the following categories for each age group and overall by treatment group:
  - less than 70%
  - at least 70%, less than 90%
  - at least 90%, less than 110%
  - greater than 110%
  - Unknown.

Treatment compliance details, including all data relevant to the calculation, will be listed for each subject by study visit and overall for all randomized subjects.

## 7.4 Analysis of Efficacy

Efficacy analyses will be conducted on the ITT population unless otherwise specified.

The categories '1-5 cycles' and '6 cycles' used at randomization for the stratification factor 'prior docetaxel use' are regrouped in the stratified analyses because of the small number of randomized patients with 1 to 5 cycles of docetaxel as prior medication. This stratification factor therefore becomes prior docetaxel use (yes versus no) in the stratified analyses.

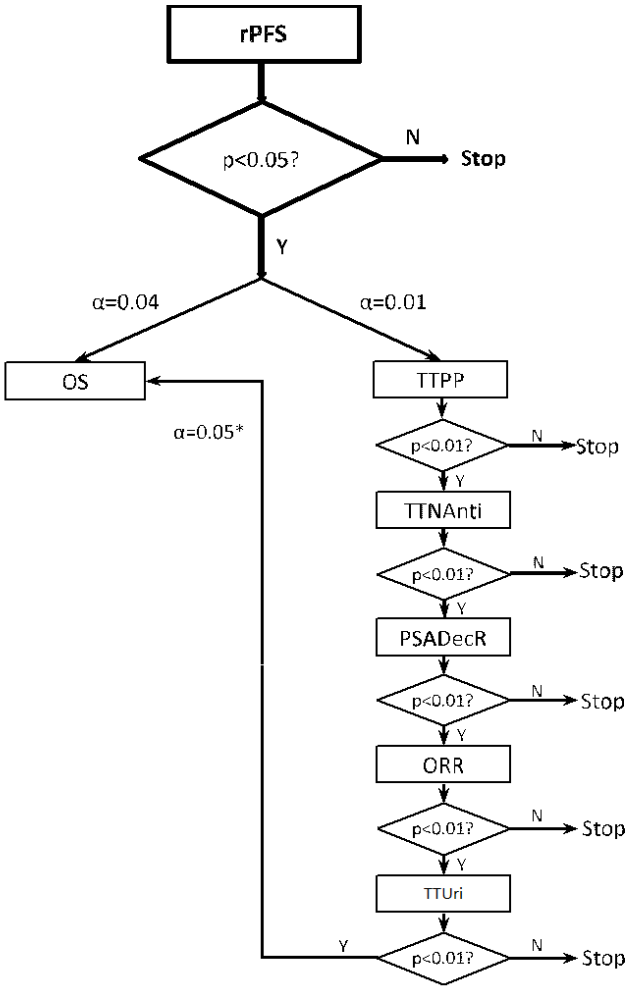
The statistical analyses in this SAP follow the methods already outlined in the main study SAP and include additional sensitivity and subgroup analyses.

### 7.4.1 Overall Survival

At the time of the primary analysis of rPFS, the interim analysis of OS was not significant (84 deaths from any cause, 39 in Enzalutamide + ADT group and 45 in Placebo + ADT group, p=0.3361 from stratified log-rank test). The final analysis of OS will be conducted when approximately 342 events (death from any cause) have occurred.

At the time of the primary analysis of rPFS, the following six key secondary endpoints were tested: OS, Time to PSA progression, time to initiation of a new antineoplastic therapy, the rate of PSA decline to <0.2ng/mL (PSADecR), objective response rate and the time to deterioration in urinary symptoms from the QLQ-PR25. To maintain the family-wise 2-sided type I error rate at 0.05, a parallel testing strategy between OS (with allocated type I error rate 0.04) and the other five endpoints (with allocated type I error rate 0.01) was performed, as summarized in Figure 1.

**Figure 1 Testing Strategy for the Primary and Six Selected Secondary Endpoints**




rPFS: radiographic progression-free survival; OS: overall survival; TTPP: time to PSA progression;
TTNAnti: time to initiation of a new antineoplastic therapy; PSADecR: rate of PSA decline to <0.2 ng/mL;
ORR: objective response rate; TTUri: the time to deterioration in urinary symptoms from the QLQ-PR25
*OS will be tested at 0.05 only, if all other 5 secondary endpoints analyses are statistically significant at 0.01.

As the analysis for time to deterioration in urinary symptoms from the QLQ-PR25 was not significant, the final analysis of OS will be conducted at the level of significance of 0.04 (2-sided). The effect of Enzalutamide+ADT compared to placebo+ADT will be tested using a log-rank test stratified by prior docetaxel use (yes versus no) and disease volume (low versus high).

The null and alternative hypotheses to be tested are as follows:

The null hypothesis: OS for Placebo+ADT and Enzalutamide+ADT are not different
The alternative hypothesis: OS for Placebo+ADT and Enzalutamide+ADT are different

The following SAS code will be used to compute the Kaplan-Meier estimates and curves, and the stratified log-rank test:

```
PROC LIFETEST DATA=INPUT
              ATRISK
```

```
                    PLOTS=SURVIVAL(CB)
                    OUTSURV=SURVPL
                    ALPHA=0.04
                    ALPHAQT=0.04 METHOD=KM;
        TIME AVAL*CNSR(1);
        STRATA STRATUM/ GROUP=TREATMENT;
    RUN;
```

where INPUT is the input dataset

AVAL is the time to the event variable,

CNSR is 0 (patients with events) or 1 (patients without no event, i.e. patient censored)

STRATUM is the stratification variable (volume of disease and prior docetaxel use)

TREATMENT is the treatment variable

Kaplan-Meier methods will be used to estimate the distribution of OS events by treatment group. The median OS will be estimated using the corresponding 50th percentile of Kaplan-Meier estimates. A two-sided 95% confidence interval will be provided for this estimate by use of the Brookmeyer and Crowley method. The 25$^{th}$ percentile and the 75$^{th}$ percentile of OS will also be provided. A Kaplan-Meier plot by treatment group will be presented. The estimates of the event free rate on a 3-monthly basis up to 1 year and every 6 months thereafter will be summarized by treatment group, as long as at least 10 patients are at risk.

The benefit of Enzalutamide+ADT compared to placebo+ADT will be summarized by a single HR with its 95% CI based on a Cox regression model stratified for the prior docetaxel use and disease volume. The null and alternative hypotheses regarding OS can be rephrased in terms of the HR, $\lambda_{ArmA} / \lambda_{ArmB}$, where $\lambda_{ArmA}$ represents the hazard of OS for Enzalutamide+ADT and $\lambda_{ArmB}$ represents the hazard of OS for placebo+ADT. A HR of < 1 indicates that the OS is prolonged for patients randomized to Enzalutamide+ADT compared with patients randomized to placebo+ADT. The null and alternative hypotheses, respectively, can be written as follows:

$$H_0: \frac{\lambda_{ArmA}}{\lambda_{ArmB}} = 1 \qquad H_1: \frac{\lambda_{ArmA}}{\lambda_{ArmB}} \neq 1$$

The estimated HR of Enzalutamide+ADT to placebo+ADT, $\lambda_{ArmA} / \lambda_{ArmB}$ , and its 95% confidence interval will be provided.

SAS PROC PHREG will be used for the analysis with the “DISCRETE” option for tie breaker as follows:

```
    PROC PHREG DATA=ADTTE;
       WHERE PARAMCD=&ENDPOINT;
       CLASS TRTP(REF='PLACEBO + ADT') STRATUM1 STRATUM2;
       MODEL AVAL*CNSR(1)= TREATMENT / RL TIES=DISCRETE;
       STRATA STRATUM1 STRATUM2;
    RUN;
```

where INPUT is the input dataset

AVAL is the time to the event variable,

CNRS is 1 (patients with no events) or 0 ( patients with events)
STRATUM are the stratification variables (volume of disease and prior docetaxel use)
TREATMENT is the treatment variable

If the estimate of the HR $\lambda_{ArmA} / \lambda_{ArmB} < 1$ and the results from the log-rank test lead to the rejection of $H_0$ in favor of $H_A$, then it will be concluded that Enzalutamide+ADT prolongs OS compared to placebo+ADT.

The primary cause of death will be summarized and listed.

The median follow-up time on study will be calculated as the 50th percentile of Kaplan-Meier estimates from the OS time analysis when reverting the censoring (flag).

**Subgroup analyses**

Subgroup analyses of OS will similarly be performed to determine whether the treatment effect is concordant among subgroups. To avoid possible issue related to small number of events, subgroup analyses will not be adjusted for the stratification factors used at randomization. Subgroups are defined in Section 7.9.

A forest plot displaying the HR for treatment comparison and 95% confidence interval will be presented by subgroup. The HR will be estimated by use of Cox proportional hazards models with treatment as covariate.

SAS PROC PHREG will be used for these subgroup analyses:

```
PROC PHREG DATA=ADTTE;
   WHERE PARAMCD=&ENDPOINT;
   CLASS TRTP(REF='PLACEBO + ADT') STRATUM1 STRATUM2;
   MODEL AVAL*CNSR(1)= TREATMENT / RL TIES=DISCRETE;
  BY SUBGROUP;
RUN;
```

**Sensitivity analyses**

- To adjust the treatment crossover effect on OS, the following methods may be used.
  - Rank-Preserving Structural Failure Time Model (RPSFTM) [Robins and Tsiatis, 1991]). This method is to assess the impact of patients who switched placebo to enzalutamide by reconstructing the survival duration of placebo patients, as if they had never received enzalutamide.
- To assess potential impact of COVID-19, the following analyses may be conducted.
  - Same as OS primary analysis, except that patients died due to COVID-19 infection will be censored at the date of death.
  - Same as OS primary analysis, but exclude the subjects died due to COVID-19 infection from the analysis.
- To estimate the size of the treatment effect separately for 2 time periods, before and after the first 6 months from randomization, piecewise exponential model may be used to estimate the HR.

### 7.4.2 Time to Initiation of a New Antineoplastic Therapy

This will be analyzed using the same analysis methods as OS, but formal statistical test will not be conducted.

## 7.5 Analysis of Safety

All analysis of safety will be presented for Enzalutamide, Placebo and Placebo crossover group on the SAF, unless specified otherwise. All AEs will be listed.

### 7.5.1 Adverse Events

The coding dictionary for this study will be MedDRA v23.0. Treatment-emergent AEs will be coded to SOC and preferred terms using MedDRA and graded using NCI-CTCAE v4.03.

Treatment-emergent AEs will be tabulated alphabetically by SOC and by preferred terms within SOC.

An overview table will include the following details for Enzalutamide, Placebo and Placebo crossover group:

- Number of TEAEs,
- Number and percentage of patients with TEAEs,
- Number of NCI-CTC grades 3 and 4 TEAEs,
- Number and percentage of patients with NCI-CTC grades 3 and 4 TEAEs,
- Number of drug related TEAEs,
- Number and percentage of patients with causally drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of patients with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of patients with serious drug related TEAEs,
- Number of TEAEs leading to death,
- Number and percentage of patients with TEAEs leading to death,
- Number of drug related TEAEs leading to death,
- Number and percentage of patients with drug related TEAEs leading to death,
- Number of TEAEs leading to withdrawal of treatment,
- Number and percentage of patients with TEAEs leading to withdrawal of treatment,
- Number of drug related TEAEs leading to withdrawal of treatment,
- Number and percentage of patients with drug related TEAEs leading to withdrawal of treatment.
- Number of TEAEs leading to dose reduction,
- Number and percentage of patients with TEAEs leading to dose reduction,
- Number and percentage of death

The number and percentage of patients with TEAEs, as classified by SOC and preferred terms will be summarized for each treatment group. Summaries will be provided for:

- TEAEs
- NCI-CTC grade 3 or higher 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 dose reduction,
- TEAEs leading to dose interruption,
- TEAEs, excluding serious AEs, that equal to or exceed a threshold of 5.0% in any treatment group,
- TEAEs leading to death,
- drug related TEAEs leading to death,

The number and percentage of patients with TEAEs, classified by preferred terms by decreasing frequency within the enzalutamide group will also be summarized.

The number and percentage of patients with TEAEs, as classified by SOC and preferred terms will also be summarized by maximum severity (reported according to NCI-CTCAE version 4.03).

In the patient count, if a patient has multiple TEAEs with the same SOC or PT, but with different severity, then the patient will be counted only once with the worst severity. However, if any of the severity values are missing then the patient will be counted only once with missing severity. In the AE count, the AEs will be presented in each category they were classified to. Summaries will be provided for:

- TEAEs by NCI- CTCAE
- drug related TEAEs by NCI- CTCAE,
- serious TEAEs by NCI- CTCAE

The number and percentage of patients with TEAEs that equal to or exceed a threshold of 5.0% in any treatment group, classified by preferred terms (by decreasing frequency within the enzalutamide group) will be summarized by treatment group and time interval. The percentage of patients are calculated based on the number of patients still on treatment at the time-point corresponding to the lower limit of the time intervals. Time intervals will be categorized according to the following categories:

- ≤3 months;
- >3 months to ≤6 months;
- >6 months to ≤12 months;
- >12 months to ≤24 months;
- >24 months to ≤36 months;
- >36 months.

To adjust for the treatment duration, the number of TEAEs per 100 patients-years will be summarized, as classified by SOC and PT, per treatment group and CTI-CTC grade (3-5 and total). The number of TEAEs per 100 patients-years is calculated as the number of events

*100 / (sum of the treatment emergent period duration of all patients treated in the corresponding treatment group, in years).

## AEs of Special Interest

AEs of special interest are defined in Table 3.

**Table 3 Selection Criteria for AEs of Special Interest**

| **Event of special interest** | |
|---|---|
| Convulsions (seizure) | Narrow SMQ of 'Convulsions' |
| Hypertension | Narrow SMQ of 'Hypertension' |
| Neutrophil count decreased | Preferred terms of 'Neutrophil count decreased', 'Neutropenia', 'Agranulocytosis',' Granulocyte count decreased', 'Granulocytopenia', 'Febrile neutropenia', 'Neutrophil percentage decreased', 'Band neutrophil count decreased', and 'Band neutrophil percentage decreased' 'Neutropenic sepsis', 'Neutropenic infection', 'Neutrophil count abnormal' |
| Cognitive and memory impairment | All preferred terms in MedDRA HLGT '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,' 'Ischaemic central nervous system vascular conditions' and 'Cardiac failure' |
| Posterior reversible encephalopathy syndrome (PRES) | Preferred term 'Posterior reversible encephalopathy syndrome' |
| Fatigue | Preferred terms of 'Fatigue', 'Asthenia' |
| Renal disorder | Broad SMQ of 'Acute Renal Failure' |
| Second primary malignancies | Narrow SMQs of 'Malignant or unspecified tumours' customized to exclude preferred terms of 'Congenital fibrosarcoma', 'Congenital malignant neoplasm', 'Congenital retinoblastoma', ', "Metastases to…", 'Metastasis', 'Metastatic neoplasm', 'Prostate cancer…', 'Carcinoid tumour of the prostate','neoplasm prostate'<br>AND (inclusive of) Narrow SMQ of 'Myelodysplastic syndrome'<br>AND (inclusive of) All preferred terms under HLT of 'Myeloproliferative disorders (excl. leukaemias)'<br><br>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') |
| *Table continued on next page* | |

| **Event of special interest** | |
|---|---|
| Fall | Preferred term of 'Fall' |
| Fracture | All preferred terms under the MedDRA HLGT of 'Fractures', 'Bone and joint injuries' |
| Loss of consciousness | Preferred terms of 'Loss of consciousness', 'Syncope',' Presyncope' |
| Thrombocytopenia | Preferred terms of 'Thrombocytopenia', 'Platelet count decreased' |
| Musculoskeletal events | Preferred terms 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' |
| Angioedema | Narrow SMQ of 'Angioedema' |
| Rash | Preferred terms 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 morbilliform', 'Rash neonatal', 'Rash papular', 'Rash papulosquamous', 'Rash pruritic', 'Rash pustular', 'Rash rubelliform', 'Rash scarlatiniform', 'Rash vesicular', 'Septic rash', 'Systemic lupus erythematosus rash', 'Vasculitic rash', 'Viral rash', 'Vulvovaginal rash' |
| Hepatic disorder | Narrow SMQs of 'hepatic failure, fibrosis and cirrhosis and other liver damage related conditions', 'hepatitis, non-infectious' and 'liver related investigations, signs and symptoms' |

An overview table of the TEAEs of special interest will be described by the number and percentage of patients with TEAEs of special interest per treatment group and overall.

### 7.5.2 Clinical Laboratory Evaluation

Laboratory assessment will be done for the following parameters:

| **Hematology** | **Biochemistry** | **Other** |
|---|---|---|
| Red blood cell count<br>White blood cell count<br>White blood cell differential<br>Hemoglobin<br>Hematocrit<br>Platelet count | Albumin<br>Alkaline phosphatase (ALP)<br>Alanine aminotransferase (ALT)<br>Aspartate aminotransferase (AST)<br>Blood urea nitrogen<br>Calcium<br>Creatinine<br>Glucose<br>Phosphorus<br>Potassium<br>Sodium<br>Total bilirubin<br>Total protein | Testosterone<br>PSA |

Quantitative clinical laboratory variables (hematology, serum chemistry and testosterone), will be summarized using mean, standard deviation, minimum, maximum and median for Enzalutamide, Placebo and Placebo crossover group at each visit. Additionally, a within-patient change will be calculated as the post-baseline measurement minus the baseline

measurement and summarized in the same way. Baseline is defined as the last available measurement prior to the first dose (double-blind or open-label extension).

Based on the NCI-CTCAE grade of laboratory data, clinical laboratory evaluations will be summarized by grade and by visit, for their comparison to the upper limit. Shift analysis tables on the enzalutamide group will present the shift from baseline to each visit and to the highest grade among the post-baseline visits, by grade. The number and percentage of patients with an increase in grade will be summarized by visit.

Each laboratory result will also be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

Laboratory data will be displayed in listings, along with their NCI-CTCAE grade.

#### 7.5.2.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria for liver tests - ALP, ALT, total bilirubin, AST, and their combination - are defined. The patient's highest value during the investigational period will be used.

| Parameter | Criteria (*Upper limit of normal[ULN]*) |
|---|---|
| ALT or AST | > 3xULN<br>> 5xULN<br>> 8xULN |
| Total Bilirubin | > 2xULN |
| ALT and/or AST AND Total Bilirubin(*) | (ALT and/or AST > 3xULN) and<br>total bilirubin > 2xULN |
| ALT and/or AST AND Total Bilirubin (*) AND Alkaline phosphatase | (ALT and/or AST > 3xULN) and<br>total bilirubin > 2xULN and Alk phos <2x ULN |

(*) Combination of values measured within same sample

The number and percentage of patients with potentially clinically significant values in liver enzyme and total bilirubin tests during the investigational period will be presented by treatment group and overall.

### 7.5.3 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be summarized using mean, standard deviation, minimum, maximum and median for Enzalutamide, Placebo and Placebo crossover group at each visit. Additionally, a within-patient change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized in the same way. Baseline is defined as the last available measurement prior to the first dose (double-blind or open-label extension).

Finally based on the patient's highest value during the treatment period, a summary will present the number and percentage of patients with blood pressure elevation (systolic: ≥ 140 mmHg, ≥ 180 mmHg; diastolic: ≥ 90 mmHg, ≥ 105 mmHg), with increase from

baseline (systolic: ≥ 10 mmHg, ≥ 20 mmHg; diastolic: ≥ 5 mmHg, ≥ 15 mmHg) or combination criteria (systolic: ≥ 140 mmHg & ≥ 20 mmHg increase from baseline, ≥ 180 mmHg & ≥ 20 mmHg increase from baseline; diastolic: ≥ 90 mmHg & ≥ 15 mmHg increase from baseline, ≥ 105 mmHg & ≥ 15 mmHg increase from baseline) or any of these criteria.

All vital signs results will be provided in a listing.

### 7.5.4 Electrocardiograms

12 Lead ECG results and change from baseline will be summarized using mean, standard deviation, minimum, maximum and median for Enzalutamide, Placebo and Placebo crossover group at each visit. Baseline is defined as the last available measurement prior to the first dose (double-blind or open-label extension).

Number and percent of patients with normal, not clinically significant abnormal and clinically significant abnormal results for the 12 lead ECG will be tabulated by treatment arm and visit.

QTc will be calculated using Fridericia Formula, QTcF= QT interval / $RR^{1/3}$.
Note: unit for RR is seconds.

All ECG results will be provided in a listing.

Any abnormal findings/conditions identified during the physical examination are reported in the medical history form or AE form. As a consequence, no separate physical examination listing can be produced.

### 7.5.5 Pregnancy

Not applicable.

### 7.5.6 Other Safety-Related Observations

The number and percentage of patients falling in each category of the performance status ECOG score will be summarized per visit and will be listed.

## 7.6 Analysis of Exploratory Endpoint

Not applicable.

## 7.7 Analysis of Pharmaco-kinetic

Not applicable

## 7.8 Analysis of Pharmaco-dynamic

Not applicable.

## 7.9 Subgroups of Interest

Subgroup analyses of OS will be conducted to assess the consistency of the treatment effect across the following subgroups of interest:

- Age category (less than 65 years old versus 65 years old or more);

- Geographic region (Europe, North America, Rest of the World);
- ECOG Performance Status (0 versus 1) at baseline;
- Gleason score (less than 8 versus 8 or more) at initial diagnosis;
- Disease location (bone only, versus soft tissue only, versus both bone and soft tissue) at baseline;
- Baseline PSA value (at or below overall median versus above overall median);
- Volume of disease at baseline (low versus high)
- Prior docetaxel use (yes versus no)
- Previous use of ADT or orchiectomy (yes versus no)

## 7.10 Other Analyses

Not applicable.

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

Not applicable

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

The baseline measurement is the last measurement taken prior to initial study drug administration (double-blind or open-label extension). Both date and time of drug administration and measurement should be considered to identify the baseline value. If the time is not available, then date only will be used, and it will be considered that assessments on day 1 are done pre-dose.

Change from baseline is defined as (post baseline value - baseline value).

To calculate time interval duration, a month is 30.4375 days and a year 365.25 days. Duration expressed in years or months are rounded up to 1 significant digit. The duration between 2 dates d1 and d2 is (d2-d1+1) in days (with d1 before d2).

Treatment day and study day will be calculated in reference to the date of the first dose of study drug. Treatment Day 1 corresponds to the date the patient received the first dose of study drug. For assessments conducted on or after the date of the first dose of study drug, treatment day will be calculated as (assessment date - date of first dose of study drug) + 1. There will be no Treatment Day 0.

Unless otherwise specified, the date of study drug discontinuation refers to the study drug last dose date.

Time to event endpoints will be based on the actual date of event rather than visit date. The date of randomization will always be considered as the start date for the time interval.

For laboratory results collected as < or > a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value unless otherwise specified.

Percentages will be calculated based on the number of patients with non-missing data as the denominator unless otherwise specified.

### 7.12.1 Missing Data

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs, previous and concomitant medications, the date of initial diagnosis (to estimate the relative study day to calculate cancer duration), dates of cancer treatment (e.g. previous procedure, previous radiotherapy, etc.…), the last dose date and the date of death.

The imputed dates will be used to allocate the relative study day, and in addition to determine whether an AE is/is not treatment emergent.

Cases where the onset date of an AE is (partially) missing, will be addressed during the data review meeting in order to determine whether the AE must be considered treatment emergent or not.

Imputation on missing non-prostate cancer related medication dates (to categorize them as previous medications or concomitant medications, or post treatment) and AE dates (to categorize them as TEAE or not) will be done as follows:

- Incomplete Start Day from start date and the corresponding end date is complete: use the later of (first day of the month, first dosing day if first dosing month); but if later than the end date, then impute the start day as the day of the end date.
- Incomplete Start Day from start date and incomplete End Day from end date: use the later of (first day of the month, first dosing day if first dosing month).
- Incomplete End Day from end date: use the earliest of (last day of the month, day of the 30-day follow-up visit if it is the month of the 30-day follow-up visit);
- Incomplete Month or Year: no imputation.

Imputation on missing date of initial diagnosis (cancer duration) and prior cancer treatment, including prostate cancer drug medication/therapies, (e.g. start date, stop date, or date of procedure) will be done as follows:

- Incomplete Day: use the 15th day of the month, if month/year is before first dosing or after last dosing (-for start date imputation- but if later than the end date, then impute the start day as the day of the end date; -for end date imputation- but if earlier than the start date, then impute the end day as the day of the start date).
- Incomplete Month: use 1st of July if the Year is before Year of first dosing, otherwise missing.
- Incomplete Year: no imputation, the derived variable is considered to be missing.

If missing for subjects who started treatment, the last dose date of treatment will be imputed as follows:

- Incomplete Day only: use the earliest of (last day of the month, end of treatment [form] day -if on the same month and year-, day of the 30-day follow-up visit-if on the same month and year-);
- If fully missing or Incomplete Month or/and Year: the date will be imputed by the earliest of (end of treatment [form] date, date of the 30-day follow-up visit)

If partially missing, the date of death will be imputed as follows:

- Incomplete Day: use the earliest of (last day of the month, end of study [form] day)
- Incomplete Month or Year: no imputation

Imputation methods will not be used to determine other endpoints.

Listings will always show the original date information without imputation, and derived parameters requiring imputation (e.g., TEAE indicator, start day, end day, study day) will be flagged.

### 7.12.2 Outliers

All values will be included in the analyses.

### 7.12.3 Visit Windows

Visit windows are allowed for certain visits per the schedule of assessments. Patient data will not be excluded from analyses due to the patient's failure to comply with the visit schedule.

For summary tables reporting results by visit, analyses of efficacy and safety variables will be performed according to the analysis visit windows described in the following Table 4.

In the case of multiple observations in the same analysis visit window, the observation which is closest to the target date will be used. If the observations have the same distance to the target visit day, the latest one will be used (using date, and time if available). Should there be two assessments documented at the same time due to the repetition of analysis of the same sample, the one reported as scheduled will be used.

**Table 4 Analysis Visit Windows**

| Visit Day Interval | Scheduled Visit | Analysis Visit* |
|---|---|---|
| Up to Day 1 | Week 1 (Day 1) | Baseline** |
| Day 2 - Day 57 | Week 5 (Day 29) | Week 5 |
| Day 58 - Day 127 | Week 13 (Day 85) | Week 13 |
| For the next visits during the treatment period:<br>Week X = Week (i*12+13), (i=1,2,3, …)<br>Week X target day = i*12*7 + 85, (i=1,2,3, …)<br>Week X (Wk X target day - 41 days; Wk X target day + 42 days) | | |
| However, for the (last) visit during the treatment period, i.e. the last dose day of study drug is recorded,<br>the upper boundary of the analysis visit window is 5 days after the last dose day, e.g.:<br>Week X = Week (i*12+13), (i=0,1,2,3, …)<br>Week X target day = i*12*7 + 85, (i=0,1,2,3, …)<br>Week X (Wk X target day - 41 days; last dose day + 5 days) | | |
| (last dose day + 6; last dose day + 42) | last dose day + 30 days | 30 Day Safety F-up<br>*(after last dose or prior to new therapy*) |

*Table continued on next page*

| Visit Day Interval | Scheduled Visit | Analysis Visit* |
|---|---|---|
| Patients who end treatment before the data analysis cut-off date and have long-term (LT) follow-up visits,<br>have visits every 12 weeks after last dose day:<br>LT F-up j = j*12 weeks visit after last dose day, (j=1,2,3, …)<br>LT F-up j target day = j*12*7 + last dose day, (j=1,2,3, …)<br>LT F-up j (j*12*7 + last dose day - 41; j*12*7 + last dose day + 42) | | |

F-up: follow-up
*Post-baseline analysis visits in the OLE are defined similarly to the analysis visits in the double-blind period and are labeled "OLE Week XXX".
**OLE baseline is defined as the last visit prior to the administration of enzalutamide + ADT in OLE period.

# 8 DOCUMENT REVISION HISTORY

| Version | Date | Changes | Comment/rationale for change |
|---|---|---|---|
| 1.0 | 18-JUL-2021 | NA | Document finalized |

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# 10 APPENDICES

## 10.1 Appendix 1 - Key Contributors and Approvers

# List of Key Contributors and Approvers

### Key Contributors

The following contributed to or reviewed this SAP as relevant to their indicated discipline or role.

**Primary author (s)**

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(E-signatures are attached at end of document)

PPD, Astellas Pharma Global Development, was the study statistician for this study.

PPD, Astellas Pharma Global Development, was the Global Statistical Lead and peer reviewer of this Statistical Analysis Plan

This Statistical Analysis Plan was approved by:

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