STATISTICAL ANALYSIS PLAN

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

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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
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
IRT	Interactive response technology
ITT	Intent-to-treat
LHRH	Luteinizing hormone-releasing hormone
mHSPC	Metastatic hormone sensitive prostate cancer
MRI	Magnetic resonance imaging
NCI	National cancer institute
ORR	Objective response rate
OS	Overall survival
PRES	Posterior reversible encephalopathy syndrome
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 60 events for the primary variable, the PSA progression, 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. 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.
Postinvestigational 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

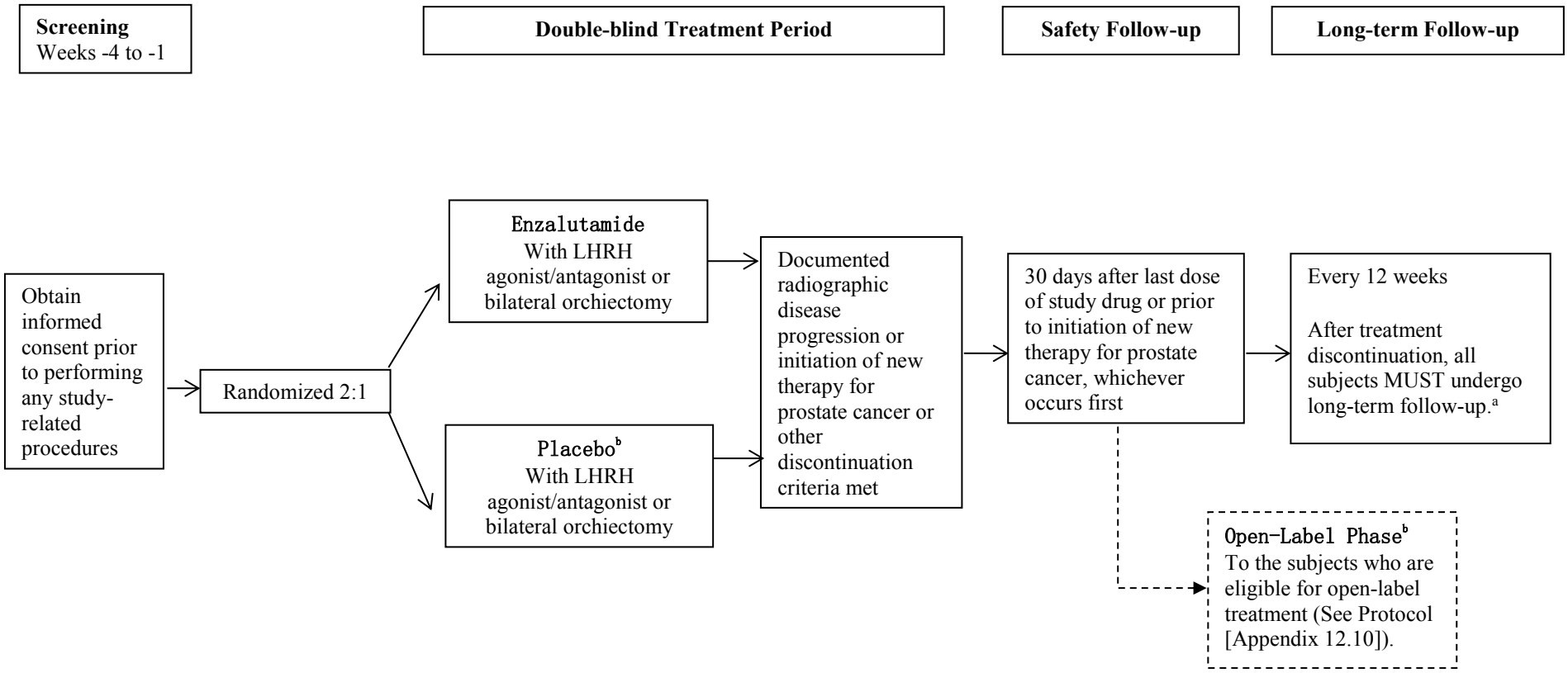
This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to database hard lock 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.

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 analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

2 FLOW CHART AND VISIT SCHEDULE



LHRH: luteinizing hormone-releasing hormone; PSA: prostate-specific antigen.

a. For those subjects who discontinue study treatment without radiographic disease progression, radiographic assessments will continue every 12 weeks until confirmed radiographic progression by investigator assessment or the number of PSA events is reached.

b. Open-label enzalutamide will be supplied for free to the subjects in placebo arm who remain on study treatment until confirmed radiographic disease progression and in the judgement of the investigator who is necessary to initiate the next course of therapy till next disease progression based on subject's informed consent (See Protocol [Appendix 12.10]).

Table 1 Schedule of Assessments

Study Day	**Screening Visit¶¶¶**	**1**	**29**	**57**	**85 and Every Subsequent 28 Days**	**Safety Follow-up**	**Unscheduled Visit†**	**Long Term Follow-up‡**	
								Post Treatment Follow-Up	**Survival Follow-Up**
Study Week	**-4 to -1 (28 Days)**	**1**	**5**	**9**	**13 and Every Subsequent 4 Weeks**	**30 Days after Last Dose§**		**Every 12 Weeks**	**Every 12 Weeks**
Window (Days)			± 3	± 3	± 3	± 7	NA	± 7	± 7
Informed Consent	X								
Medical History	X								
Inclusion/Exclusion Criteria	X	X							
Randomization (IRT)		X							
Vital Signs	X	X	X	X	X	X	X		
Physical Examination including Weight¶	X	X	X	X	X	X	X		
Height	X								
12-lead ECG	X	X				X			
Clinical Labs††	X	X	X	X	X	X	X		
PSA‡‡	X	X	X	X	X	X		X	
Testosterone‡‡					X‡‡‡			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, Brief Pain Inventory-Short Form)		X			X‡‡‡	X		X‡	X‡
Adverse Events§§§	X	X	X	X	X	X	X		
Previous and Concomitant Medications	X	X	X	X	X	X	X		
Study Drug Dispensing		X	X	X	X				
Study Drug Treatment		X	X	X	X				

CT: computed tomography; ECG: electrocardiogram; 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; PSA: prostate-specific antigen;
FACT-P: Functional Assessment of Cancer Therapy-Prostate; QLQ-PR25: Quality of Life Prostate-specific Questionnaire; QoL: quality of life

Open-label enzalutamide will be supplied for free to the subjects in placebo arm who remain on study treatment until confirmed radiographic disease progression and in the judgement of the investigator who is necessary to initiate the next course of therapy till next disease progression based on subject's informed consent (See Protocol [Appendix 12.10]). Subjects who will go to open-label phase will not enter the long-term follow-up.

The alternative approaches which are only permissible in the event of a crisis, is presented in [Protocol Section 12.11].

† Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events at the subject's request or if deemed necessary by the investigator. Procedures and assessments are to be performed as clinically indicated.

‡ After treatment discontinuation, all subjects MUST undergo long-term follow-up. Long-term follow-up assessments will be composed of post-treatment follow-up and survival follow-up. For those subjects who discontinue study treatment without radiographic disease progression confirmed will undergo post-treatment follow-up (calculated from baseline), include monitoring for survival status, disease progression, new antineoplastic therapies for prostate cancer and symptomatic skeletal events. Subjects will continue to be scanned along with collecting PSA and testosterone every 12 weeks until radiographic progression is confirmed by investigator assessment or the number of PSA events is reached. For those subjects who discontinue study treatment due to confirmed radiographic disease progression will undergo survival follow-up (calculated from date of progression), include monitoring for survival status, new antineoplastic therapies for prostate cancer and symptomatic skeletal events, and the follow-up may be conducted by telephone interview. 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.

§ Or prior to initiation of another investigator agent or 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.

‡‡ For subjects who discontinue study treatment without confirmed radiographic progression, subjects will continue to be collected PSA and testosterone every 12 weeks until radiographic progression is confirmed or the number of PSA events is reached.

§§ The abdominal-pelvic contrast CT scan or MRI, bone scan, chest x-ray or chest contrast 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.

¶¶ The window for all radiological (CT/MRI) assessments is ± 7 days. For subjects who discontinue study treatment without radiographic progression, subjects will continue to be scanned every 12 weeks until radiographic progression is confirmed or the number of PSA events is reached.

††† Chest contrast CT or chest MRI 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 subject signs the consent form 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 another investigator agent or new antineoplastic therapy for prostate cancer.

‡‡‡ Testosterone, CT/MRI and Bone Scan, Chest X-ray or Chest CT or MRI, QoL Assessment and ECOG Performance Status will only be performed at day 85 and every subsequent 84 days (13 and every subsequent 12 weeks).

¶¶¶ The Screening period is 28 days. Re-screening may be allowed once and upon discussion with the medical monitor.

Table 2 Open-Label Phase Schedule of Assessments

Study Period or Visit	**OL Screening**	**OL Treatment**			**Unscheduled Visit**	**OL Safety Follow-up**	**OL Long Term Follow-up**
Study Week	**NA**	**OL 1 (Day 1)**	**OL 5 (Day 29)**	**OL 13 and Every Subsequent 12 Weeks (Day 85 and Every Subsequent 84 Days)**	**Varies[1]**	30 Days after Last Dose[2]	**Every 12 Weeks**
Window (Days)	NA	NA	± 3	± 5	NA	± 7	± 7
Informed Consent[3]	X						
Inclusion/Exclusion Criteria	X						
Open-Label Enrollment		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	
12-lead Electrocardiogram		X				X	
Clinical Labs[4]		X	X	X	X	X	
Adverse Events[5]		X	X	X	X	X	
Concomitant Medication Review		X	X	X	X	X	
Study Drug Dispensing		X	X	X			
Study Drug Accountability		X	X	X		X	
Long-Term Follow-up Assessments[6]							X

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

With the exception of those procedures and processes indicated below, this phase of the study will be performed using the same general approach as described in the protocol.

At OL1 Visit, the following assessments (ECG; vital signs; physical examination; clinical labs; ECOG) do not need to be repeated if they were completed within 7 days in Safety Follow-up Visit during double blind phase.

1 As necessary to assess or follow up adverse events.

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

3 Informed consent must be obtained during screening before performing any study-specific procedures for all subjects participating in OL Period.

4 Laboratory assessments include serum chemistries and hematology.

5 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).

6 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)

The objective of this phase 3 study is to evaluate the efficacy and safety of enzalutamide plus Androgen Deprivation Therapy (ADT) versus placebo plus ADT in Chinese patients with metastatic hormone sensitive prostate cancer (mHSPC).

3.1.1 Primary Objective

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to prostate-specific antigen (PSA) progression based on central laboratory test

3.1.2 Secondary Objectives

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by radiographic progression-free survival (rPFS)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to first Symptomatic Skeletal Event (SSE)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to castration resistance
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by PSA response (≥ 50%)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by PSA response (≥ 90%)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to start of new antineoplastic therapy
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by PSA undetectable rate (< 0.2 ng/mL)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by objective response rate (ORR)

3.1.3 Exploratory Objectives

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by Quality of Life (QoL) (as measured by QoL Prostate-specific Questionnaire [QLQ-PR25] / Functional Assessment of Cancer Therapy-Prostate [FACT-P] and EuroQol Group-5 Dimension-5 Level Instrument [EQ-5D-5L])
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by worsening of pain (using the Brief Pain Inventory-Short Form [BPI-SF])

3.1.4 Safety Objectives

- To determine the safety of enzalutamide plus ADT as compared to placebo plus ADT

3.2 Study Design

This is a multicenter phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of enzalutamide plus ADT versus placebo plus ADT in Chinese subjects with mHSPC, followed by an open-label phase (only for the subjects in placebo arm who discontinue from the study treatment and unblinding of the study treatment assignment are performed after radiographic progression in the judgement of the investigator and in consultation with the medical monitor. This information is necessary to determine the next course of therapy).

Approximately 180 Chinese subjects will be randomized centrally enzalutamide plus ADT or placebo plus ADT (2:1), and the randomization will be stratified by volume of disease (low versus high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, prior docetaxel). 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. Re-screening may be allowed once after screening failure upon discussion with the medical monitor.

Study drug therapy should be continued as long as the subject is tolerating the study drug and continues ADT until radiographic disease progression is documented as outlined in table 3 or starting another investigational agent or new therapy for treatment of prostate cancer. It is recommended that subjects remain on study treatment until confirmed radiographic disease progression. Subjects who discontinue study treatment without confirmed radiographic disease progression will continue to follow the PSA and radiographic assessment schedule until confirmed radiographic disease progression event. In the judgment of the Investigator, for subjects who discontinue study treatment with confirmed PSA progression by central review, blinding suggests to be continued until confirmed radiographic disease progression. In consultation with the medical monitor, unblinding of the study treatment assignment may be performed after radiographic progression if the subject discontinues from the study treatment and in the judgement of the investigator this information is necessary to determine the next course of therapy. Open-label enzalutamide will be supplied for free to the subjects in placebo arm who remain on study treatment until confirmed radiographic disease progression and in the judgement of the investigator who is necessary to initiate the next course of therapy till next disease progression based on the subject's informed consent.

Study films (CT/MRI and bone scan) should be read on site and also be submitted in digital format to the sponsor-designated facility in case independent central review is required after the end of study. Each site should ideally designate the same reader who will evaluate the images for any one subject for the duration of the trial.

Radiographic disease progression is defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for soft tissue disease or the appearance of 2 or more new lesions on bone scan. The documentation and confirmation required for the determination of radiographic progression is listed in full protocol [Section 5.3.1.2 CT/MRI and Bone Scan].

The following assessments of prostate cancer status will be collected during the course of the study: PSA, soft tissue disease on CT scan or on MRI, bone disease on radionuclide bone scans, EQ-5D-5L, QLQ-PR25, FACT-P for QoL and BPI-SF for pain symptom assessment.

Throughout the study, safety and tolerability will be assessed by the recording of AEs, vital signs, physical examinations, 12-lead ECGs, and safety laboratory evaluations.

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 antineoplastic therapy for prostate cancer, whichever occurs first.

The sponsor will monitor study enrollment for proportion of subjects enrolled with a history of prior docetaxel treatment, and may either change the sample size, or cap the number of subjects who received prior docetaxel to ensure that the primary endpoint is not driven either by the subjects who received prior docetaxel, or by the subjects who did not receive prior docetaxel.

3.3 Randomization

Subjects will be entered into the IRT system at screening and assigned a subject number. Randomization will be performed via the IRT system and treatment assigned in a 2:1 ratio to enzalutamide 160 mg/day or placebo. Prior to the initiation of the study treatment, on day 1, the site staff will contact the IRT system in order to determine the randomly assigned treatment. Subjects will be stratified by prior docetaxel (no prior docetaxel, prior docetaxel) and disease volume (low versus high). High-volume 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. Specific procedures for randomization through the IRT system are contained in the study procedures manual.

4 SAMPLE SIZE

As originally planned, approximately 180 Chinese subjects will be randomized in the study (120 subjects in enzalutamide+ADT arm and 60 subjects in placebo+ADT arm).

The final analysis of TTPP will be conducted with a planned 75 PSA progression events, based on the following considerations:

- A target HR is 0.5. The expected median TTPP for the ADT arm is 9 months as measured from the date of randomization. A target HR of 0.5 corresponds to approximately 100% increase in median TTPP for the enzalutamide plus ADT arm relative to the placebo plus ADT arm (approximately 18 versus 9 months, with 10% dropout rate).
- The planned 75 PSA progression events (a 25% increase in PSA and at least 2 ng/mL above the nadir according to Prostate Cancer Clinical Trials Working Group 3 criteria) provides approximately 80% power to detect a target HR of 0.5 based on a 2-sided log-rank test and overall significance level of 0.05.

- There will be 1 interim analysis at 80% of the total planned events (about 60 PSA progression events), providing 61% power to demonstrate superiority at a 2-sided alpha of 0.0244.

5 ANALYSIS SETS

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

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

5.1 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 based on randomization assignment). The ITT population will be used to conduct efficacy analyses, unless otherwise specified. For the ORR, only ITT subjects with measurable disease at baseline will be included in the analysis.

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). The safety population will be used to conduct safety analyses.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint(s)

6.1.1.1 Primary analysis

The primary endpoint is time to PSA progression (TTPP), where PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir (i.e., lowest PSA value observed post baseline or at baseline), which is confirmed by a second consecutive value at least 3 weeks later.

There are 2 planned analyses, one final analysis at the total planned 75 PSA progression events and one interim analysis at 80% of the total planned events (about 60 PSA progression events). TTPP will be formally tested at both interim analysis and final analysis at 2-sided 0.0244 and 0.0429 significance level, respectively, for efficacy according to the O'Brien-Fleming boundary as implemented by Lan-DeMets alpha spending function [Lan-DeMets, 1983]. Data cut-off dates will be set when the planned number of events is reached for the interim and final analyses. If the exact number of events at interim and final analyses are different than planned, the significance level will be adjusted accordingly, based on the O'Brien-Fleming method with

a Lan-DeMets alpha spending function. The family-wise type I error rate for this study is strongly controlled at 5% (2-sided) that allows the study to declare positive on primary endpoint TTPP on the ITT population.

Only results from central lab PSA samples taken before the initiation of any new antineoplastic prostate cancer therapy after the start of study drug will be considered and are referred to in this section.

The date of PSA progression is the first date the PSA progression is observed. In patients with PSA progression, TTPP will be calculated as the time from randomization to the date of first observation of PSA progression.

In patients with no PSA progression, TTPP will be censored on the date of the last PSA sample taken. Patients entering the open-label phase without PSA progression would be censored on the last PSA prior to first open-label treatment.

In patients with no baseline PSA and patients with no post-baseline PSA results, TTPP will be censored on the date of randomization.

6.1.1.2 Sensitivity analyses of primary endpoint

Appendix 1 - Summary of Sensitivity Analyses of Primary Endpoint summarizes the different TTPP definitions used in sensitivity analyses of the primary endpoint.

Sensitivity analysis 1 - TTPP_1 - Assess the Impact of Treatment Discontinuation
The impact of treatment discontinuation will be assessed in two sensitivity analyses.
In the first sensitivity analysis, subjects with study treatment discontinuation prior to PSA progression will be censored at the date of last PSA assessment before treatment discontinuation without evidence of PSA progression. The primary analysis of TTPP will be repeated after accounting for this change in censoring rules. The hazard ratio and 95% CIs will be reported.

In the second sensitivity analysis, subjects who discontinued study treatment without evidence of PSA progression or on-study death will be considered as having a TTPP event at the date of last dose of study drug. The primary analysis of TTPP will be repeated after accounting for these new events. The hazard ratio and 95% CIs will be reported.

Sensitivity analysis 2 - TTPP_2 - Assess the Impact of Subsequent Anti-neoplastic Therapy
In this sensitivity analysis, subjects' PSA samples taken after the initiation of any new antineoplastic prostate cancer therapy after the start of study drug will also be considered, which means subjects who start new anti-neoplastic treatment prior to PSA progression will not be censored at the date of last PSA assessment before initiation of subsequent anti-neoplastic therapy without evidence of PSA progression. The primary analysis of TTPP will be repeated after accounting for this change in censoring rules. The hazard ratio and 95% CIs will be reported.

Sensitivity analysis 3 – TTPP_3 - rPD (INV), SSE, New therapy, and Death as event impact

TTPP_3 events are defined as the PSA progression, rPD (Investigator), SSE, New antineoplastic therapy, and Death (within 24w after EOT).

In patients with a TTPP_3 event, TTPP_3 is calculated as the time interval from the date of randomization to the first date of the PSA progression, rPD (Investigator) or SSE, New antineoplastic therapy, death, whichever occurs first.

In patients with no TTPP_3 event, TTPP_3 will be censored on the date of PSA assessment prior to the data analysis cut-off date. In those patients, patients with no baseline PSA assessment, patients with no post baseline radiographic assessments, TTPP_3 will be censored on the date of randomization.

Sensitivity analysis 4 - TTPP_4 - Assess the Impact of PSA results from local laboratory tests.

In this sensitivity analysis, subjects' PSA results, which are collected from local laboratory assessment instead of central, will be taken as central records, and the primary analysis of TTPP will be repeated after accounting for this change in PSA assessments. The hazard ratio and 95% CIs will be reported.

6.1.2 Secondary Efficacy Endpoints

For variables derived, unless otherwise specified, only results taken before the data analysis cut-off date will be considered and are referred to in this section.

6.1.2.1 rPFS

Radiographic progression-free survival (rPFS), where rPFS event is defined as the time from randomization to the first objective evidence of radiographic disease progression assessed by Investigators or death (defined as death from any cause within 24 weeks from study drug discontinuation), whichever occurs first.

Radiographic disease progression is defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for soft tissue disease or the appearance of 2 or more new lesions on bone scan. The documentation and confirmation required for the determination of radiographic progression is listed in the following table.

Table 3 Protocol-specified Documentation for Radiographic Evidence of Disease Progression

Date Progression Detected (Visit)†	Criteria for Progression	Criteria for Confirmation of Progression (Requirement and Timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 13	Bone lesions: ≥ 2 new lesions compared to **baseline** bone scan	Timing: ≥ 6 weeks after progression identified or at week 25 visit	≥ 2 new bone lesions on bone scan compared to week 13 scan (≥ 4 new lesions compared to **baseline** bone scan)

	Soft tissue lesions: progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	Not applicable
Week 25 or Later	Bone lesions: ≥ 2 new lesions on bone scan compared to best response on treatment	No confirmatory scan required	Not applicable
	Soft tissue lesions: progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	Not applicable

CT: computed tomography; MRI: magnetic resonance imaging; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1.
† Progression detected by bone scan at an unscheduled visit prior to week 25 will require the same criteria for documentation of disease progression as week 13 with a confirmatory scan at least 6 weeks later or at the next scheduled scan.

In patients with no rPFS event, rPFS will be censored on the date of last radiographic assessment prior to the data analysis cut-off date. In those patients, patients with no baseline radiographic assessment, patients with no post baseline radiographic assessments and patients with all post-baseline radiographic assessments documented as "Not Evaluable", the radiographic progression free survival will be censored on the date of randomization. Patients entering the open-label phase without rPFS event would be censored on the date of last radiographic assessment prior to first open-label treatment.

6.1.2.2 Time to First Symptomatic Skeletal Event

SSE is defined as radiation to bone, surgery to bone, clinically apparent pathological bone fracture or spinal cord compression.

In patients with SSE, the time to first SSE is defined as the time from randomization to the occurrence of the first SSE prior to the data analysis cut-off date.

In patients with no SSE by the time of the data analysis cut-off date, the time to first SSE will be censored on the last visit date or the date of randomization, or the death date, whichever occurs last. Patients entering the open-label phase without SSE would be censored on the date entering the open-label treatment.

6.1.2.3 Time to Castration Resistance

A castration resistance event is defined as the occurrence of radiographic disease progression by Investigator, PSA progression (as defined in Section 6.1.1.1), or SSE (as defined in Section 6.1.2.2), whichever occurs first with castrate levels of testosterone (< 50 ng/dL). As testosterone was not reported at baseline, testosterone is considered <50 ng/dL up to the first post baseline measurement. The latest testosterone value measured prior to or at the date of radiographic

disease progression by Investigators, PSA progression or SSE, is used to determine if this event is a castration resistance event.

In patients with castration resistance event, time to castration resistance is defined as the time from randomization to the first castration-resistant event.

In patients with no documented castration resistance event, the time to castration resistance will be censored on the latest date from: the date of last radiographic assessment, the last PSA sample taken prior to the start of any new antineoplastic prostate cancer therapy, and the last visit date performed. In those patients, patients with no baseline radiographic assessment, patients with no post baseline radiographic assessments, patients with all post-baseline radiographic assessments documented as "Not Evaluable", patients with no baseline PSA, and in patients with no post-baseline PSA results, the time to castration resistance will be censored on the date of randomization. Patients entering the open-label phase without any castration resistance event would be censored on the date entering the open-label treatment.

6.1.2.4 PSA Response ≥50%, PSA Response ≥90%:

Only results from PSA samples taken before the start of any new antineoplastic prostate cancer therapy will be considered and are referred to in this section.

The PSA response rate ≥50%/90% is defined as the percentage of patients in the analysis population with maximal PSA declines of at least 50%/90% at any time and at each visit for subjects with detectable PSA at baseline and at least 1 post-baseline assessment.

6.1.2.5 Time to Initiation of a New Antineoplastic Therapy

The start of a new antineoplastic therapy is based on the information collected in the (new) prostate cancer drug 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 after randomization, time to start of a 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 after randomization, time to start of new antineoplastic therapy will be censored on the last visit date or the date of randomization, whichever occurs last. Patients entering the open-label phase without initiation of a new antineoplastic therapy would be censored on the date entering the open-label phase.

6.1.2.6 PSA Undetectable Level

The undetectable level of PSA is defined as a level < 0.2 ng/mL.

For patients with a detectable level of PSA at baseline, a dichotomous variable ('Y'/'N') is derived to assign 'Y' to patients with any post-baseline PSA sample results < 0.2 ng/mL. otherwise 'N' is assigned. For patients with undetectable level of PSA at baseline, this variable is kept missing.

6.1.2.7 Overall Objective Response Assessment

The overall response assessment is based on RECIST version 1.1 for soft tissue lesion on CT/MRI, and for bone lesions on bone scans. The overall objective response is based on RECIST version 1.1 for soft tissue lesions.

The following categories were used:

- CR = complete response
- PR = partial response (option only for target lesions and overall)
- SD = stable disease (option only for target lesions and overall)
- PD = progressive disease
- Non CR/non PD= not complete response and not progressive disease
  (not an option for target lesions)
  (option only for non-target lesions, bone lesions, and overall)
- Unconfirmed PD (not an option in RECIST on soft tissue lesions)
- NE = not evaluable (option for bone lesions)
  = not evaluated/ not all evaluated (option for target and non target lesions)
  = inevaluable (option for overall)
- NA = not applicable (postbaseline assessment in case of no lesion of the kind at baseline)
  (not an option for overall response assessed by Investigator)

At each time point, the RECIST overall time point response, in patients with measurable soft tissue lesions at study entry (all patients, who have at least one target lesion), can be derived according to RECIST for all possible combinations of tumor response assessments in target and non-target lesions in soft tissues with or without the appearance of new unequivocal lesions. RECIST overall time point response derivation is described in Table 4. The RECIST overall time point response will be derived from the assessments provided by the investigators.

Investigator additionally considers image quality to perform their assessments.

For patients with no target and no non-target soft tissue lesion at baseline, the RECIST overall time point response is set to ‘NA’, unless an unequivocal new lesion is identified (in which case the assessment is PD) or unless imaging is not evaluable (in which case the assessment is NE).

Table 4 RECIST Overall Time Point Response for all Combinations of Tumor Responses in Target and Non-target Lesions with or without Appearance of new Lesions as assessed by Investigators

Target Lesions*	Non-Target Lesions*	Unequivocal New Lesions^	RECIST Overall Response^
CR	CR	No	CR
CR	Not applicable	No	CR
Not applicable	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Not PD	No	PR
SD	Not PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
Not applicable	Non-CR/Non-PD	No	Non-CR/Non-PD
Not applicable	Not applicable	No	Not applicable [$]
Not applicable	Not evaluated or Not Done	No	NE
Not evaluated or Scan not Done	Not PD	No	NE

***** The category "Any" includes all possible categories (incl. NE or NA or Not Done). The category "Not PD" includes: CR, Non-CR/Non-PD, NA, NE and Not Done.

^ Missing assessments during study visits will not be imputed. Missing assessments for "Unequivocal new lesions" will be reported as "Missing" and will lead to "NE" for the derived RECIST Overall Response.

[$] The RECIST overall time point response will only be derived to "Not applicable" for patients with no target and no non-target soft tissue lesions at study entry in absence of new unequivocal lesion.

Definition of Best RECIST Overall Response

In patients with measurable soft tissue lesions at study entry (all patients, who have at least one target lesion), the best RECIST overall response in the soft tissue disease is the best of the RECIST overall time point response assessment reported at any time during or at the end of the treatment period, up to the start of any other antineoplastic prostate cancer therapy. The best RECIST overall response assessment is according to the following decreasing order, starting with the possible best response: CR, PR, SD, Non-CR/Non-PD, PD, NA, NE. For patients still on treatment after or by the cut-off date, the best RECIST overall response can be derived as the best of the RECIST overall time point response assessments recorded for the time on study up to the data cut-off date. Patients with no post-baseline assessment at any visit are reported in the 'Not evaluated' category.

The best RECIST overall response will be derived from the assessments provided by the investigators.

Definition of Best Overall Response

At each time point, the overall time point response assessment reported by the investigators are based on the combination of the time point assessments on soft tissue on target lesions, non-

target lesions and apparition of new lesions (i.e. RECIST), and the time point response assessment on bone scan.

The best overall response is the best of the overall time point response assessment reported at any time during or at the end of the treatment period, up to the start of any other prostate cancer therapy. The best of the overall time point response assessments is according to the following decreasing order, starting with the possible best response: CR, PR, SD, Non-CR/Non-PD, unconfirmed PD, PD, NA (for Investigator only), NE. For patients still on treatment after or by the cut-off date, the best overall response can be derived as the best of the overall time point response assessments recorded for the time on study up to the data cut-off date. Patients with no post-baseline assessment at any visit are reported in the 'Not evaluated' category.

The best overall response will be derived from the overall time point response assessments provided by the investigators.

Table 5 describes the possible combinations of tumor response to report the overall timepoint response assessment.

Table 5 RECIST Combined Time Point Response Provided for any Combinations of Tumor Responses in Soft tissue Lesions and Bone Lesions

RECIST 1.1	Bone Scan		The Combined (i.e., Overall) Time Point Response
CR	CR		CR
CR	NA		CR
NA	CR		CR
CR	NON-CR/NON-PD		PR
CR	PDu		PR
PR	CR	Not NE = & not PD	PR
PR	NON-CR/NON-PD		PR
PR	PDu		PR
PR	NA		PR
SD	CR	Not NE = & not PD	SD
SD	NON-CR/NON-PD		SD
SD	PDu		SD
SD	NA		SD
PD	Any		PD
Any	PD		PD
NON-CR/NON-PD	CR	Not NE = & not PD	NON-CR/NON-PD
NON-CR/NON-PD	NON-CR/NON-PD		NON-CR/NON-PD
NON-CR/NON-PD	PDu		NON-CR/NON-PD
NON-CR/NON-PD	NA		NON-CR/NON-PD
NA	NON-CR/NON-PD		NON-CR/NON-PD
NA	PDu		PDu
Any but PD	NE		NE
NE	Any but PD		NE
NA	Not applicable		NA

PDu: unconfirmed Progression of Disease.

6.1.3 Exploratory Efficacy Endpoints

6.1.3.1 Quality of Life

BPI-SF

The BPI-SF pain questionnaire is a validated instrument that is a patient self-rating scale assessing level of pain, effect of the pain on activities of daily living and analgesic use. The BPI used in this study is the short form. The BPI uses simple numeric rating scales from 0 to 10.

The BPI-SF scoring will be provided by two dimensions:

- Pain severity: worst, least, average and current pain (Question 3 to 6);
- Pain interference: general activity, mood, work, walking ability, relations, sleep and enjoyment of life (item A to G of Question 9).

Composite scores of pain severity and the pain interference will be produced by averaging their subscales. To calculate the composite score of severity, all four items should be completed; otherwise, the score will be treated as a missing value. For the interference score, if there are missing items, the score will be prorated as follows:

Prorated score = (sum of item scores)/(number of items answered), as long as more than 50% of the items are answered in Question 9 (i.e., a minimum of 4 of 7 items).

Each score ranges from 0 to 10 with higher scores representing a higher level of pain or interference.

QLQ-PR25

The QLQ-PR25 is a 25-item module designed to assess QoL in prostate cancer patients. It includes scales assessing urinary symptoms, bowel symptoms, and treatment-related symptoms; use of incontinence aids; and sexual active and sexual function. Each score ranges from 1 (not at all) to 4 (very much).

Item scores are summed and transformed to a 0-100 scale, as described in Section 7.4.3.1; higher scores represent higher functioning for the two sexual domains but, conversely, higher scores represent more symptoms (i.e. worse HRQoL) for the symptom scales.

EQ-5D-5L

The EQ-5D-5L is an international standardized nondisease specific (i.e., generic) instrument for describing and valuing health status. It is a measure of HRQoL.

The EQ-5D-5L has 5 domains: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Each domain has 5 response levels (coded as 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, 5 = extreme problems). In addition, EQ-5D-5L has a Visual Analogue Scale (VAS) that elicits a self-rating by the respondent of his/her health status from the worst health status (0) to the best health status (100).

There should be only one response for each domain. Ambiguous values (e.g. 2 boxes were ticked for a single domain) should be treated as missing values.

FACT-P

The FACT-P questionnaire is a multi-dimensional, self-reported QoL instrument specifically designed for use with prostate cancer patients. It is composed of 27 core items which assess patient function in four domains and 12 prostate-related items, grouped into 5 subscales as follows:

- Physical well-being (PWB): 7 items;
- Social/family well-being (SWB): 7 items;
- Emotional well-being (EWB): 6 items;
- Functional well-being (FWB): 7 items;
- Prostate cancer subscale (PCS): 12 items.

Each item is rated on a 0 to 4 Likert-type scale as: 0=not at all; 1= a little bit; 2= somewhat; 3= quite a bit; 4= very much. For some items a response of "4= very much" is better than a response of "3= quite a bit" (e.g., "I get support from my friends"), while for other items a response of "4= very much" is worse than a response of "3= quite a bit" (e.g. "I have pain"). Before calculating the subscale and global scores, the items for which "4" is worse than "3" must be reversed, by subtracting the response from 4. The reversals are performed in the following:

- PWB: reverse all items (GP1 - GP7);
- SWB: do not reverse any items;
- EWB: reverse items GE1 and GE3 - GE6;
- FWB: do not reverse any items;
- PCS: reverse items C2, P1 - P3, P6 - P8 and BL2.

After reversing proper items, for all FACT-P scales, the higher the score the better the QoL.

Each subscale score is the sum of the scores for the items in the subscale. If there are missing items, subscale scores can be prorated, as long as more than 50% of the items are answered in any given subscale (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc). The score is prorated as follows:

Prorated subscale score = (sum of item scores) * (number items in the subscale)/(number of items answered).

The Table 6 lists each FACT-P item and its appropriate scoring.

The FACT-P total score is the sum of all 5 subscale scores. The total score will be calculated only if the overall item response rate is greater than 80% (i.e., a minimum of 32 of 39 items currently scored in the FACT-P have been answered), and no subscale scores are missing.

A deterioration of QoL is defined as a decrease of at least 10-point in the total FACT-P score from baseline.

Table 6 Scoring of FACT-P items

		Scoring				
	Item number	**Not at all**	**A little bit**	**Somewhat**	**Quite a bite**	**Very much**
PWB	GP1	4	3	2	1	0
	GP2	4	3	2	1	0
	GP3	4	3	2	1	0
	GP4	4	3	2	1	0
	GP5	4	3	2	1	0
	GP6	4	3	2	1	0
	GP7	4	3	2	1	0
SWB	GS1	0	1	2	3	4
	GS2	0	1	2	3	4
	GS3	0	1	2	3	4
	GS4	0	1	2	3	4
	GS5	0	1	2	3	4
	GS6	0	1	2	3	4

		Scoring				
	Item number	**Not at all**	**A little bit**	**Somewhat**	**Quite a bite**	**Very much**
	GS7	0	1	2	3	4
EWB	GE1	4	3	2	1	0
	GE2	0	1	2	3	4
	GE3	4	3	2	1	0
	GE4	4	3	2	1	0
	GE5	4	3	2	1	0
	GE6	4	3	2	1	0
FWB	GF1	0	1	2	3	4
	GF2	0	1	2	3	4
	GF3	0	1	2	3	4
	GF4	0	1	2	3	4
	GF5	0	1	2	3	4
	GF6	0	1	2	3	4
	GF7	0	1	2	3	4
PCS	C2	4	3	2	1	0
	C6	0	1	2	3	4
	P1	4	3	2	1	0
	P2	4	3	2	1	0
	P3	4	3	2	1	0
	P4	0	1	2	3	4
	P5	0	1	2	3	4
	P6	4	3	2	1	0
	P7	4	3	2	1	0
	BL2	4	3	2	1	0
	P8	4	3	2	1	0
	BL5	0	1	2	3	4

In patients with QoL deterioration, the time to deterioration of QoL is defined as the time interval from the date of randomization to the first date a decline from baseline of 10 points or more in the total FACT-P score is recorded.

In patients without FACT-P deterioration, the time to deterioration of QoL will be censored on the date of the last FACT-P total score is calculable. Patients with no baseline FACT-P total score and patients with no post baseline FACT-P total score, time to deterioration of QoL will be censored on the date of randomization. Patients entering the open-label phase without deterioration would be censored on the date of last FACT-P assessment prior to first open-label treatment.

6.1.3.2 Time to Pain Progression:

Pain progression event is defined as an increase of ≥ 30% from baseline in the average BPI-SF item scores (pain severity dimension). An alternative definition for the pain progression event will also be used which is defined as increase of ≥2 points from baseline in the score at a post-baseline assessment as compared to baseline in the average BPI-SF item scores (pain severity dimension).

In patients with pain progression event, time to pain progression is defined as time from randomization to the first pain progression event.

In patients with no pain progression event, time to pain progression will be censored on the last visit date where BPI-SF was collected. In patients with baseline score missing or no post-baseline score, the time to pain progression will be censored on the date of randomization. Patients entering the open-label phase without pain progression event would be censored on the date of last BPI-SF assessment prior to first open-label treatment.

6.1.4 Other Efficacy Variables

Not Applicable.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent AEs (TEAEs; frequency, severity, seriousness, and relationship to study drug).
- Clinical laboratory variables (hematology, biochemistry, PSA and testosterone)
- Vital signs (systolic and diastolic blood pressure and pulse rate) and weight
- 12-lead ECG

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

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 drug taken'* 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 and an increased NCI-CTCAE grade).

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.

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

Drug-Related TEAE

A drug related TEAE is defined as any TEAE with a causal relationship to study drug as assessed by the investigator in the eCRF (by answering 'YES) or with missing assessment of the causal relationship.

AEs of Special Interest

AEs of special interest are defined in Table 7

Table 7 Selection Criteria for AEs of Special Interest

Event of special interest	Selection based on MedDRA 23.0
Convulsion	Narrow SMQ of 'Convulsions'
Hypertension	Narrow SMQ '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', 'Band neutrophil percentage decreased', 'Neutropenic sepsis', 'Neutropenic infection' and 'Neutrophil count abnormal'
Cognitive/memory impairment	All preferred terms under the MedDRA High Level Group Term: 'Mental impairment disorders'
Ischemic Heart Disease	Narrow SMQs of 'Myocardial Infarction' and 'Other Ischaemic 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	Preferred term 'Posterior reversible encephalopathy syndrome'
Fatigue	Preferred terms of 'Fatigue', 'Asthenia'
Fall	Preferred term 'Fall'
Fractures	All preferred terms under the MedDRA High Level Group Terms: 'Fractures' and '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	All preferred terms including term 'Rash'

Event of special interest	Selection based on MedDRA 23.0
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', and 'Neoplasm prostate' AND (inclusive of) Narrow SMQ of 'Myelodysplastic syndrome' AND (inclusive of) All preferred terms under High Level Term 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') Note: Those selected SPM cases will be adjudicated by medical review, which will confirm the evidence of a second primary malignancy

Note: Second primary malignancy reported as TEAEs of special interest will be presented for the entire duration of the study, not merely for the treatment-emergent period.

6.3 Exploratory Endpoint

Not applicable.

6.4 Other Variables

Previous, Concomitant, and Post-treatment Medication or Non-Medication

Previous medications or non-medications are defined as prostate cancer (PC) or non-PC related medications or non-medications taken within 28 days prior to the screening visit and up to the first dose of study.

Concomitant medications or non-medications are defined as PC or non-PC related medication or non-medication with at least one dose taken between the date of first dose (inclusive) and up to 30-day safety follow-up visit after study drug ended.

Post-treatment medication or non-medication are defined as PC or non-PC related medication or non-medication with at least one dose taken after the date of last dose (inclusive) after study drug ended.

A medication or non-medication can be both flagged as previous and concomitant, or both flagged as concomitant and post-treatment.

Dose Reduction and Interruption

During the study, patients who experience a NCI-CTCAE (version 4.03) grade 3 or higher AE (except liver function test AE) that is attributed to the study drug and cannot be ameliorated by the use of adequate medical intervention and/or dose reduction, may interrupt study drug for 1 week or until the toxicity grade improves to grade 2 or lower in severity. Study drug may be restarted at the original dose (160 mg/day) or a reduced dose (120 mg or 80 mg/day) in consultation with the Medical Monitor. After dose reduction, based on patient tolerance, study drug may be increased to a maximum dose of 160 mg/day per Investigator discretion.

Enzalutamide must be interrupted during the evaluation of symptoms suspicious of PRES (headache, lethargy, confusion, blindness and other visual and neurological disturbances, with or without associated hypertension).

Restarting treatment at a reduced dose or after treatment interruption for > 2 weeks must be discussed with the Medical Monitor.

The total number of dose reduction and the total number of interruption will be calculated.

Duration of Exposure

The length of time on treatment will be calculated in days and in months.

For patients who discontinued treatment prior to the data analysis cut-off date

Duration of exposure (months) = [(date last dose of study - date of first dose) + 1]/ 30.4375

For patients who did not discontinue treatment prior to the data analysis cut-off date

Duration of exposure (months) = [(data cut-off date - date of first dose) + 1]/30.4375

Average Daily Dose

The average daily dose is based on the actual dose taken while taking into account dose reduction and dose interruption periods as recorded in the dosing page of the eCRF. The average daily dose is;

$$\frac{\text{The cumulative dose}}{\text{Duration of exposure (in days)}}$$

where the cumulative dose is defined as the sum of all daily dose actually taken.

Percent Overall Compliance (compared to the theoretical full dose of 160 mg/day)
Percent overall compliance is based on the drug accountability data as recorded in the IVRS system.

Percent overall compliance is defined as the total number of capsules taken divided by the total number of capsules that should have been taken:

$$\frac{\text{[Total number of capsules consumed]}}{\text{[('Date last study drug returned' - 'Date first dose') + 1] x 4}} \times 100$$

The total number of capsules consumed will be calculated based on the number of capsules dispensed at all study visits minus the number of capsules indicated as returned, from the kits returned. The kits dispensed at the last visit for patients still on treatment by the data analysis cut-off date and for which the number of capsules returned is unknown will not be considered.

Refer to Appendix 2 - Adjustments in Calculation of Dose Compliance Details on the calculations for dose compliance.

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 summary tables and figures will be presented by treatment arm and overall for double-blind treatment period, unless stated otherwise. For open-label phase, only selected summaries will be presented , the titles of selected tables, listings and figures for open-label phase summaries will be written out to indicate the “Open-label Phase”, refer to Appendix 3 for detailed analyses for open-label phase. All listings will be produced by site and patient id numbers in ascending order.

Disposition, demographics and other baseline characteristics as well as efficacy data will 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 comparing double-blind enzalutamide to double-blind placebo. All null hypotheses will be of no treatment difference. All analyses will be based on IRT captured strata. Multiplicity adjustment was incorporated within the interim and final analysis of the primary endpoint according to the O’Brien-Fleming method with a Lan-DeMets alpha spending function (refer to Section 6.1.1.1). And no adjustment for multiplicity will be made for this study on the other endpoints, hence any p-values displayed for those endpoints are intended to be read descriptively.

All data processing, summarization, and analyses will be performed using SAS® Version 9.1.3 or higher. 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 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:

- Number of patients with informed consent form (ICF), discontinued before randomization, randomized, based on patients with ICF (not presented by treatment);
- Number and percentage of patients randomized in each analysis set, patients who took study drug, patients who did not take study drug
- Number and percentage of patients by study visit, based on the SAF
- Number and percentage of subjects who discontinued from the treatment by primary reason for discontinuation
- Number and percentage of subjects who discontinued from the safety follow-up (30 day follow-up) by primary reason for discontinuation
- Number and percentage of subjects discontinued from the post-treatment follow-up by primary reason for discontinuation;
- Number and percentage of subjects who discontinued from the long term follow-up (end of study) by primary reason for discontinuation
- Number of subjects with protocol deviations
- Number of subjects per protocol version

Screen failures information, inclusion/exclusion from analysis set, treatment disposition, 30 day follow-up disposition, post-treatment follow-up disposition, and long term follow-up disposition, randomization information and dates of first and last evaluations 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 8.3 Major Protocol Deviations) will be assessed for all randomized subjects.

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.

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. Other deviations outside of the categories defined above will be summarized where applicable.

The number and percentage of subjects meeting any criteria will be summarized for each criterion and in total, by treatment group, as well as by study site. Inclusion and exclusion criteria will be summarized for PD1 by treatment group and overall.

A data listing will be provided by site and subject.

7.2.3 Demographic and Other Baseline Characteristics

Descriptive statistics for age and height at study entry will be presented along with frequency tabulations for age group (< 65, 65- <75 and >= 75), race, at study entry. The weight, body mass index (BMI), ECOG status, PSA, and alkaline phosphatase (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.

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

Medical history is coded in the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0, and will be summarized by System Organ Class (SOC) and preferred terms, as well as by preferred terms alone, by treatment group and overall on the ITT population.

Prostate cancer history will be summarized by presenting the number and percentage of subjects for tumor and lymph node stages, Gleason scores (less than 8 versus 8 or more) at initial diagnosis, volume of disease (Low versus High), incidence and location of metastases (incl. the number of bone lesions per category: 1, 2-4, 5-9, 10-19, 20 or more, and TNC; if a range which does not fall in one of these categories is reported, it will be reported in the category that includes the lower limit of the reported range) as well as per summary category (Bone only versus Soft tissue only versus Both bone and soft tissue), and previous therapies: prior docetaxel therapy use (none, yes) and ADT prior use or orchiectomy (none, ≤3 months, >3 months; considering the ATC 4th level ‘gonadotropin releasing hormone analogues’ or Preferred WHO name ‘degarelix’). Descriptive statistics will also be used to summarize the duration of disease, which is the duration between the date of randomization and the date of initial diagnosis (expressed in months).

Prior radiation and prior procedures will also be summarized.

Non-prostate cancer related medical history including data up to the start of study drug will be coded using MedDRA. The summary table (number and percentage of subjects) will be presented alphabetically by SOC and decreasing order of frequency of preferred terms within each SOC. An additional summary table will be presented only by preferred terms in decreasing order of frequency.

The underlying conditions and malignancy risk factors will be listed.

7.2.4 Previous, Concomitant, and Post-treatment Medications or Non-medications, and New Antineoplastic Therapy

Previous, concomitant, and post-treatment medications (both PC and non-PC related for previous and concomitant, and only PC related for post-treatment) reported in the corresponding eCRFs, will be coded with World Health Organization Drug Reference List

(WHO-DD), and will be summarized separately by presenting the number and percentage of subjects 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. Subjects taking the same medication multiple times will be counted once per medication and period.

Previous and concomitant non-medications reported in the corresponding eCRF will be summarized separately by presenting the number and percentage of subjects by reported name. It will be ordered alphabetically and decreasing order of frequency of reported name. Subjects having the same non-medication multiple times will be counted once per non-medication and period.

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

All (new) antineoplastic prostate cancer therapies (started on or after first dose of study drug date) will also be summarized separately on the first new antineoplastic prostate cancer after study drug ended. The summary of first new antineoplastic prostate cancer therapy will be provided for the ITT and SAF population.

All previous, concomitant and post-treatment medications or non-medications recorded in the eCRFs will be listed, as well as all new antineoplastic prostate cancer therapies.

7.3 Study Drugs

7.3.1 Exposure

The following information on drug exposure will be presented for each treatment group for 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, increases or interruptions, the reasons for these, as well as the number of these per patient.
- Descriptive statistics for the total dose and the average daily dose of the drug patient was exposed to.

7.3.2 Treatment Compliance

Percent overall compliance with the dosing schedule will be examined on drug accountability data for patients in the SAF for whom, at least a kit was returned and the first and last days of treatment (or the patient still on treatment by the cut-off date) are known.

Percent overall compliance will be summarized as follows:

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

7.4 Analysis of Efficacy

Primary and secondary efficacy analysis will be conducted on the ITT population only for double-blind treatment period unless otherwise specified.

Double-blind treatment period is defined as the period subjects being randomized to receive enzalutamide or placebo in a double-blind fashion such that neither the investigator, sponsor's study management team, clinical staff, nor the subject will know which agent is being administered.

7.4.1 Analysis of Primary Endpoint(s)

The primary efficacy variable is time to PSA progression (TTPP): PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 μg/L (2 ng/mL) above the nadir (i.e., lowest PSA value observed post baseline or at baseline), which is confirmed by a second consecutive value at least 3 weeks later.

The primary efficacy analysis will be performed on the TTPP for the subjects in the ITT population. TTPP is defined as the time from randomization to the date of the first confirmed observation of PSA progression. For subjects who have not had confirmed PSA progression at the time of analysis, the following censoring rules will be applied.

- Subjects who have no baseline or no post-baseline PSA assessments will be censored at the date of randomization
- Subjects who have not progressed by the data cutoff date will be censored at the date of the last PSA assessment prior to the data cutoff date
- Subjects who have not progressed but died due to any cause will be censored at the date of the last PSA assessment prior to the data cutoff date
- Subjects who discontinued from the entire study prior to the data cutoff date without evidence of PSA progression will be censored at the date of the last PSA assessment
- Subjects who have had unconfirmed PSA progression by the data cutoff date will be censored at the date of the last PSA assessment without evidence of confirmed PSA progression prior to the data cutoff date

If a subject meets the criteria for more than one censoring rule, they will be censored with the earliest censoring date. The PSA progression date is the first date where progression definition is met, not confirmed.

There are 2 planned analyses (as defined in Section 6.1.1), one final analysis at the total planned 75 PSA progression events and one interim analysis at 80% of the total planned events (about 60 PSA progression events).

The effect of Enzalutamide+ADT compared to placebo+ADT will be formally tested using a stratified log-rank test at both interim analysis and final analysis at 2-sided 0.0244 and 0.0429 significance level, respectively, according to the O'Brien-Fleming boundary as implemented by Lan-DeMets alpha spending function [Lan-DeMets, 1983]. Stratification factors are the factors used at randomization, 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: TTPP for Placebo+ADT and Enzalutamide +ADT are not different
- The alternative hypothesis: TTPP 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=0.05
                    ALPHAQT=0.05 METHOD=KM;
    TIME AVAL*CNSR(1);
    STRATA STRATUM1 STRATUM2/ 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 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 TTPP events by treatment group. The median TTPP 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. 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 TTPP can be rephrased in terms of the HR ($\lambda_{ArmA} / \lambda_{ArmB}$), where λ_{ArmA} represents the hazard of TTPP for Enzalutamide+ADT and λ_{ArmB} represents the hazard of TTPP for placebo+ADT. A HR of < 1 indicates that the

TTPP 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, 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 = INPUT;
  MODEL AVAL*CNSR(1) = TREATMENT / 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_1, then it will be concluded that Enzalutamide+ADT prolongs TTPP compared to placebo+ADT.

The PSA results will be summarized descriptively by visit, by presenting the mean, standard deviation, minimum, maximum and median of the results and change from baseline for the subjects in the ITT population and also for the subjects in the ITT population with detectable PSA at baseline.

Sensitivity analyses

The efficacy sensitivity analyses for TTPP as defined in Section 6.1.1.2 will be conducted on the ITT population using the same analysis methods as described above.

A forest plot displaying the HR for treatment comparison and 95% confidence interval will be presented for the different TTPP sensitivity analyses. The HR will be estimated by use of Cox proportional hazards models stratified for the prior docetaxel use and disease volume and treatment as covariate, as in the primary analysis.

SAS PROC PHREG will be used for these sensitivity analyses:

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

Subgroup analyses

Subgroup analyses of TTPP and rPFS will 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 = INPUT;
  MODEL AVAL*CNSR(1) = TREATMENT / TIES=DISCRETE;
  BY SUBGROUP;
RUN;
```

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 rPFS

Time to Radiographic progression-free survival (rPFS) will be analyzed using the same analysis methods as for primary analysis of TTPP.

7.4.2.2 Time to First SSE

Time to first SSE will be analyzed using the same analysis methods as for primary analysis of TTPP.

7.4.2.3 Time to Castration Resistance

Time to first castration resistance will be analyzed using the same analysis methods as for primary analysis of TTPP.

7.4.2.4 PSA Response ≥50%, PSA Response ≥90%

The serum PSA response rate ≥50% and ≥90% at any time and at each visit for subjects with detectable PSA at baseline and at least 1 post-baseline assessment will be summarized. The largest decrease from baseline in PSA will be additionally presented by treatment group using a waterfall plot. PSA response ≥50% and ≥90% will be calculated by treatment group on the entire ITT population who have detectable PSA at baseline and at least 1 post-baseline assessment.

In patients of the ITT population with detectable PSA at baseline and at least 1 post-baseline assessment, the PSA Response ≥50%, and PSA Response ≥90% in enzalutamide+ADT and placebo+ADT will be compared by use of the stratified Cochran-Mantel-Haenszel score test.

The SAS code used to implement the Cochran-Mantel-Haenszel score test will be:

```
PROC FREQ DATA=INPUT;
    TABLES STRATUM*TREATMENT*RESPONSE / CMH;
RUN;
```

where INPUT is the input dataset

RESPONSE is the analysis variable with the PSA>=50% or PSA>=90%,

STRATUM is the stratification variables (volume of disease and previous docetaxel use)

TREATMENT is the treatment variable

7.4.2.5 Time to Initiation of a New Antineoplastic Therapy

Time to initiation of a new antineoplastic therapy will be analyzed using the same analysis methods as for primary analysis of TTPP.

7.4.2.6 PSA Undetectable Rate

The PSA undetectable rate (also referred as the rate of PSA decline to <0.2 ng/mL) is defined as the percentage of patients with detectable (≥ 0.2 ng/mL) PSA at baseline, which becomes undetectable (< 0.2 ng/mL) during study drug.

In patients of the ITT population with detectable PSA at baseline, the PSA undetectable rates in enzalutamide+ADT and placebo+ADT will be compared by use of the stratified Cochran-Mantel-Haenszel score test.

The SAS code used to implement the Cochran-Mantel-Haenszel score test will be the same as PSA Response ≥50% and PSA Response ≥90% in Section 7.4.2.4.

In addition to providing the planned 95% CI for PSA undetectable rate (using the Clopper-Pearson method based on the exact binomial distribution), the difference in response rates between the treatment groups was summarized along with the 95% CI based on the asymptotic distribution.

7.4.2.7 Objective Response Rate and Tumor Response

The ORR is calculated as the percentage of patients of the ITT population with measureable disease at baseline who achieved a complete or partial response in their soft tissue disease using the RECIST version 1.1 criteria; that is with CR or PR as best RECIST overall response.

The stratified Cochran-Mantel-Haenszel score test will be used to compare enzalutamide+ADT versus placebo+ADT.

The SAS code used to implement the Cochran-Mantel-Haenszel score test is similar as described in Section 7.4.2.4.

On patients of the ITT population with measureable disease at baseline, descriptive statistics will be provided, based on investigator assessments, for:

- the best RECIST overall response,
- the ORR

On the ITT population, descriptive statistics will be provided, based on investigator assessments, for:

- the best overall response

- the percentage of patients who achieved a complete or partial response as best overall response
- the RECIST overall time point response, along with the bone lesion response, the overall time point response by visit

The target lesion description, non-target lesion description, new lesions description will be listed by visit. The target lesion response, non-target lesion response, unequivocal new lesions presence along with the overall RECIST time point response derived from investigator assessments, bone lesion response, and the overall time point response as assessed by the investigator will be listed by visit. The best RECIST overall response will be marked in the listing as well. The best overall response will also be listed for investigator assessments.

The number and percentage of CR, PR and non-responders as assessed by the investigator will be included.

In addition to providing the planned 95% CI for ORR (using the Clopper-Pearson method based on the exact binomial distribution), the difference in response rates between the treatment groups was summarized along with the 95% CI based on the asymptotic distribution.

7.4.3 Analysis of Exploratory Efficacy Endpoints

7.4.3.1 Quality of Life

BPI-SF average score will be summarized descriptively by visit, by presenting the mean, standard deviation, minimum, maximum and median of the results and change from baseline. A listing of all items scores will be provided.

The 5 FACT-P subscales (Physical, Social/Family, Emotional, Functional, Prostate Cancer Subscale) and the total FACT-P will be summarized descriptively by visit, by presenting the mean, standard deviation, minimum, maximum and median of the results and change from baseline. A listing of all items scores will be provided along with a listing of the EQ-5D-5L will be provided as well.

The QLQ-PR25 questionnaire will be summarized by descriptive statistics after scoring their scales and items. QLQ-PR25 will also be analyzed on the subgroup of patients who reached the 1 year time point.

The QLQ-PR25 is composed of both multi-item scales and single-item measures as follows:

- ➔ Urinary symptoms and problems (8 items: Q31 – Q37, Q39)
- ➔ Incontinence aids (Q38)
- ➔ Bowel symptoms/function (4 items: Q40 – Q43)
- ➔ Treatment-related symptoms (6 items: Q44 – Q49)
- ➔ Sexual activity (2 items: Q50, Q51)
- ➔ Sexual functioning (4 items: Q52 – Q55)

In order to score a (sub)scale, first the raw score (RS) is computed by averaging the raw values of the individual items that contribute to the (sub)scale and then the RS is linearly transformed using the range of item raw values so that scores range from 0 to 100. Specifically, the scores of these scales and the individual items will be calculated based on

[(RS-1)/range]×100. However, for Q53 to Q55, before scoring the raw value of an individual item will be subtracted from 5 (i.e., 5 – raw value).

For handling missing items, if half or more questions within scale are answered then a score will be calculated for that scale. Otherwise the patient score for that scale will be missing. A high scale score represents a higher response level. The scale scores and change from baseline will be summarized by descriptive statistics by visit. A listing of all items scores and a (sub)scale scores will be provided.

Time to Deterioration of QoL

Time to deterioration of QoL will be analyzed using the same analysis methods as for primary analysis of TTPP.

7.4.3.2 Time to Pain Progression

Time to pain progression will be analyzed using the same analysis methods as for primary analysis of TTPP.

7.4.4 Analysis of Other Efficacy Variables

Not applicable.

7.5 Analysis of Safety

All analysis of safety will be presented by treatment group for 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 per treatment group and overall:

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

An overview table of the TEAE of interest will describe by the number and percentage of patients with TEAEs of interest per treatment group and overall.

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

- TEAEs
- NCI-CTC grade 3 or higher TEAEs
- drug related NCI-CTC grade 3 or higher TEAE
- drug related TEAEs,
- serious TEAEs,
- drug related serious TEAEs,
- TEAEs leading to withdrawal of treatment,
- TEAEs leading to dose reduction,
- TEAEs leading to dose interruption,
- drug related TEAEs leading to withdrawal of treatment,
- 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 overall group will also be summarized.

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 overall group, on a 6 monthly basis (0- <3 months; 3-<6 months; 6-<12 months; 12 months or more). 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.

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 overall. 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).

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. An AE can be reported multiple times in the AE module if its toxicity grade changes. Summaries will be provided for:

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

7.5.2 Clinical Laboratory Evaluation

Laboratory assessment will be done for the following parameters as applicable:

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

*Testosterone and PSA will not be assessed for open-label phase.

**PSA may be taken locally for assessments affected by COVID-19.

Quantitative clinical laboratory variables (hematology, serum chemistry and testosterone), will be summarized using mean, standard deviation, minimum, maximum and median for each treatment 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.

Based on the NCI-CTCAE grade of laboratory data, clinical laboratory evaluations will be summarized by grade and by visit as applicable, 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. PSA results from local laboratory will be flagged in the listings.

7.5.2.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria for liver tests - defined as ALP, ALT, total bilirubin, AST, 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 > 5xULN > 8xULN
Total Bilirubin	> 2xULN
ALT and/or AST AND Total Bilirubin(*)	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN
ALT and/or AST AND Total Bilirubin (*) AND Alkaline phosphatase	(ALT and/or AST > 3xULN) and 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

The baseline visit is the last measurement taken prior to initial study drug administration.

Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) including weight will be summarized using mean, standard deviation, minimum, maximum and median by treatment group at each time point. Additionally, a within-patient change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group at each time point. 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 for each visit by treatment group using mean, standard deviation, minimum, maximum and median. Baseline is defined as the last available measurement prior to the first dose.

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 / $RR^{0.33}$.

All ECG results will be provided in a listing.

7.5.5 Physical Examination

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.

7.5.6 Pregnancy

Not applicable.

7.5.7 Other Safety-Related Observations

The number and percentage of patients falling in each category of the performance status ECOG score 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 TTPP 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);
- 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

Assessments affected by COVID-19 will be summarized and listed.

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

An interim analysis is planned to occur after approximately 60 PSA progression events (about 80% of the total planned events) are observed. TTPP will be tested for efficacy according to the O'Brien-Fleming boundary as implemented by Lan-DeMets alpha spending function [Lan-DeMets, 1983]. The IDMC may recommend terminating the trial at the interim analysis based on statistically significant TTPP results favoring enzalutamide. In case IDMC recommend continuing the trial after the interim analysis, the final TTPP analysis will be conducted when total PSA progression events reach 75. Data cut-off dates will be set when the planned number of events is reached for the interim and final analyses. If the exact number of events at interim and final analyses are different than planned, the significance level will be adjusted accordingly, based on the O'Brien-Fleming method with a Lan-DeMets alpha spending function.

The interim analysis will be conducted by independent data analysis group (DAC) with randomized treatment assignments and reviewed by the IDMC. The full procedures for IDMC and interim analysis will be described in a separate IDMC charter and Interim Analysis Plan.

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. 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. Should that date be partially missing, the end of treatment date recorded on the end of treatment form will be used.

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, and also the date of initial diagnosis (to estimate the relative study day to calculate cancer duration) and 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 of the medication/therapies and AEs to treatment, in addition to determining 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) and SSE dates will be done as follows:

- Incomplete Start Day 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 and End Day is incomplete: use the later of (first day of the month, first dosing day if first dosing month).
- Incomplete End Day: 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 (partially) missing, the last dose date of treatment will be imputed as follows:

- Incomplete Day: use the earliest of (last day of the month, end of treatment [form] day, day of the 30-day follow-up visit);

- Incomplete Month or Year: no imputation

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: use the earliest possible date (next day of the last visit/contact date the participant is known to be alive).

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 and unscheduled visits are also assigned analysis visit window based on the visit day.

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 8.

Table 8 Analysis Visit Windows

Visit Day Interval	**Scheduled Visit**	**Analysis Visit***
For double-blind treatment period:		
-28<=Visit Day<1	Week -4 to -1 (Day -28 to -1)	Screening
Up to Day 1	Week 1 (Day 1)	Baseline
Day 2 - Day 43	Week 5 (Day 29)	Week 5
Day 44 - Day 71	Week 9 (Day 57)	Week 9
Day 72 - Day 99	Week 13 (Day 85)	Week 13
For the next visits after week 13 during the double-blind treatment period: Week X = Week (i*4+13) (i=1,2,3,…) Week X target day = i*4*7 + 85 (i=1,2,3,…) Week X (Wk X target day - 13 days ; Wk X target day + 14 days) Special case for Testosterone, CT/MRI and Bone Scan, Chest X-ray or Chest CT or MRI, QoL Assessment and ECOG Performance Status: Week 13 (Day 85) day interval is Day 72 - Day 127 and for the visits after Week13: Week X = Week (i*12+13) (i=1,2,3,…) Week X target day = i*12*7 + 85 (i=1,2,3,…) Week X (Wk X target day - 41 days ; Wk X target day + 42 days)		
However for the (last) visit during the double-blind treatment period, i.e. the last dose day of study drug is recorded, the upper boundary of the analysis visit window is 3 days after the last dose day, e.g.: Week X = Week (i*4+13) (i=0,1,2,3,…) Week X target day = i*4*7 + 85 (i=0,1,2,3,…) Week X (Wk X target day - 13 days ; last dose day + 3 days) Special case for Testosterone, CT/MRI and Bone Scan, Chest X-ray or Chest CT or MRI, QoL Assessment and ECOG Performance Status: Week 13 (Day 85) day interval is Day 72 - Day 127 and for the visits after Week13: Week X = Week (i*12+13) (i=1,2,3,…) Week X target day = i*12*7 + 85 (i=1,2,3,…) Week X (Wk X target day - 41 days ; last dose day + 3 days)		
(last double-blind dose day + 4 ; last double-blind dose day + 42 if not entering open-label phase) or (last double-blind dose day + 4, up to CRF collected last visit prior to the CRF collected open-label phase day 1 visit)	last double-blind dose day + 30 days	30 Day Safety F-up *(after last dose or prior to new therapy*)
For open-label phase: all eCRF collected Open Label visits		

Visit Day Interval	**Scheduled Visit**	**Analysis Visit***
eCRF collected open-label day 1 visit up to open-label dose Day 1, or up to open-label informed consent date if not dosed	Open Label Phase Week 1 (Day 1)	Open Label Phase Baseline
Day 2 - Day 43	Open Label Phase Week 5 (Day 29)	Open Label Phase Week 5
Day 44 - Day 127	Open Label Phase Week 13 (Day 85)	Open Label Phase Week 13
For the next visits after week 13 during the open-label phase: Open Label Phase Week X = Week (i*12+13) (i=1,2,3,…) Open Label Phase Week X target day = i*12*7 + 85 (i=1,2,3,…) Open Label Phase Week X (Wk X target day - 41 days ; Wk X target day + 42 days)		
However for the (last) visit during the open-label treatment period, i.e. the last dose day of study drug is recorded, the upper boundary of the analysis visit window is 5 days after the last dose day, e.g.: Open Label Phase Week X = Week (i*12+13) (i=0,1,2,3,…) Open Label Phase Week X target day = i*12*7 + 85 (i=0,1,2,3,…) Open Label Phase Week X (Wk X target day - 41 days ; last dose day + 5 days)		
(last open-label dose day + 6, last assessment)	last open-label dose day + 30 days	Open Label Phase 30 Day Safety F-up *(after last dose or prior to new therapy*)
For long-term follow-up visits conducted after double-blind treatment period or open-label phase:		
Patients who end treatment before the data analysis cut-off date and have long-term (LT) follow-up visits, have visits every 12 weeks after last dose day: LT F-up j = j*12 weeks visit after last dose day (j=1,2,3,…) LT F-up j target day = j*12*7 + last dose day (j=1,2,3,…) LT F-up j (j*12*7 + last dose day - 41 ; j*12*7 + last dose day + 42)		

F-up: follow-up; WK: Week

*At OL1 Visit (open-label day 1), the following assessments (ECG; vital signs; physical examination; clinical labs; ECOG) do not need to be repeated if they were completed within 7 days in Safety Follow-up Visit during double blind treatment period, and the corresponding data captured in Safety Follow-up Visit could be captured repeatedly in OL1 CRF forms, thus those assessments will serve the analysis needs for both double blind treatment period and open-label phase where applicable. And "open-label" will be reflected in the open-label phase visits' label as applicable, e.g. OLP Baseline, Open Label Week X, etc..

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, but for the exceptional case where both the two

assessments are reported as scheduled the primary assessment (i.e. not the repetition assessment) will be used.

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.0	21-Dec-2022	Not Applicable	Original Version

9 REFERENCES

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10 APPENDICES

10.1 Appendix 1 - Summary of Sensitivity Analyses of Primary Endpoint

		Uninformative censoring	The impact of Treatment Discontinuation 1	The impact of Treatment Discontinuation 2	The impact of New therapy (anti-neoplastic therapy)	rPD (INV), SSE, New therapy, and Death as event impact	The impact of PSA results from local laboratory tests
		TTPP_Primary	TTPP_1-1	TTPP_1-2	TTPP_2	TTPP_3	TTPP_4
EVENT	PSA ⩾ 25% increase and an absolute increase of ⩾ 2 µg/L (2 ng/mL) above the nadir	X	X	X	X	X	X
	rPD (INV)					X	
	SSE					X	
	New therapy (anti-neoplastic therapy)					X	
	Death (within 24w after EOT)					X	
	Treatment discontinuation without evidence of PSA progression or on-study death			X (the date of last dose of study drug)			
Censoring (date)	Treatment discontinuation prior to PSA progression		X (the date of last PSA assessment before treatment discontinuation)				
	New therapy (anti-neoplastic treatment) prior to PSA progression	X (last PSA assessment before initiation of subsequent					X (last PSA assessment before initiation of subsequent anti-neoplastic therapy)

		anti-neoplastic therapy)					
	If no baseline or no post-baseline PSA	**X (rando date)**	**X (rando date)**	**X (rando date)**	**X (rando date)**	**X (rando date)**	**X (rando date)**
	If not progress by the cutoff date	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**
	If not progress but died due to any cause by the cutoff date	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**
	If discontinued without evidence of PSA progression by the cutoff date	**X (last PSA assessment)**			**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**
	If had unconfirmed progression by the cutoff date	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**	**X (last PSA assessment)**

10.2 Appendix 2 - Adjustments in Calculation of Dose Compliance Details

The steps described below are used for the calculation of the ***cumulative dose*** based on the drug accountability data. The calculation of the ***cumulative dose*** based on the dose records in eCRF is not covered in this appendix.

By protocol, the dispensed kits should be returned at the next scheduled visit, but that may not always happen in reality and for some patients the kits may be returned later or not all returned. The protocol study visits are scheduled at equal time intervals. Patients who are ongoing treatment by the time of data cut-off may have not returned all the dispensed kits and some patients may return all or some of the treatment kits after the end of treatment date.

The following general rules apply to the calculation of percent dose compliance:

1. Percent dose compliance should not be calculated for kits not returned, or for which the number of capsules returned are unknown, or returned on the same day or earlier than dispensed
2. Percent dose compliance calculations should be based on treatment kits returned
3. Every kit dispensed should have a total of X capsules, where X=number of capsules that should be taken per day*number of days until next refill. In this study, this number should be 124 (4 capsules per day*31 days) at week 1 day 1 visit and all treatment period visits thereafter.

The aim is to calculate a running sum of the drug dose at each visit where kit/s is/are dispensed, while adjusting the calculation for time interval between visits, time returned and the time of return in regards to end of treatment date. The cumulative dose is then used to calculate the percent overall compliance using the formula specified in Section 6.4.

I. For patients with kits returned prior to the end of treatment

1. <u>At week 1 day 1 visit</u>

- Patients receive one kit only (1 bottle of 124 capsules)
- It is possible that patients forget to return their kit at the next visit and bring it at a later visit than planned
- 124 capsules is maximum 31 days of treatment which is more than the 28 days planned between visits
- the last day of any period will be added to the first kit taken, therefore 1 is added

➔ So, the theoretical cumulative number of capsules used between day 1 and week 5 for a kit returned prior to the end of treatment is:

4*((date of return - start date) +1 or 31 at most)

2. <u>At week 5 visit and every visit thereafter</u>

- patients receive 1 kit
- It is possible patients forget to return their kit at the next visit, as requested by protocol, and bring it at a later visit or even after treatment ended

- The treatment can also end during the use of the kit (but it will be assumed that the drug will then be returned after end of treatment for at least one kit or on that day at the earliest)
- 124 capsules is maximum 31 days of treatment

➔ So, ***per kit***, for kits returned prior to the end of treatment, the theoretical number of capsules between 2 of the 4-weekly visits, to add to the cumulative number, is:
4*((date of return - date of dispense) or 31 at most)

II. For patients with kits returned on or after end of treatment

The following points should be considered when going through the steps outlined below:

- It is possible that some patients return their kits (some or all of them) after end of treatment (i.e. kits were dispensed before end of treatment and then returned after end of treatment)
- In theory for patients who end treatment there should always be at least one kit returned on or after the end of treatment date
- In these cases the date the kit/s was/were returned should not be considered and the end of treatment date should be used instead
- Such cases would be the last ones to consider in the calculation of the cumulative dose

1. <u>At week 1 day 1 visit</u>

- Patients receive one kit only (1 bottle of 124 capsules)
- It is possible patients forget to return their kits at the next visit and instead bring them after EOT despite that they might have continued with treatment for a much longer time
- 124 capsules is maximum 31 days of treatment which is more than the 28 days planned with next visit
- The last day of any period will be added to the first kit taken => +1 is added

➔ So, the cumulative theoretical number of capsules between day 1 and week 5 for kit returned after the end of treatment, is:
4* ((date of end of treatment - start date) +1 or 31 at most)

2. <u>During 2 consecutive 4-weekly visit</u>

- Patients receive 1 kit
- It is possible patients forget to return their kits at the next visit and instead bring them after EOT despite that they might have continued with treatment for a much longer time
- 124 capsules is maximum 31 days of treatment

➔ So, the theoretical cumulative number of capsules between those 2 consecutive 4-weekly visits is:
4*((date of end of treatment - dispense date) or 31 at most)

10.3 Appendix 3 - Statistical Methods for Open-Label Phase

An open-label phase data summary will be presented for subjects who switched treatment from placebo + ADT to enzalutamide + ADT. Data collected in the open-label phase will only be summarized by descriptive statistics unless otherwise specified.

10.3.1 Disposition of Subjects

Subject disposition data (patients who continued to the open-label phase and primary reasons for treatment discontinuation and study discontinuation) will be summarized descriptively in the ITT population for patients who started open-label enzalutamide for the open-label phase.

The following subject data will be presented:

- Number of patients with informed consent form (ICF), discontinued before open-label phase
- Number and percentage of patients by open-label phase study visit
- Number and percentage of subjects who discontinued from the open-label phase treatment by primary reason for discontinuation
- Number and percentage of subjects who discontinued from the open-label phase 30 day follow-up by primary reason for discontinuation
- Number and percentage of subjects who discontinued from the long term follow-up (end of study) by primary reason for discontinuation

Screen failures information, inclusion/exclusion from open-label phase, treatment disposition, 30 day follow-up disposition, and long term follow-up disposition will be listed.

10.3.2 Exposure

Enzalutamide exposure will be summarized and listed in the open-label phase.

- 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 total dose and the average daily dose of the drug patient was exposed to.

10.3.3 Adverse Events

Adverse events will be coded using MedDRA. The number and percentage of AEs, SAEs, and AEs leading to death, discontinuation, reduction, or interruption to study drug for treatment emergent period for open-label phase will be summarized by system organ class and preferred term as applicable. The number and percentage of AEs by severity (reported according to NCI-CTCAE version 4.03) will also be summarized. All AEs will be listed.

10.3.4 Other Analyses

For quantitative laboratory measurements and vital signs, descriptive statistics will be used to summarize results and change from baseline by visit. Baseline will be defined as the latest value recorded prior to or on the first enzalutamide administration in open-label phase. Using the NCI-CTCAE version 4.03, laboratory values will be classified as Grade 1 through 4, where possible. Laboratory and vital sign data will be displayed in listings. Other assessments conducted during open-label phase, such like ECOG performance status, concomitant medications will also be listed where applicable.

11 SIGNATURE

(E-signatures are attached at the end of document)

Prepared by:	*E-signatures are attached at end of document*	Date:	Date (DD Mmm YYYY)
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