STATISTICAL ANALYSIS PLAN

SAP Final 2.1, dated 23 JAN-2024

A Randomized, Double-Blind, Placebo-Controlled, Phase IIIb Study of the Efficacy and Safety of Continuing Enzalutamide in Chemotherapy Naïve Metastatic Castration Resistant Prostate Cancer Patients Treated with Docetaxel plus Prednisolone Who Have Progressed on Enzalutamide Alone

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
APEL	Astellas Pharma Europe Ltd
ASCM	Analysis Set Classification Meeting
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BDRM	Blinded Data Review Meeting
BMI	Body Mass Index
BPI-SF	Brief Pain Inventory – Short Form
CI	Confidence Intervals
CM	Concomitant Medication
CR	Complete Response
CRF	Case Report Form
CS	Classification Specifications
CSR	Clinical Study Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FAS	Full Analysis Set
FU	Follow-Up
H	High
HR	Hazard Ratio
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRT	Interactive Response Technology
L	Low
LDH	Lactate Dehydrogenase
LHRH	Luteinizing Hormone-Releasing Hormone
mCRPC	metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
N	Normal
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria Adverse Events
PCWG2	Prostate Cancer Working Group 2
PD1-x	Protocol Deviation 1-x
PFS	Progression Free Survival
PR	Partial Response
PSA	Prostate-specific Antigen
PT	Preferred Term
QTc	Corrected Q-T Interval

Abbreviations	Description of abbreviations
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Stable Disease
SOC	System Organ Class
SRE	Skeletal-related Event
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings and Figures
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO-DD	World Health Organization Drug Dictionary

List of Key Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
Chronic opiate analgesia	Parenteral opiate use for ≥7 days or use of WHO Analgesic Ladder Level 3 oral opiates for ≥3 weeks.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
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 (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet one or more criteria required for participation in a trial.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1. INTRODUCTION

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

The SAP is finalized and signed prior to database soft lock. For operational efficiency an earlier time is usually targeted (before first subject in target date). If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

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

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

2. FLOW CHART AND VISIT SCHEDULE

Figure 1 Flow Chart

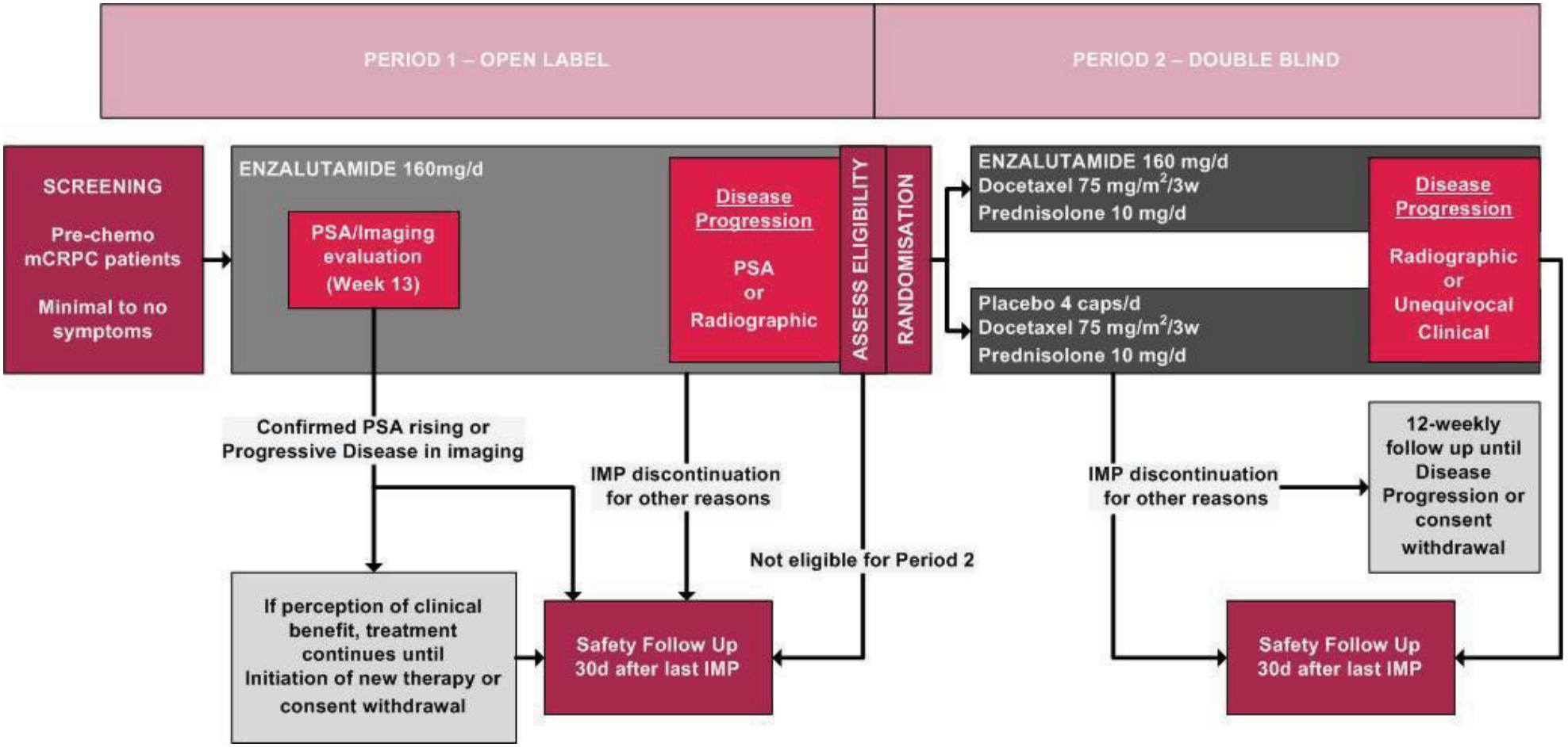

Table 1 Schedule of Assessments – Period 1

Visit	Screening	Open label Enzalutamide				Unsched[i]	Extension Period 1[n]	FU After last drug[j or q]
Week	-4 to -1	1	5	13	25 then q12wk	n/a	q12wk	30d after last drug
Day	-28 to -1	1	29	85	169 + q84d	n/a	n/a	n/a
Window (days)	n/a	n/a	±7	±7	±7	n/a	±7	±3
Informed Consent	X							
Demographics/Medical History[a]	X							
Inclusion/Exclusion	X	X						
Vital Signs	X	X	X	X	X	X	X[p]	X
Physical Examination[b]	X	X	X	X	X	X	X[p]	X
12-lead ECG	X							
Hematology/Clinical Chemistry[c]	X	X	X	X	X	X	X[o]	X
PSA	X	X		X[g]	X	X	X[o]	
Informed Consent for Biomarker samples[k]	X					X[k]		
Biomarker sample		X[l]	X	X		X[m]		
Testosterone	X							
ECOG	X	X	X	X	X	X	X[p]	X
BPI-SF	X							
FACT-P, EQ-5D-5L	X							
Health Resource Use	X			X	X			
Radiographic assessments[d]	X[f]			X[h]	X	X	X[p]	
Enzalutamide dispensing		X		X	X		X	
Enzalutamide accountability			X	X	X		X	X
Adverse Events[e]	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X

a. Includes age, initial diagnosis of prostate cancer, Gleason score at time of diagnosis along with details and dates of all treatments for prostate cancer;

b. All physical examinations will include weight.
Screening physical examination will be a full examination including height, subsequent examinations will be brief only and symptom-focused;

c. Clinical labs (also PSA and testosterone) will be collected for central laboratory assessment;
d. Whole body radionuclide bone scan and abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) for soft tissue may be performed up to 7 days prior to the scheduled visit to permit review of results at the visit;
e. All Adverse Events (AEs) and Serious adverse events (SAEs) including death will be collected from the time the subject signs the consent form until 30 days after last dose of IMP.
f. Screening imaging assessments should include a Chest X-ray (CXR) or chest CT as well as whole body radionuclide bone scan and abdominopelvic CT/MRI. Radiographic assessments collected within 42 days prior to Day 1 may be used to establish the presence of metastatic disease;
g. Subjects will be assessed for PSA response at Week 13 which should be confirmed by a subsequent test at least 3 weeks later. Subjects without a confirmed PSA response at Week 13 will be ineligible for participation in Period 2;
h. Radiographic progression by bone scan at the first assessment at Week 13 requires a confirmatory scan 6 or more weeks later. Subjects with confirmed radiographic progression at Week 13 will be ineligible for participation in Period 2 and will typically have safety follow up; however, Period 1treatment may continue for some subjects as long as the investigator considers it to be of clinical benefit (stopping on initiation of any new antineoplastic therapy);
i. Unscheduled visit assessments are optional and should be dictated by the clinical reason for visit attendance (e.g. if progression is suspected, radiographic assessments may be performed);
j. Safety follow-up in subjects not progressing to Period 2 before the data cut off will be 30 days after the last dose of IMP or prior to initiation of new antineoplastic therapy, whichever is earliest.
k. Participation in the Biomarker sub-study is optional, and a separate Informed Consent is to be signed prior to collecting any samples for it. If a subject is already enrolled in Period 1 of the study, but agrees to provide biomarker samples, consent for the biomarker collection for Period 2 can be taken at any time prior to the biomarker sample collection;
l. To be taken pre-enzalutamide administration;
m. Sample to be taken when subject progresses clinically, as part of the baseline samples for Period 2 of the study. If a subject misses week 1/day 1 samples in Period 1, and consents to the sub-study, this should be the first sample taken.
n. Open-label enzalutamide treatment may be continued for subjects still in treatment in Period 1 when enrollment to Period 2 closes or when the 182 primary endpoints events are reached, whichever occurs first (approximately 274 subjects randomized into Period 2)
o. Laboratory tests to be performed locally as required for the subject's standard of care. Relevant results will only be collected in the event of SAEs and AEs.
p. Results to be collected in the eCRF if the assessments are performed as part of the standard of care of the subject.
q. Safety follow up in subjects after the data cut off will be 30 days after the last dose of IMP or prior to initiation of new antineoplastic therapy, whichever is earliest. Laboratory tests to be performed locally as required for the subject's standard of care. Relevant results will only be collected in the event of SAEs and AEs.

ECG – Electrocardiogram; PSA - Prostate-specific Antigen; ECOG - Eastern Cooperative Oncology Group; BPI-SF - Brief Pain Inventory – Short Form; FACT-P - Functional Assessment of Cancer Therapy - Prostate, EQ-5D-5L - EuroQol 5 dimension, 5 level health state utility index; FU – Follow up

Table 2 Schedule of Assessments – Period 2

Visit	Eligibility Assessment for Period 2[e]	Randomized (Double-Blind) Treatment on background of Docetaxel + Prednisolone[g]							Ongoing (Double-Blind) Treatment[p]	Unsched[k]	Extension Period 2		FU After last IMP[l] or s
Cycle	n/a	1	2-4	5	6-8	9	10	Additional	n/a	n/a	Additional	n/a	n/a
Week	-4 to -1	1	4/7/10	13	16/19/22	25	28	Varies q3wk cycles[j]	37 then q12wk	n/a	Varies q3wk cycles	37 then q12wk	30d after last drug
Day	-28 to -1	1	22/43/64	85	106/127/148	169	190	n/a	253 then q84d	n/a	n/a	q84d	n/a
Window (days)		n/a	±3	±3	±3	±3	±3	±3	±7	n/a	±7	±7	±7
Inclusion/Exclusion[a]	X	X											
Randomization		X											
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X			X		X			X				X
Hematology/Clinical Chemistry[c]	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X	X[q]	X[q]	X
PSA	X	X		X	X	X	X	X	X	X	X[q]	X[q]	X
Biomarker sample		X[m]	X[n]	X		X				X[o]			X
Testosterone	X												
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X
BPI-SF	X	X	X	X	X	X	X	X	X	X			X
FACT-P, EQ-5D-5L		X		X		X			X				
Health Resource Use		X		X		X			X				
Radiographic Assessments[d]	X[f]			X[i]		X			X	X	X[r]	X[r]	
IMP dispensing		X		X		X			X			X	
Docetaxel administration		X	X	X	X	X	X	X			X		
IMP accountability		X		X		X			X			X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Eligibility will be checked against criteria for Period 2;

b. All physical examinations will include weight;

c. Clinical labs (also PSA and testosterone) will be collected for central laboratory assessment during scheduled clinic visits;

d. Whole body radionuclide bone scan and abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) for soft tissue may be performed up to 7 days prior to the scheduled visit to permit review of results at the visit;
e. The window for assessment of suitability to continue into Period 2 will commence from the point that progression is determined in Period 1 (i.e. confirmation of PSA or radiographic progression). Assessments collected at the last visit in Period 1 may be used to determine eligibility for Period 2 if collected within 4 weeks prior to randomization;
f. Period 2 baseline scans may utilize the most recent scans collected in Period 1 if collected within 4 weeks prior to randomization.
Scans should include a Chest X-ray (CXR) or chest CT;
g. Subjects who discontinue docetaxel before completion of 10 cycles (e.g. for toxicity) may continue with double-blind treatment and continue to attend study visits (at 12 weekly intervals) for assessments until IMP discontinuation criteria or endpoint criteria are met.
h. Local laboratory hematology samples for nadir count assessment will be collected approximately 1 week after docetaxel administration in all cycles; during the first 3 cycles additional hematology samples will be collected approximately 2 weeks after docetaxel administration.
Local laboratory hematology should also be collected to support dosing decisions prior to administration of docetaxel.
Patients with elevated liver function tests (LFTs) should have LFTs assessed prior to administration of docetaxel;
i. Radiographic progression by bone scan at the first assessment at Week 13 requires a confirmatory scan 6 or more weeks later;
j. If docetaxel treatment continues such that there is overlap with the subsequent 12-weekly visit cycle (e.g. Week 37, Week 49) then all assessments of those visits should be performed in addition to those required for docetaxel treatment;
k. Unscheduled visit assessments are optional and should be dictated by the clinical reason for visit attendance (e.g., if progression is suspected radiographic assessments may be performed);
l. Safety follow-up will be 30 days after the last dose of IMP or prior to initiation of new antineoplastic therapy, whichever is earliest
Subjects who discontinue IMP for a reason other than disease progression will continue to attend study visits (at 12 weekly intervals) for assessments until withdrawal of consent, disease progression or death.
m. Biomarker sample to be taken prior to first dose of double-blind study medication in Period 2;
n. Biomarker sample to be taken at Cycle 2 (Week 4);
o. Biomarker sample to be taken when the subject progresses clinically or reaches one of the endpoints of the study.
p. Double blind treatment may be continued for any subjects still in treatment in Period 2 between data cut-off and unblinding
q. Laboratory tests to be performed locally as required for the subject's standard of care. The results will only be collected in the event of SAEs and AEs.
r. Results to be collected in the eCRF if the assessments are performed as part of the standard of care of the subject.
s. Safety follow up in subjects after unblinding will be 30 days after the last dose of IMP or prior to initiation of new antineoplastic therapy, whichever is earliest. Laboratory tests to be performed locally as required for the subject's standard of care. Biomarker sampling will cease. Relevant results will only be collected in the event of SAEs and AEs.

ECG – Electrocardiogram; PSA - Prostate-specific Antigen; ECOG - Eastern Cooperative Oncology Group; BPI-SF - Brief Pain Inventory – Short Form; FACT-P - Functional Assessment of Cancer Therapy - Prostate, EQ-5D-5L - EuroQol 5 dimension, 5 level health state utility index; FU – Follow up.

3. STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to compare the efficacy of continuing treatment with enzalutamide after adding docetaxel and prednisolone versus placebo plus docetaxel and prednisolone, as measured by Progression Free Survival (PFS) in subjects with chemotherapy-naïve metastatic Castration-Resistant Prostate Cancer (mCRPC) with progression during treatment with enzalutamide alone.

3.1.2 Secondary Objectives

The secondary objectives of the study are to evaluate the effect of continuing treatment with enzalutamide and adding docetaxel and prednisolone versus placebo plus docetaxel and prednisolone, as measured by the following in subjects with chemotherapy-naïve mCRPC with progression during treatment with enzalutamide alone:

- Time to Prostate-Specific Antigen (PSA) progression
- PSA response
- Objective response rate
- Time to pain progression
- Time to opiate use for cancer-related pain
- Time to first Skeletal-related Event (SRE)
- Quality of life

Safety profile, including cumulative dose of docetaxel, and Health Resource Use will be described for these subjects. The safety profile as well as Health Resource Use of enzalutamide alone when administered to chemotherapy naïve subjects will also be described.

3.1.3 Exploratory Objective

To analyze candidate biomarkers in circulation for association with response or progression and for identifying mechanisms of resistance.

3.2 Study Design

This is a double-blind, randomized, placebo controlled trial of subjects with chemotherapy naïve mCRPC to evaluate the efficacy and safety of continued treatment with enzalutamide after adding docetaxel and prednisolone compared with treatment with placebo in combination with docetaxel and prednisolone.

The study will be conducted in consecutive periods of open label treatment with enzalutamide followed by randomized double-blind treatment with continued enzalutamide or placebo, adding with docetaxel and prednisolone.

In period 1 subjects will attend a Screening visit to determine eligibility for open label treatment with enzalutamide (160 mg/day). At Week 13, all subjects will be assessed by PSA and imaging. The initial PSA response (stable or declining) must be confirmed by a second consecutive value at least 3 weeks later. Subjects with no confirmed PSA response or evidence of radiographic progression (assessed at Week 13) will be ineligible for participation in Period 2 and will typically have safety follow up. Those subjects with confirmed PSA response will continue Period 1 until disease progression as supported by evidence of at least one of the following criteria:

- PSA progression with rapid PSA doubling time (PSA-DT) defined as:
  - PSA rise of ≥ 25% and an absolute increase of ≥ 2 ng/mL above nadir, confirmed by a second PSA value at least 3 weeks later, and
  - PSA-DT of ≤ 12 weeks determined in at least 3 PSA measurements collected at intervals of 4 or more weeks apart during a period of 3 or more months;
- Radiographic progression, defined as:
  - Bone disease progression, or;
  - Soft tissue disease progression.

Administration of open label enzalutamide will continue until randomization to Period 2 treatment, confirmation of ineligibility for Period 2 treatment (subjects will be discontinued from the study), intolerable toxicity, subject withdrawal, or death, whichever occurs first.

Subjects with confirmed disease progression on enzalutamide alone who continue to meet all eligibility criteria may proceed to randomization. Randomization must occur within 4 weeks of progression observed in Period 1.

Treatment allocation will be in a 1:1 ratio, stratified by disease progression (evidence of radiographic progression or not) in Period 1 to the following treatments:

- Enzalutamide (160 mg daily) in combination with docetaxel (75 mg/m^2 every 3 weeks) and prednisolone (10 mg daily);
- Enzalutamide placebo (daily) in combination with docetaxel (75 mg/m^2 every 3 weeks) and prednisolone (10 mg daily).

Administration of docetaxel will continue for up to 10 cycles, however subjects assessed by the Investigator to be benefiting from treatment may continue on docetaxel for additional cycles. Subjects who discontinue docetaxel before completion of 10 cycles (e.g., for toxicity) may continue treatment with Investigational Medicinal Product (IMP) and will continue to attend study visits (at 12 weekly intervals) for assessments until IMP discontinuation criteria or endpoint criteria are met.

Administration of blinded enzalutamide/placebo will continue until disease progression, intolerable toxicity, subject withdrawal or death, whichever occurs first.

All subjects will have a safety follow-up visit 30 days after the last dose of IMP or prior to the initiation of a subsequent antineoplastic therapy for prostate cancer, whichever occurs first.

In Period 2, subjects who discontinue IMP for a reason other than disease progression will continue to attend study visits (at 12 weekly intervals) for assessments until withdrawal of consent, disease progression or death.

Two extension periods may be available in the study:

- Extension period 1: For those subjects who are still receiving study drug in Period 1 when enrollment to Period 2 closes (approximately 274 subjects randomized in Period 2).
- Extension period 2: When the data cut-off for analysis is reached in Period 2 (when at least 182 endpoint events have been reached), for patients still in the study who did not not reach primary endpoint, there will be the opportunity to continue their treatment in an extension period in another Astellas-sponsored study (see CTP section 4.5.3).

3.3 Randomization

Subjects who meet the inclusion/exclusion criteria will be randomly assigned to receive enzalutamide or placebo using a 1:1 randomization schedule. Subjects will be stratified by disease progression (evidence of radiographic progression or not). The sponsor or designee will generate the randomization schedule.

The Investigator or designee will contact the Interactive Response Technology (IRT) to randomize the subject into the study prior to the initiation of IMP in Period 2.

4. SAMPLE SIZE

The following assumptions were used to determine the sample size calculation for the primary endpoint of PFS at the timepoint of the primary analysis:

- The estimated median PFS is 6 months for the control group (placebo plus docetaxel and prednisolone).
- Assuming the true treatment effect has a hazard ratio (HR) of 0.66, with 2-sided type 1 error rate of 0.05 and 80% power, 182 progression events are needed. This will allow statistical significance be claimed at the conclusion of the study if the observed HR is <=0.75, approximately.
- If the recruitment period is up to 18 months, the follow-up of subjects in Period 2 is approximately 6 months, and the recruitment rate is non-uniform, at least 274 subjects will need to be randomized.

Allowing for attrition prior to randomization, it is estimated that approximately 650 subjects will be enrolled. During the study, discontinuation rate, PSA response and disease progression rates will be monitored and if necessary, the total number of subjects enrolled may be adjusted to reach the required number of events at the end of Period 2 (182 events).

5. ANALYSIS SETS

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

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

5.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all subjects who are randomized and receive at least one dose of IMP.

The selection of subjects for the FAS will be confirmed in the Analysis Set Classification Meeting (ASCM), held prior to unblinding.

This will be the primary analysis set for efficacy analyses. Demographics and all baseline characteristics except non-prostate cancer medical history will also be presented in the FAS.

Subjects in the FAS will be presented by the treatment they were randomized, even if the actual treatment received was different from the treatment to which they were randomized.

Note that FAS will be equal to SAF2 if all subjects take in fact the same medication they were randomized to.

5.2 Safety Analysis Set (SAF)

Two sets of Safety Analysis Set (SAF) will be defined for this study.

5.2.1 Safety Analysis Set 1 (SAF1)

SAF1 consists of all subjects who took at least one dose of IMP during Period 1.

SAF1 will be used for previous medications, ECOG performance status and health resources use in Period 1 and all safety data in Period 1.

5.2.2 Safety Analysis Set 2 (SAF2)

SAF2 consists of all subjects who took at least one dose of IMP during Period 2.

SAF2 will be used for demographic and baseline characteristics, CMs, ECOG performance status and health resources use in Period 2 and all safety data in Period 2.

Subjects in the SAF2 will be presented by the treatment they actually received, even if the actual treatment received was different from the treatment to which they were randomized.

If the subject, at any moment during Period 2, accidently received the wrong treatment, then the subject will be analyzed as if they received enzalutamide as at least one of the actual treatments given was enzalutamide.

Note that SAF2 will be equal to FAS if all subjects take in fact the same medication they were randomized to.

6. ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS with progression defined as radiographic progression, unequivocal clinical progression, or death on study.

- Radiographic disease progression is defined for bone disease by the appearance of 2 or more new lesions on whole-body radionuclide bone scan per Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria (i.e., unconfirmed progressive disease) that needs to be confirmed in the next assessment (i.e., progressive disease in the next assessment) or for soft tissue disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

  Note: For disease progression in bone disease, when a subject has unconfirmed progression with confirmed progression disease in the next assessment, the date of unconfirmed progression will be used for the analysis.
- Unequivocal clinical progression is defined as any of the following:
  - new onset cancer pain requiring chronic administration of opiate analgesia,
  - deterioration from prostate cancer of Eastern Cooperative Oncology Group (ECOG) performance status score to 3 or higher, within the investigational period
  - initiation of subsequent lines of cytotoxic chemotherapy or radiation therapy or surgical intervention due to complications of tumor progression.
- Death on study is defined as death within 112 days of treatment discontinuation without objective evidence of radiographic progression.

PFS is defined as the time (in months) from randomization (Period 2 Week 1) to the earliest progression event. Subjects who do not show progression as defined above at the data analysis cutoff date will be censored on the date of the last assessment of disease progression before data analysis cutoff date , and subjects discontinuing for any reason before data analysis cutoff date and without progression will be censored at the last assessment of disease progression before discontinuation. The data analysis cutoff date will take place after the disease progression date that corresponds to the 182nd disease progression event.

PFS = ((‘Date progression event or censored date’ - ‘Date randomization’) + 1) / 30.4375.

More detailed information on derivation of the primary endpoint can be found in Appendix 7 of this SAP.

6.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Time to PSA progression.

- PSA response.
- Objective response rate.
- Time to pain progression.
- Time to opiate use for cancer-related pain.
- Time to first SRE.

6.1.2.1 Time to PSA Progression

Time to PSA progression is defined as the time (in months) from randomization (Period 2 Week 1) to the date of the first PSA value in Period 2 demonstrating progression.

The PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir recorded in Period 2 is documented, which must be confirmed by a second consecutive value obtained at least 3 weeks later. The date of PSA progression is the date the first evidence of PSA progression is documented.

Subjects who do not show PSA progression at the data analysis cutoff date (see Section 6.1.1 for details) will be censored on the date of the last assessment of PSA before data analysis cutoff date . Subjects without PSA progression prior to 2 or more consecutive missed PSA assessments will be censored on the date of last PSA assessment prior to missed assessments without PSA progression. Subjects who have no PSA at baseline (last available non-missing value, usually Period 2 Week 1) or have the PSA at baseline only will be censored on the date of randomization. And subjects discontinuing for any reason before data analysis cutoff date and without PSA progression will be censored at the last assessment of PSA before discontinuation.

Time to PSA Progression = ((‘Date PSA progression or censored date’ - ‘Date randomization’) + 1) / 30.4375.

6.1.2.2 PSA Response

Percentage change in PSA levels from randomization (Period 2 Week 1) to Week 13 (or earlier for those that discontinue therapy), as well as the maximum decrease in percentage change from randomization in PSA levels that occur at any point after randomization in Period 2 will be derived.

Percentage change from Period 2 Week 1 to Week 13 of PSA levels will be calculated as:

Percentage change from Period 2 Week 1 = [(Week 13 PSA value – Randomization PSA value) / Randomization PSA value] x 100.

PSA response is defined as a decrease in percentage change from randomization of 50% or more. PSA response will be derived at Week 13 and at any time after randomization in Period 2.

6.1.2.3 Objective Response Rate

Objective response rate is defined as the best overall radiographic response after randomization as per Investigator assessments of response for soft tissue disease per RECIST 1.1, in subjects who have a measurable tumor.

6.1.2.4 Time to Pain Progression

Time to pain progression is defined as the time (in months) to an increase of ≥ 30% from randomization (Period 2 Week 1) in the average of Brief Pain Inventory Short Form (BPI-SF) pain intensity item scores (items 3, 4, 5 and 6) observed at 2 consecutive evaluations ≥3 weeks apart without decrease in analgesic usage score according to the World Health Organization (WHO) scale (0 for no medication, 1 for non-opioid pain medication, 2 for opioids for moderate pain, and 3 for opioids for severe pain). Only subjects experiencing average pain intensity item scores (items 3, 4, 5 and 6) of ≥4 at the time of progression will be included in the calculation.

Subjects who do not show pain progression at the data analysis cutoff date (see Section 6.1.1 for details) will be censored on the date of the last assessment of BPI-SF before data analysis cutoff date , and subjects discontinuing for any reason before data analysis cutoff date and without pain progression will be censored at the last assessment of BPI-SF before discontinuation.

Time to Pain Progression = ((‘Date pain progression or censored date’ - ‘Date randomization’) + 1) / 30.4375.

The BPI-SF is an instrument to document pain-related functional impairment. It will be completed by the subjects at Screening in Period 1 and then at every scheduled visit during Period 2. The BPI used in this study is modified from the short form (BPI-SF) and contains 7 questions (questions 2 and 7 from the standard BPI-SF will not be collected). It is a questionnaire that includes:

- Pain intensity (items 3, 4, 5 and 6): worst pain, least pain, average pain and current pain, with scales from 0 (no pain) to 10 (pain as bad as you can imagine)
- Pain interference (items 9A to 9G): general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life, with scales from 0 (does not interfere) to 10 (completely interferes).

The BPI-SF total score for pain intensity will be calculated as the mean of the 4 scores for the 4 items of pain intensity, if any individual item is not completed the mean cannot be calculated.

The BPI-SF total score for pain interference will be calculated as the mean of the 7 scores of pain interference questions, if less than 50% of the items (i.e., 3 or less items out of 7) are not completed the mean cannot be calculated.

Change from baseline, defined as the post-baseline value minus the baseline value (last non missing value prior to first dosing in the analysis period) will be calculated for each assessment.

6.1.3 Time to opiate use for cancer-related pain

Time to opiate use for cancer-related pain is defined as the time (in months) from randomization (Period 2 Week 1) to initiation of chronic administration of opiate analgesia, defined as parenteral opiate use for ≥7 days or use of WHO Analgesic Ladder Level 3 oral opiates (strong opioids [e.g., buprenorphine, diamorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, pethidine, tramadol]) for ≥3 weeks.

Subjects who do not initiate chronic administration of opiate analgesia at the data analysis cutoff date (see Section 6.1.1 for details) will be censored on the date of the last assessment done before data analysis cutoff date , and subjects discontinuing for any reason before data analysis cutoff date and without initiating chronic administration of opiate analgesia will be censored at their last assessment in study before discontinuation.

Time to Opiate Use for Cancer-Related Pain = ((‘Date event or censored date’ - ‘Date randomization’) + 1) / 30.4375.

6.1.4 Time to First Skeletal Related Event

Time to first SRE is defined as the time from randomization (Period 2 Week 1) to radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.

Subjects who do not have any skeletal related event at the data analysis cutoff date (see Section 6.1.1 for details) will be censored on the date of the last assessment done before data analysis cutoff date , and subjects discontinuing for any reason before data analysis cutoff date and without having any skeletal related event will be censored at the last assessment in study before discontinuation.

Time to First SRE = ((‘Date event or censored date’ - ‘Date randomization’) + 1) / 30.4375.

6.1.5 Exploratory Endpoints

Biomarker from EPIC laboratory will be summarized using descriptive statistics.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs).
- Clinical laboratory variables (hematology and biochemistry including liver enzymes and total bilirubin).
- Vital signs (systolic and diastolic blood pressure, pulse rate and temperature).
- Weight.
- 12-lead electrocardiogram (ECG)

6.2.1 Adverse Events

The coding dictionary for adverse events (AEs) will be the Medical Dictionary for Regulatory Activities (MedDRA). Version number of MedDRA will be provided in the TLFs specifications document.

Pre-treatment AEs

AEs which started or worsened during the pre-investigational period (i.e., during the period from obtaining informed consent to the start of Period 1).

Period 1 TEAEs

TEAEs which started or worsened during Period 1 (i.e., during the period from first enzalutamide intake during the Period 1 and before first intake of randomized study medication in Period 2). If a subject experiences an event both during the pre-investigational period and during Period 1, the event will be considered as TEAE only if it has changed in NCI CTCAE Grade or seriousness after the first dose of enzalutamide (i.e. it is reported with a new start date).

Period 2 TEAEs

TEAEs which started or worsened during Period 2 (i.e., from first dose of randomized study medication in Period 2), and until the Follow-up Visit. If a subject experiences an event both during Period 1 and during Period 2, the event will be considered as Period 2 TEAE only if it has changed in NCI CTCAE Grade or seriousness after the first dose of IMP in Period 2 (i.e., it is reported with a new start date).

The following counting rules for AEs are used:

- A subject having experienced the same event more than once will be counted only once in the number of subjects with AEs within a system organ class or preferred term.
- When the table counts AEs only by NCI CTCAE Grade, then only the highest NCI CTCAE Grade will be counted for each event within a system organ class or preferred term.

A treatment related AE is defined as any AE whose relationship to IMP is assessed as "possible" or "probable" by the investigator, or where the relationship to IMP is missing.

See Section 7.11.1.1 of this document for imputation rules regarding missing/incomplete AE start and end dates.

6.2.2 Safety Laboratory Tests

Blood samples for hematology and biochemistry will be collected at each visit of the study as depicted in the schedule of assessments (Table 1 and Table 2). All evaluations will be done by a central laboratory.

The following variables will be derived for laboratory tests:

- Change from baseline, defined as the post-baseline value minus the baseline value (last non-missing value prior to first dose in the analysis period).

- Classification of results according to the National Cancer Institute-Common Toxicity Criteria Adverse Events (NCI-CTCAE) v4.03, and worst post-baseline toxicity grade by Period.

6.2.2.1 Liver Enzymes and Total Bilirubin

Liver tests (Alanine Aminotransferase [ALT], Aspartate Aminotransferase [AST], total bilirubin [TBL] and Alkaline Phosphatase [ALP]) will be assessed at each visit of the study. The following levels will be defined, as flags on a subject level, during the treatment period, based on the maximum on-treatment (for Period 1 and for Period 2 separately) value, according to the Upper Limit of Normal (ULN):

- ALT > 3X ULN, > 5X ULN, > 8X ULN
- AST > 3X ULN, > 5X ULN, > 8X ULN
- AST or ALT > 3X ULN > 5X ULN
- TBL > 2X ULN
- ALP > 1.5X ULN
- ALT or AST > 3X ULN or TBL > 2X ULN
- ALT or AST > 5X ULN or TBL > 2X ULN
- ALT or AST > 3X ULN and TBL > 2X ULN
- ALT or AST > 3 × ULN and INR > 1.5

For the ALT and/or AST > 3X ULN and TBL > 2X ULN criteria, the subject's ALT and/or AST and the TBL values must be measured within the same sample to be counted.

The maximum on-treatment value is defined as the maximum value of all post-baseline assessments for each period.

Note that the above levels are meant to facilitate the review and reporting and do not fully correspond to the protocol defined criteria for liver abnormalities that would define subjects who require further liver investigation:

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 x ULN (in patients without liver metastases), > 5 x ULN (in patients with liver metastases)	or	> 2 x ULN
Severe*	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases)
- ALT or AST > 3 × ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The Investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

6.2.3 Vital Signs

Vital signs including blood pressure (systolic and diastolic), pulse rate and temperature will be measured at all visits of the study.

Change from baseline, defined as the post-baseline value minus the baseline value (last non-missing value prior to first dose in the analysis period) will be calculated for each assessment.

Systolic and diastolic blood pressure values will be classified according to NCI-CTCAE v4.03 hypertension grading scores at each visit.

6.2.4 Weight

Weight will be measured at all visits in the study as indicated on the schedule of assessment (Table 1 and Table 2).

Change from baseline, defined as the post-baseline value minus the baseline value (last non-missing value prior to first dose in the analysis period) will be calculated for each assessment.

6.2.5 Electrocardiogram

A 12-lead ECG will be performed at Screening in Period 1, at the Eligibility Assessment for Period 2 and then every 12 weeks during Period 2 from Week 13 as indicated on the schedule of assessments (Table 1 and Table 2).

The interpretation of the ECGs will be recorded as normal, abnormal not clinically significant, or abnormal clinically significant. Any abnormal clinically significant results will be reported in electronic Case Report Form (eCRF) as AE.

Parameters that include heart rate, PR interval, RR interval, QRS interval, QT interval will also be collected on the eCRF.

Parameters QTcB, using Bazett's correction formula:

$$QTcB=QT/(RR \text{ in seconds})^{1/2}$$

And QTcF, using Fridericia correction formula:

$$QTcF=QT/(RR \text{ in seconds})^{1/3}$$

Will be calculated for each subject and assessment.

Change from baseline for ECG parameters, defined as the post-baseline value minus the baseline value last non-missing value prior to first dose in the analysis period) will be calculated for each assessment.

6.3 Other Variables

6.3.1 Demographics and Baseline Characteristics

The subject's age, gender, race, height, body weight and Body Mass Index (BMI), calculated as:

$$BMI\ (kg/m^2) = weight\ (kg) / (height\ (m) \times height\ (m))$$

will be recorded at Screening.

At the Screening visit a detailed non-prostate cancer medical history for each subject will be obtained. All relevant past and present conditions, as well as any relevant prior surgical procedures, will be recorded for the main body systems documenting diagnoses and durations of the diseases.

With regards to disease history and previous prostate cancer therapies the following variables will be recorded or derived:

- Time since initial diagnosis, defined as time (in years) since initial diagnosis of prostate cancer until date of informed consent
- Gleason score at diagnosis, which will be categorized as low (2-4), medium (5-7) and high (8-10), and also as low/medium (<8) and high (≥8).
- Localization of disease (bone, soft tissue, both)
- Target/non-target soft tissue disease
- Distribution of metastatic disease (bone, lymph, visceral [split to lung, liver, both], other)
- Time since diagnosis of metastases, defined as time (in months) since diagnosis of metastases until date of informed consent
- Diagnostic test confirming metastases
- For subjects with nodal disease, time since confirmed nodal disease, defined as time (in days) since confirmed nodal disease until date of informed consent
- Luteinizing Hormone-Releasing Hormone (LHRH) agonist/antagonist initiation or bilateral orchiectomy relative to diagnosis of metastasis (before or after diagnosis of metastasis)
- Localization of metastases
- Number of bone metastases categorized as 0, 1, 2-4, 5-9, 10-20
- Previous radiation therapy (yes, no) and area irradiated
- Previous surgeries or procedures (yes, no) and type of procedure
- Number of previous prostate cancer therapies categorized as 0, 1, 2, 3 and ≥4
- Number of unique previous hormonal therapies (see appendix 1) categorized as 0, 1, 2, 3 and ≥4
- Previous anti-androgen (see appendix 2) use (yes, no) and number of previous anti-androgen therapies categorized as 0, 1, 2, 3 and ≥4
- Previous bisphosphonate (see appendix 3) use (yes, no)
- Results of chest x-ray and chest CT scan

See Section 7.11.1 of this document for imputation rules regarding missing/incomplete diagnosis dates.

6.3.2 Duration of exposure

The length of time on treatment for both Period 1 and Period 2 will be calculated in weeks, using the following formula:

Duration of exposure= ((‘Date last dose of IMP during the period’ - ‘Date first dose during the period’) + 1) / 30.4375

Dose reductions and dose interruptions of enzalutamide/placebo will be counted and categorized as 0, 1, 2 and >2 in each Period (for Period 1 only enzalutamide).

The number of cycles received of docetaxel will also be counted.

6.3.3 Cumulative dose of Docetaxel

Cumulative dose of docetaxel (mg/m²) per subject will be calculated as the sum of the total doses that the subject received during the study.

6.3.4 Previous and Concomitant Medications

Previous medications and CMs will be coded with World Health Organization Drug Dictionary (WHO-DD).

Previous Medications

Previous medications are defined as medications for which a subject took at least one dose during the pre-investigational period (i.e., during the period from obtaining informed consent to the start of Period 1).

Period 1 CMs

Period 1 CMs are defined as medications for which a subject took at least one dose during Period 1 (i.e., during the period from first enzalutamide intake during the Period 1 and before first intake of randomized study medication in Period 2).

Period 2 CMs

Period 2 CMs are defined as medications for which a subject took at least one dose during Period 2 (i.e., from first dose of randomized study medication in Period 2), and until the Follow-up Visit.

See Section 7.11.1 of this document for imputation rules regarding missing/incomplete previous and concomitant medication dates.

6.3.5 Treatment Compliance

Treatment compliance of enzalutamide for Period 1 and enzalutamide/placebo for Period 2 will be calculated separately for subjects for whom total number of capsules taken and the complete date of the first dose and last dose are known. Subjects are to take 4 capsules once daily in both periods. Percentage compliance is defined as the total number of capsules taken divided by the total number of capsules that should have been taken:

[Total number of capsules consumed in Period x]

$$\frac{\text{total number of capsules consumed}}{[(\text{'Date last dose of IMP in Period x'} - \text{'Date first dose in Period x'}) + 1] \times 4} \times 100$$

where, total number of capsules consumed will be calculated as:
(total number of capsules dispensed) – (total number of capsules returned).

Missing data will not be imputed so missing dispensed/returned information will lead to missing compliance calculations to avoid incorrect results.

Compliance will only be calculated for the main study part, treatment extension will be excluded from the compliance calculations.

6.3.6 Performance Status

The ECOG scale will be used to assess performance status at all visits in the study.

Table 3 ECOG Grades

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

Baseline score for each period is defined as last non-missing value prior to first dose in the analysis period

Post-baseline ECOG scores will be classified as follows according to baseline score in each Period:

- Better or same score as baseline, defined as a post-baseline score lower or equal than baseline score.
- Worse than baseline, defined as a post-baseline score higher than baseline score.
- Another classification of post-baseline ECOG scores will be:
- Better than baseline, defined as a post-baseline score lower than baseline score.
- Same as baseline, defined as a post-baseline score equal to baseline score.
- Worse than baseline, defined as a post-baseline score higher than baseline score.

6.3.7 Functional Assessment of Cancer Therapy - Prostate

The FACT-P quality of life questionnaire is a multi-dimensional, self-reported quality of life instrument specifically designed for use with prostate cancer patients. It consists of 27 core items which assess patient function in four domains: physical, social/family, emotional, and functional well-being, which is further supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale (0=Not at all, 1=A little bit, 2=Some-what, 3=Quite a bit, 4=Very much), and then combined to produce subscale scores for each domain, as well as a global quality of life score with higher scores representing better quality of life.

Table 4 Functional Assessment of Cancer Therapy – Prostate Scoring

Domain	Item Codes	Score Calculation	Score Range
Physical Well-Being (PWB)	GP1, GP2, GP3, GP4, GP5, GP6, GP7	[((4-GP1) + (4-GP2) + (4-GP3) + (4-GP4) + (4-GP5) + (4-GP6) + (4-GP7)) * 7] / [No. items answered]	0-28
Social/Family Well-Being (SWB)	GS1, GS2, GS3, GS4, GS5, GS6, GS7	[(GS1 + GS2 + GS3) + GS4 + GS5 + GS6 + GS7) * 7] / [No. items answered]	0-28
Emotional Well-Being (EWB)	GE1, GE2, GE3, GE4, GE5, GE6	[((4-GE1) + GE2 + (4-GE3) + (4-GE4) + (4-GE5) + (4-GE6)) * 6] / [No. items answered]	0-24
Functional Well-Being (FWB)	GF1, GF2, GF3, GF4, GF5, GF6, GF7	[(GF1 + GF2 + GF3 + GF4 + GF5 + GF6 + GF7) * 7] / [No. items answered]	0-28
Prostate Cancer Subscale (PCS)	C2, C6, P1, P2, P3, P4, P5, P6, P7, BL2, P8, BL5	[((4-C2) + C6 + (4-P1) + (4-P2) + (4-P3) + P4 + P5 + (4-P6) + (4-P7) + (4-BL2) + (4-P8) + BL5) * 12] / [No. items answered]	0-48
Global Score	PWB, SWB, EWB, FWB, PCS	PWB + SWB + EWB + FWB + PCS	0-156

Subjects will be asked to complete a FACT-P survey at Screening in Period 1 and then every 12 weeks during Period 2 from Week 1.

Change from baseline, defined as the post-baseline value minus the baseline value (last non-missing value prior to first dose in the analysis period) will be calculated for each assessment.

Post-baseline domain scores and global score will be classified as follows according to baseline scores in each Period:

- Better or same score as baseline, defined as a post-baseline score higher or equal than baseline score.
- Worse than baseline, defined as a post-baseline score lower than baseline score.
- Another classification of post-baseline domain scores and global score will be:

- Better than baseline, defined as a post-baseline score higher than baseline score.
- Same as baseline, defined as a post-baseline score equal to baseline score.
- Worse than baseline, defined as a post-baseline score lower than baseline score.

Time to degradation of FACT-P will also be calculated as time (in months) from randomization (Period 2 Week 1) to the date of post-randomization degradation.

Degradation of FACT-P for the global score is defined as at least a 10-point decrease from randomization for the global score. Degradation of FACT-P for the subscales is defined as at least a 3-point decrease from randomization for each subscale.

Subjects who do not show degradation of FACT-P at the data analysis cutoff date (see Section 6.1.1 for details) will be censored on the date of the last assessment of FACT-P before data analysis cutoff date, and subjects discontinuing for any reason before data analysis cutoff date and without degradation of FACT-P will be censored at the last assessment of FACT-P before discontinuation.

6.3.8 EuroQol 5-Dimensions 5-Levels

Quality of life is also to be assessed using the EQ-5D-5L questionnaire at Screening in Period 1 and then every 12 weeks during Period 2 from Week 1. This is an international and standardized non-disease specific (i.e., generic) instrument for describing and valuing health status.

This questionnaire consists of two parts:

- 5-dimensions (EQ-5D-5L): mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
- Visual Analog Scale (VAS) where 0 represents the worst imaginable health state and 100 the best imaginable health state.

Change from baseline for the VAS score, defined as the post-baseline value minus the baseline value (last non-missing value prior to first dose in the analysis period) will be calculated for each assessment.

6.3.9 Health Resource Use

Health resource use, including:

- Visits to general practitioner/family doctor, hospital doctor, practice/district nurse and hospital nurse,
- Length of hospital stay (in days) for routine admission or for unscheduled/emergency room, if applicable,
- Reason for admission to hospital, if applicable.

will be assessed at the Period 1 Screening Visit and then every 12 weeks, and every 12 weeks during Period 2 from Week 1.

7. STATISTICAL METHODOLOGY

7.1 General Considerations

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

Summaries based on FAS will be presented by planned treatment group, unless specifically stated otherwise. Safety analysis and other summaries based on SAF will be presented by actual treatment received.

All tables based on SAF2 and FAS will be presented by treatment group, strata (evidence of radiographic progression or not [PSA progression]) and overall unless specifically stated otherwise.

All statistical comparisons will be made using two sided tests at the α=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference, all alternative hypotheses will be two-sided, unless specifically stated otherwise.

The primary analysis (with data cut-off after at least 182 events) should be considered as the main analysis for this trial and will contain all the outputs as defined in the TLF Specs document.

At the time of database lock, both safety and primary efficacy TLFs will be rerun on the complete data up to the extension period. This analysis is to be viewed as descriptive in nature.

Separate listings will be provided to report key safety information on the extension period using the safety population (all subjects treated)

No separate baseline will be calculated for the extension period so the baseline for extension period 1 and extension period 2 will be period 1 and period 2 baseline respectively

All data listings will be sorted by centre, treatment group and visit time point (where applicable).

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

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be presented:

- For all subjects with informed consent, subjects who discontinued before Period 1 (screen failures), subjects who received Enzalutamide in Period 1, subjects who discontinued before Period 2 and subjects randomized;

- Number and percentage of subjects that completed, discontinued, and the reason for discontinuation of treatment for all subjects who entered Period 1, overall, during Period1 and for all randomized subjects, by treatment group and overall, during Period 2;
- Number and percentage of subjects in each analysis set for all subjects who entered Period 1, overall, for Period 1 and for all randomized subjects, by treatment group and overall for Period 2;

Data collected or derived for informed consent, inclusion/exclusion criteria not met, completion and discontinuation dates, and reasons for discontinuation and/or exclusion from analysis sets will be listed.

7.2.2 Protocol Deviations

Protocol deviations will be assessed for all randomized subjects. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by treatment group, strata and total as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

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

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

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

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics.

Number and percentage of subjects randomized in each country and site will be presented by treatment group, strata and overall for all randomized subjects.

Descriptive statistics for age, weight, BMI and height at study entry and frequency tabulations for gender and race will be presented by treatment group and strata, and overall for SAF2 and FAS.

Disease history variables described in Section 6.3.1 of this document, will also be presented by treatment group and stratum, and overall for SAF2 and FAS.

Additionally the following variables will also be presented in the same way:

- Baseline ECOG performance status
- Baseline pain intensity total score from the BPI-SF
- Baseline (Period 1 Week 1, or Screening if missing) haemoglobin value
- Baseline (Period 1 Week 1, or Screening if missing) alkaline phosphatase value
- Baseline (Period 1 Week 1, or Screening if missing) lactate dehydrogenase (LDH) value

- Baseline (Period 1 Week 1, or Screening if missing) serum albumin
- Baseline (Period 1 Week 1, or Screening if missing) serum PSA
- Baseline (Period 1 Week 1, or Screening if missing) creatinine value
- Baseline (Period 1 Week 1, or Screening if missing) neutrophil:lymphocyte ratio value
- Baseline (Screening) testosterone value
- History of prior cardiovascular disease(*) (yes, no)
- Baseline (at Period 1 Week 1) use of corticosteroids (see Appendix 4) (yes, no)
- Baseline (at Period 1 Week 1) use of anticoagulants (see Appendix 5) (yes, no)

(*) History of cardiovascular diseases can be identified by selecting the SOC terms "vascular disorders" and "cardiac disorders".

All demographics and baseline characteristics data will be listed.

Non-prostate cancer medical history is coded using MedDRA. The number and percent of subjects by System Organ Class (SOC) and PT will be summarized by treatment group and stratum, and overall for the SAF2.

Subjects will only be counted once per MedDRA level. Medical History will be sorted by decreasing incidence of the overall treatment group by SOC and within that by PT. Medical history will also be listed by SOC and PT.

7.2.4 Previous and Concomitant Medications

For both prostate cancer drug therapies and non-prostate cancer drug therapies, the number and percentage of subjects within therapeutic subgroup (Anatomical Therapeutic Chemical (ATC) level 2) and chemical subgroup (ATC level 4) will be presented for all the medications summaries overall for Period 1 and by treatment group, stratum and overall for Period 2.

Subjects will only be counted once per ATC level. Previous prostate cancer and non-prostate cancer medications and CMs will be sorted by decreasing incidence of the overall treatment group by ATC level 2 and within that by ATC level 4.

A summary will be produced for the following:

- Previous medications (SAF1)
- Previous prostate cancer drug therapies (SAF1)
- CMs in Period 1 (SAF1)
- CMs in Period 2 (SAF2)
- Concomitant prostate cancer drug therapies in Period 1 (SAF1)
- Concomitant prostate cancer drug therapies in Period 2 (SAF2)

Subjects taking the same medication multiple times will be counted once per medication and period.

All medications data will be provided in a listing. Listings will only contain data for subjects who reported taking medication.

Non-medication treatment will also be listed.

7.3 Study Drugs

7.3.1 Exposure

Duration of exposure will be summarized by Period in two ways.

- Descriptive statistics will be presented overall in Period 1 and by treatment group, strata and overall in Period 2.
- For Period 1 exposure time will be categorized according to the following categories:
  - ≤6 weeks (42 days)
  - >6 weeks (42days), and ≤12 weeks (84 days)
  - >12 weeks (84 days), and ≤24 weeks (168 days)
  - >24 weeks (168 days), and ≤48 weeks (336 days)
  - >48 weeks (336 days), and ≤96 weeks (672 days)
  - >96 weeks (672 days), and ≤192 weeks (1344 days)
  - >192 weeks (1344 days)
- For Period 2 exposure time will be categorized according to the following categories by treatment group, strata and overall:
  - ≤6 weeks (42 days)
  - >6 weeks (42 days), and ≤12 weeks (84 days)
  - >12 weeks (84 days), and ≤18 weeks (126 days)
  - >18 weeks (126 days), and ≤24 weeks (168 days)
  - >24 weeks (168 days), and ≤30 weeks (210 days)
  - >30 weeks (210 days), and ≤36 weeks (252 days)
  - >36 weeks (252 days), and ≤42 weeks (294 days)
  - >42 weeks (294 days), and ≤48 weeks (336 days)
  - >48 weeks (336 days), and ≤54 weeks (378 days)
  - >54 weeks (378 days), and ≤60 weeks (420 days)
  - >60 weeks (420 days)

Counts and percentages of subjects in each of these categories will be summarized for each treatment group for the SAF1 in Period 1 and for the SAF2 in Period 2.

Descriptive statistics will be presented for cumulative dose of docetaxel by treatment group, strata and overall for the SAF2.

All exposure data will be provided in a listing.

7.3.2 Treatment Compliance

Compliance with IMP will be summarized overall in Period 1 for SAF1 and by treatment group, strata and overall in Period 2 for SAF2. Refer to Section 6.3.5 for definition of treatment compliance.

Percentage compliance by treatment period will be summarized in two ways:

- Descriptive statistics.
- Number and percentage of subjects within the following categories:
  - <80%

- ≥80% to 100%
- ≥100%
- Unknown (not enough data to calculate compliance)

All compliance data will be listed.

7.4 Analysis of Efficacy

All efficacy data will be presented using descriptive statistics and will be summarized in tabular and/or graphical form.

All efficacy data will be included in listings.

7.4.1 Analysis of Primary Endpoint

The primary efficacy endpoint is PFS, with progression defined as radiographic progression, unequivocal clinical progression, or death on study.

7.4.1.1 Primary Analysis of Primary Endpoint

The survival functions in both treatment groups will be estimated using the Kaplan-Meier method and displayed graphically. Median (50^{th} percentile) with its corresponding 95% CI, together with the number of subjects with and without progression, will be summarized by treatment group and strata for FAS. The comparison of the survival curves of the two treatment groups will be done using a stratified log-rank test, stratified by disease progression in Period 1 (evidence of radiographic progression or not), at the 0.05 2-sided significance level (based on 182 events).

The following SAS code may be used:

```
PROC LIFETEST data=dataset;
   STRATA progression_P1 / GROUP=treatment;
   TIME time*censor(1);
RUN;
```

where, *progression_P1* is disease progression in Period 1 (evidence of radiographic progression or not).

A Cox proportional hazards model will be performed with covariates for treatment and evidence of radiographic progression in Period 1. HR for treatment group, 95% profile likelihood confidence interval (CI) and the correspondent p-value will be shown.

The following SAS code may be used:

```
PROC PHREG data=dataset;
   CLASS treatment progression_P1;
   MODEL time*censor(1) = treatment progression_P1 / TIES=DISCRETE RL=PL;
RUN;
```

where, *progression_P1* is disease progression in Period 1 (evidence of radiographic progression or not).

Proportional hazards assumption will be tested by examining plots of complementary log(-log(survival)) versus log(time).

For doing this, the first line in the first PROC LIFETEST statement above may be changed by:

```
PROC LIFETEST data=dataset PLOT=(S,LLS);
```

If the proportional hazards assumption is not met the Cox model will not be applied and treatment effect will only be estimated using the median time to event in each treatment group.

7.4.1.2 Secondary Analysis of Primary Endpoint

A sensitivity analysis for PFS will be conducted using an unstratified log-rank test for the FAS.

The following SAS code may be used:

```
PROC LIFETEST data=dataset;
   STRATA treatment;
   TIME time*censor(1);
RUN;
```

As part of the sensitivity analysis a Cox proportional hazards model will be performed for the FAS with covariate for treatment only. HR for treatment group, 95% profile likelihood CI and the correspondent p-value will be shown. Proportional hazards assumption will also be tested firstly in the same way as explained in Section 7.4.1.1 but excluding variable disease progression in Period 1 from the model.

7.4.1.3 Subgroup Analysis of Primary Endpoint

Subgroup analyses for the primary endpoint will be performed using the FAS for the following factors:

- Disease progression in Period 1 (evidence of radiographic progression or not).
- ECOG performance status (0 or 1 or 2) at baseline
- Age category (<75 or ≥75 years) at eligibility assessment for Period 2 visit
- Total Gleason score (<8 and ≥8) at diagnosis
- Disease location (bone only versus soft tissue only versus both bone and soft tissue) at Screening
- Visceral disease (yes or no) at screening
- Baseline (Period 1 Week 1, or Screening if missing) serum PSA value (≤median, >median)
- Baseline (Period 1 Week 1, or Screening if missing) LDH value (≤median, >median)
- Baseline (Period 1 Week 1, or Screening if missing) hemoglobin value (≤median, >median)
- Baseline (Period 1 Week 1, or Screening if missing) ALP value (≤median, >median)
- Previous anti-androgen therapy (see) use (yes, no)
- Previous bisphosphonate (see) use (yes, no)

The same analysis as described in Section 7.4.1.1, excluding the stratification factor for the first subgroup defined above, will be performed in each subgroup category.

P-values resulting from inferential tests conducted in context of the subgroup analysis are of descriptive nature only and should be interpreted cautiously.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Time to PSA Progression

Time to PSA progression will be described and analyzed in the same way as the primary endpoint (see Section 7.4.1.1) for FAS.

7.4.2.2 PSA Response

Percentage change from baseline (see Section 6.1.2.2 for definition) of PSA levels will be summarized at Week 13 by treatment group and strata for FAS. Maximum decrease in percentage change from baseline will also by summarized by treatment group and strata for FAS.

PSA response (see Section 6.1.2.2 for definition) at Week 13 and at any time after randomization will also be summarized by treatment group and strata for FAS.

Percentage change from baseline to Week 13 and maximum decrease in percentage change from baseline will also be reported using waterfall plots for each treatment group.

7.4.2.3 Objective Response Rate

Rates of complete response (CR), partial response (PR), stable disease (SD), objective response (CR+PR), and CR+PR+SD will be tabulated along with exact binomial 95% confidence intervals (Clopper Pearson) by treatment group stratified by disease progression in Period 1 (evidence of radiographic progression or not) for FAS.

The following SAS code may be used:

```
PROC FREQ data=dataset;
   BY progression_P1 treatment;
   TABLE response / BINOMIAL;
RUN;
```

where, *progression_P1* is disease progression in Period 1 (evidence of radiographic progression or not).

The proportion of subjects with objective response will be compared between treatment groups using a Cochran-Mantel-Haenszel test stratified by disease progression in Period 1 (evidence of radiographic progression or not) for FAS.

The following SAS code may be used:

```
PROC FREQ data=dataset;
   TABLES progression_P1 * treatment * obj_response / CMH;
RUN;
```

where, *progression_P1* is disease progression in Period 1 (evidence of radiographic progression or not) and *obj_response* is objective response.

7.4.2.4 Time to Pain Progression

Time to pain progression will be described and analyzed in the same way as the primary endpoint (see Section 7.4.1.1) for FAS.

Total scores for pain intensity and pain interference will be summarized by treatment group, strata and visit, including change from baseline to each post baseline assessment for FAS.

7.4.3 Time to Opiate Use for Cancer-Related Pain

Time to opiate use for cancer-related pain will be described and analyzed in the same way as the primary endpoint (see Section 7.4.1.1) for FAS.

7.4.4 Time to First Skeletal Related Event

Time to first SRE will be described and analyzed in the same way as the primary endpoint (see Section 7.4.1.1) for FAS.

7.5 Analysis of Safety

All safety and tolerability data will be presented using descriptive statistics and will be listed and summarized in tabular and/or graphical form for SAF1 when referring to Period 1 and for SAF2 when referring to Period 2. No formal statistical testing will be performed on these data except otherwise specified.

7.5.1 Adverse Events

TEAEs will be summarized for Period 1 and Period 2 separately, overall and by treatment group, strata and overall respectively, by SOC and PT.

Overview summary tables will be provided for each Period with the following information:

- Number and percentage of subjects with AEs/TEAEs
- Number of TEAEs
- Number and percentage of subjects with drug-related TEAEs
- Number of drug-related TEAEs
- Number and percentage of subjects with docetaxel-related TEAEs (only for Period 2)
- Number of docetaxel-related TEAEs (only for Period 2)
- Number and percentage of deaths
- Number and percentage of subjects with serious TEAEs
- Number of serious TEAEs
- Number and percentage of subjects with drug-related serious TEAEs
- Number of drug-related serious TEAEs
- Number and percentage of subjects with docetaxel-related serious TEAEs (only for Period 2)
- Number of docetaxel-related serious TEAEs (only for Period 2)

- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug
- Number of TEAEs leading to permanent discontinuation of study drug
- Number and percentage of subjects with drug-related TEAEs leading to permanent discontinuation of study drug
- Number of drug-related TEAEs leading to permanent discontinuation of study drug
- Number and percentage of subjects with docetaxel-related TEAEs leading to permanent discontinuation of study drug (only for Period 2)
- Number of docetaxel-related TEAEs leading to permanent discontinuation of study drug (only for Period 2)

The following summaries of subjects with TEAE will be produced and presented overall for Period 1 by treatment group, strata and overall for Period 2:

- The number (percentage) of subjects with at least one TEAE, classified by SOC and PT, will be summarized; subjects will be counted only once within a PT or a SOC;
- The number (percentage) of subjects with at least one TEAE, classified by SOC and PT, will be summarized by NCI CTCAE Grade (V4.03); subjects will be counted only once with the worst (maximum) NCI CTCAE Grade within a PT or a SOC;
- The number (percentage) of subjects with at least one TEAE, excluding serious AEs, that equal to or exceed a threshold of 2% in either treatment group, classified by SOC and PT, will be summarized; subjects will be counted only once within a PT or a SOC;
- The number (percentage) of subjects with at least one TEAE considered to be treatment related (relationship type identified as possibly, probably or missing on the eCRF), classified by SOC and PT, will be summarized; subjects will be counted only once within a PT or a SOC;
- The number (percentage) of subjects with at least one TEAE considered to be docetaxel related (relationship type identified as possibly, probably or missing on the eCRF), classified by SOC and PT, will be summarized; subjects will be counted only once within a PT or a SOC;
- The number (percentage) of subjects with at least one TEAE considered to be treatment related (relationship type identified as possibly, probably or missing on the eCRF), classified by SOC and PT, will be summarized by NCI CTCAE Grade (V4.03); subjects will be counted only once for the worst (maximum) NCI CTCAE Grade within a PT or a SOC;
- The number (percentage) of subjects with at least one TEAE considered to be docetaxel related (relationship type identified as possibly, probably or missing on the eCRF), classified by SOC and PT, will be summarized by NCI CTCAE Grade (V4.03); subjects will be counted only once for the worst (maximum) NCI CTCAE Grade within a PT or a SOC;
- The number (percentage) of subjects with at least one serious TEAE, classified by SOC and PT, will be summarized; subjects will be counted only once within a PT or a SOC;
- The number (percentage) of subjects with at least one serious TEAE considered to be treatment related (relationship type identified as possibly, probably or missing on the

eCRF), classified by SOC and PT, will be summarized; subjects will be counted only once within a PT or a SOC;
- The number (percentage) of subjects with at least one serious TEAE considered to be docetaxel related (relationship type identified as possibly, probably or missing on the eCRF), classified by SOC and PT, will be summarized; subjects will be counted only once within a PT or a SOC;
- The number (percentage) of subjects with a TEAE leading to permanent discontinuation of study drug, classified by SOC and PT, will be summarized; subjects will be counted only once within a PT or a SOC;
- The number (percentage) of subjects with a TEAE leading to permanent discontinuation of study drug considered to be treatment related (relationship type identified as possibly, probably or missing on the eCRF), classified by SOC and PT, will be summarized; subjects will be counted only once within a PT or a SOC.
- The number (percentage) of subjects with a TEAE leading to permanent discontinuation of study drug considered to be docetaxel related (relationship type identified as possibly, probably or missing on the eCRF), classified by SOC and PT, will be summarized; subjects will be counted only once within a PT or a SOC.

Listings by treatment period will be provided for the following:

- All subjects experiencing an AE;
- All subjects experiencing a drug-related AE;
- All deaths;
- All subjects experiencing a serious AE;
- All subjects experiencing AEs leading to permanent discontinuation of study drug.

7.5.2 Clinical Laboratory Evaluation

Clinical laboratory test results (hematology and biochemistry) will be summarized for Period 1 and Period 2 separately, overall and by treatment group, strata and overall respectively, and will be presented in SI units.

Additionally, within-subject changes from baseline (see Section 6.2.2 for definition) will be calculated.

Each hematology and biochemistry result will be classified as grades 1 to 4 according to NCI-CTCAE at each visit. Number and percentage of subjects in each grade by laboratory test and visit, overall in Period 1 and treatment group, strata and overall in Period 2 will be shown. Shift tables of NCI CTC grade changes from baseline to each post-baseline assessment will be calculated for each Period by laboratory test, overall in Period 1 and treatment group, strata and overall in Period 2. Listings of all laboratory measurements, including flagging of abnormal value with high and low, will be made.

Clinically significant abnormal values will be reported as AEs.

7.5.2.1 Liver Enzymes and Total Bilirubin

For the groups defined in Section 6.2.2.1, the number and percent of subjects who meet the criteria at any time during Period 1 and during Period 2 will be summarized overall and by treatment group, strata and overall respectively.

The following listings will be included for subjects who require further liver investigation:

- Results of ALT, AST, TBL, ALP and International Normalized Ratio (INR)
- Study drug interruptions due to liver abnormalities
- Alcohol history and drug abuse
- Liver imaging
- Serology
- Investigator Comments on the liver abnormalities

7.5.3 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, temperature and pulse rate) will be summarized by visit for Period 1 and Period 2, overall and by treatment group, strata and overall respectively. Additionally, within-subject change from baseline (see Section 6.2.3 for definition) will also be summarized by visit in both periods.

Number and percentage of subjects in each hypertension grade according to NCI-CTCAE by visit, overall in Period 1 and treatment group, strata and overall in Period 2 will be shown.

7.5.4 Weight

Weight will be summarized by visit for Period 1 and Period 2, overall and by treatment group, strata and overall respectively. Additionally, within-subject change from baseline (see Section 6.2.4 for definition) will also be summarized by visit in both periods.

7.5.5 Electrocardiograms (ECGs)

ECG interpretation will be summarized by treatment group, strata and overall, and visit.

ECG variables (PR interval, RR interval, heart rate, QRS interval, QT interval, QTcF interval and QTcB interval) will be summarized for each treatment group, strata and overall at each visit and including changes from baseline to each visit.

All of the QTc analyses will be presented for both the Fridericia and Bazett correction methods.

7.6 Analysis of PK

Not applicable.

7.7 Analysis of PD

Not applicable.

7.8 Subgroups of Interest

Primary efficacy endpoint will be summarized by treatment group for the subgroup defined on the basis of the categorized variables listed below:

Grouping variable	Subgroups
Disease Progression in Period 1	Evidence of radiographic progression
	No evidence of radiographic progression (PSA progression)
ECOG performance status	0
	1
	2
Visceral disease	Yes
	No
Age category	<75 years
	≥75 years
Total Gleason score at diagnosis	≤7
	≥8
Disease location at Screening	Bone only
	Soft tissue only
	Bone and soft tissue
Baseline serum PSA value	≤median
	>median
Baseline LDH value	≤median
	>median
Baseline hemoglobin value	≤median
	>median
Baseline ALP value	≤median
	>median
Previous anti-androgen therapy use	Yes
	No
Previous bisphosphonate use	Yes
	No

For more details refer to Section 7.4.1.3.

7.9 Other Analyses

7.9.1 Performance Status

Number and percentage of subjects in each category of ECOG will be presented by visit, overall in Period 1 for the SAF1 and by treatment group, strata and visit in Period 2 for the FAS.

Number and percentage of subjects with better or equal score and worse score at each post-baseline assessment vs. baseline and number and percentage of subjects with better, equal and worse score at each post-baseline assessment vs. baseline in each Period will be presented, overall in Period 1 for the SAF1 and by treatment group and strata in Period 2 for the FAS.

7.9.2 Functional Assessment of Cancer Therapy - Prostate

Each of the 4 domain scores, the prostate cancer subscale and the global quality of life score will be summarized by treatment group, strata and overall, and visit for FAS, including change from baseline to each post baseline assessment.

For each domain score and global score, number and percentage of subjects with better or equal score and worse score at each post-baseline assessment vs. baseline and number and percentage of subjects with better, equal and worse score at each post-baseline assessment vs. baseline will be presented by treatment group, strata and overall for FAS.

Time to degradation of FACT-P for each domain and global score will be described and analyzed in the same way as the primary endpoint (see Section 7.4.1.1) for FAS.

7.9.3 EuroQol 5-Dimensions 5-Levels

Each of the 5 dimensions for EQ-5D-5L will be summarized by treatment group, strata and overall, and visit as categorical variables for FAS.

EQ-5D-5L VAS score will be summarized by treatment group, strata and overall, and visit, including change from baseline to each post baseline assessment for FAS.

7.9.4 Health Resource Use

Number of visits to general practitioner/family doctor, hospital doctor, practice/district nurse and hospital nurse for all subjects and length of hospital stay for a routine admission and for unscheduled/emergency room in subjects admitted to hospital will be summarized overall in Period 1 and by treatment group, strata and overall in Period 2.

Reason for admission to hospital in subjects admitted to hospital will be listed.

7.9.5 Impact of Covid 19 Pandemic

Following the Covid 19 pandemic, impact of Covid 19 on the trial conduct and results is reported according to Astellas guidelines with the inclusion of appropriate categories in existing outputs and addition of dedicated outputs to report the impact on both visit based and non-visit based assessments in the trial.

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

Not applicable.

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

All "time to" analysis will be right-censored based on one of the following conditions:

- Lost to follow-up since randomization;
- Not known to have the event at the data analysis cut-off;
- Death will also be a censoring condition for all events that do not include death.

7.11.1 Missing Data

7.11.1.1 Missing Adverse Event Dates

For AEs with incomplete or missing start or end date, a worst-case scenario will be used to determine treatment emergence of this adverse event and imputation of dates (see Appendix 6 for incomplete or missing start dates rules).

For incomplete or missing end dates the following rule will be adopted:

- If day and month are missing, month and day should be imputed by 31st December
- If day is missing, day will be imputed with the last day of the month

7.11.1.2 Other Missing Dates

For other incomplete or missing dates a worst-case scenario will be used.

For start dates the following rule will be adopted:

- If day and month are missing, month and day should be imputed by 1st January
- If day is missing, day will be imputed with the first day of the month

For end dates the following rule will be adopted:

- If day and month are missing, month and day should be imputed by 31st December
- If day is missing, day will be imputed with the last day of the month

7.11.2 Outliers

All values will be included in the analyses.

7.11.3 Visit Windows

The study protocol gives the overall study schedule and the permissible intervals for these visits expressed as the number of days relative to Screening for Period 1 and to eligibility assessment for Period 2.

Analyses will not exclude subject data due to the subject's failure to comply with the visit schedule.

The value which assessment day is the closest to the defined target day within these windows is used. If two values are equally close, the later is used in the analysis.

8. UPDATES IN CSR

Primary CSR was signed on 28 Apr 2021. Data cut performed 30 Apr 2020.
Updated (FINAL) CSR will be done when last patient has left the study, anticipated to occure Q1 2024.

This CSR will include ALL data available in the database that are linked to the described endpoints.

9. DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.00	12-Nov-2014	NA	Document finalized
1.1	27-Oct-2016	CTA included	Update to include CTP changes
1.2	12-Apr-2019	CTP v 5.0	Include changes from CTP v5 and refine treatment extension
2.0	23-Apr-2021	Categorizations Covid 19 Clarifications	Implement decissions w.r.t. changes of categorization categories made during DRM meetings. Inclusion of impact assessment General clarifications to existing defenitions
2.1	23-Jan-2024	Updated to refine final analysis wording	Include full rerun of safety and primary efficacy, handling of extension period

10.REFERENCES

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

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

11.APPENDICES

10.1 Appendix 1: List of Hormonal Therapies

ATC Code	Name	Defined Daily Dose	Units	Route of Administration	Note
L02AE01	Buserelin	0.11	mg	Implant	
		1.2	mg	N	
		1.5	mg	P	
L02AE02	Leuprorelin	60	mcg	Implant	
		0.134	mg	P	Depot inj
		1	mg	P	
L02AE03	Goserelin	0.129	mg	Implant	
L02AE04	Triptorelin	0.134	mg	P	Depot inj
		0.1	mg	P	
L02AE05	Histrelin	0.137	mg	Implant	
L02BX01	Abarelix				
L02BX02	Degarelix	2.7	mg	P	

10.2 Appendix 2: List of Anti-Androgens

ATC Code	Name	Defined Daily Dose	Units	Route of Administration	Note
L02BB01	Flutamide	0.75	g	O	
L02BB02	Nilutamide	0.3	g	O	
L02BB03	Bicalutamide	50	mg	O	

10.3 Appendix 3: List of Bisphosphonates

ATC Code	Name	Defined Daily Dose	Units	Route of Administration	Note
M05BA01	etidronic acid	0.4	g	O	
		1.5	g	P	Course dose
M05BA02	clodronic acid	1.6	g	O	
		1.5	g	P	Course dose
M05BA03	pamidronic acid	60	mg	P	Course dose
M05BA04	alendronic acid	10	mg	O	
M05BA05	tiludronic acid	0.4	g	O	
M05BA06	ibandronic acid	6	mg	P	Course dose
		5	mg	O	
M05BA07	risedronic acid	5	mg	O	
M05BA08	zoledronic acid	4	mg	P	
M05BB01	etidronic acid and calcium, sequential	0.4	g	O	Refers to etidronic acid
M05BB02	risedronic acid and calcium, sequential				
M05BB03	alendronic acid and colecalciferol	10	mg	O	Refers to etidronic acid
M05BB04	risedronic acid, calcium and colecalciferol, sequential	5	mg	O	Refers to etidronic acid
M05BB05	alendronic acid, calcium and colecalciferol, sequential	10	mg	O	Refers to etidronic acid
M05BB06	alendronic acid and alfacalcidol, sequential	10	mg	O	Refers to etidronic acid

10.4 Appendix 4: List of Corticosteroids

ATC Code	Name
H02AB	Glucocorticoids
H02BX	Corticosteroids for systemic use, combinations

10.5 Appendix 5: List of Anticoagulants

ATC Code	Name
B01AA	Vitamin K antagonists
B01AB	Heparin group

10.6 Appendix 6: Identification of Start Date of AE/TEAE

Availability of start date of AE	Comparison of Available Values	Onset BEFORE/AFTER first dose of study drug Period 1	Onset BEFORE/AFTER first dose of study drug Period 2	Type of AE	Imputation for Start Date of AE
[year, month] is available	Start [year, month] of AE is earlier than [year, month] of the first dose of study drug Period 1	BEFORE or MISSING	BEFORE or MISSING	Pre-Treatment AE	1st will be imputed
	Start [year, month] of AE is same as [year, month] of the first dose of study drug Period 1	BEFORE	BEFORE or MISSING	Pre-Treatment AE	1st will be imputed
		AFTER or MISSING#	BEFORE or MISSING	Period 1 TEAE	The day of the first dose of study drug Period 1 will be imputed
	Start [year, month] of AE is • later than [year, month] of the first dose of study drug Period 1 and • earlier than [year, month] of the first dose of study drug Period 2	AFTER or MISSING	BEFORE or MISSING	Period 1 TEAE	1st will be imputed
	Start [year, month] of AE is • later than [year, month] of the first dose of study drug Period 1 and • same as [year, month] of the first dose of study drug Period 2	AFTER or MISSING	BEFORE	Period 1 TEAE	1st will be imputed
			AFTER or MISSING#	Period 2 TEAE	The day of the first dose of study drug Period 2 will be imputed
	Start [year, month] of AE is later than [year, month] of the first dose of study drug Period 2	AFTER or MISSING	AFTER or MISSING	Period 2 TEAE	1st will be imputed

Otherwise – generally options not listed should be flagged as data issues

Onset before / after flags may be missing.

- If the onset flag is required but missing for Period 1, then assume AFTER.
- If the onset flag is required but missing for Period 2, then assume AFTER, unless the flag for Period 1 is BEFORE

Flag to check data

Availability of start date of AE	Comparison of Available Values	Onset BEFORE/AFTER first dose of study drug Period 1	Onset BEFORE/AFTER first dose of study drug Period 2	Type of AE	Imputation for Start Date of AE
[year] is available	Start [year] of AE is earlier than [year] of the first dose of study drug Period 1	BEFORE or MISSING	BEFORE or MISSING	Pre-Treatment AE	January 1st will be imputed
	Start [year] of AE is • same as [year] of the first dose of study drug Period 1 and • earlier than [year] of the first dose of study drug Period 2	BEFORE	BEFORE or MISSING	Pre-Treatment AE	January 1st will be imputed
		AFTER or MISSING#	BEFORE or MISSING	Period 1 TEAE	The day and the month of the first dose of study drug Period 1 will be imputed
	Start [year] of AE is • same as [year] of the first dose of study drug Period 1 and • same as [year] of the first dose of study drug Period 2	BEFORE	BEFORE or MISSING	Pre-Treatment AE	January 1st will be imputed
		AFTER or MISSING#	BEFORE	Period 1 TEAE	The day and the month of the first dose of study drug Period 1 will be imputed
			AFTER or MISSING#	Period 2 TEAE	The day and the month of the first dose of study drug Period 2 will be imputed
	Start [year] of AE is • later than [year] of the first dose of study drug Period 1 and • same as [year] of the first dose of study drug Period 2	AFTER or MISSING	BEFORE	Period 1 TEAE	January 1st will be imputed
			AFTER or MISSING#	Period 2 TEAE	The day and the month of the first dose of study drug Period 2 will be imputed
	Start [year] of AE is later than [year] of the first dose of study drug Period 2	AFTER or MISSING	AFTER or MISSING	Period 2 TEAE	January 1st will be imputed

Otherwise – generally options not listed should be flagged as data issues

Onset before / after flags may be missing.

- If the onset flag is required but missing for Period 1, then assume AFTER.
- If the onset flag is required but missing for Period 2, then assume AFTER, unless the flag for Period 1 is BEFORE

Flag to check data

Availability of start date of AE	Comparison of Available Values	Onset BEFORE/AFTER first dose of study drug Period 1	Onset BEFORE/AFTER first dose of study drug Period 2	Type of AE	Imputation for Start Date of AE
Nothing is available		BEFORE	BEFORE	Pre-Treatment AE	Keep complete missing date
		AFTER or MISSING#	BEFORE	Period 1 TEAE	The date of the first dose of study drug Period 1 will be imputed
			AFTER or MISSING#	Period 2 TEAE	The date of the first dose of study drug Period 2 will be imputed

Otherwise – generally options not listed should be flagged as data issues

Onset before / after flags may be missing.

- If the onset flag is required but missing for Period 1, then assume AFTER.
- If the onset flag is required but missing for Period 2, then assume AFTER, unless the flag for Period 1 is BEFORE

Flag to check data

10.7 Appendix 7: PFS Derivation

The objective of this document is to provide a detailed description of the derivation of the Progression Free Survival (PFS), as defined in Section 6.1.1 of the SAP.

The analysis requires the derivation of the progression events and their corresponding dates.

The primary efficacy endpoint is PFS with progression defined as radiographic progression, unequivocal clinical progression, or death on study.

At first, the collection of all dates is required for the derivation:

- Date of randomization:

	Table	**Variable**
Randomization date	SDTM.ADSL	RANDDT

- Date of progression events:

	Table, and selection if necessary	**Variable**
Date of radiographic disease progression	- Bone: SDTM.RS.RSTESTCD= "BONERESP" and SDTM.RS.RSORRES = "PROGRESSIVE DISEASE" (choose unconfirmed PD data, if available) - Soft tissue: SDTM.RS.RSTESTCD=" OVSTRESP" and SDTM.RS.RSORRES = "PROGRESSIVE DISEASE"	SDTM.RS.RSDTC where RSDTC>= RANDDT (in order to select only the progression appear after the randomization) For bone disease progression: - If a subject has an unconfirmed progression with confirmed progression, the date of unconfirmed progression will be used. - If a subject has only an unconfirmed progression, it won't be used for the analysis.
Date of unequivocal clinical progression	- New onset cancer pain requiring chronic administration of opiate analgesia: SDTM.RS rstestcd=CAPAINOP - Deterioration from prostate cancer of ECOG PS score to 3 or Higher: SDTM.QS.QSTESTCD="ECOG" and SDTM.QS.QSSTRESN>=3 - Initiation of subsequent lines of cytotoxic chemotherapy or radiation therapy or surgical	CMSTDTC1=SDTM.CM.CMSTDTC where CMSTDTC ≥ RANDDT SDTM.QS.QSDTC where QSDTC >= RANDDT

	intervention due to complications of tumor progression: SDTM.RS rstestcd=COMPTUPR	CMSTDTC2=SDTM.CM.CMSTDTC where CMSTDTC ≥ RANDDT
Date of death	SDTM.DS.DSTERM="DEATH" and SDTM.DS.EPOCH="30 DAY FOLLOW-UP"	SDTM.DSDTC where DSDTC ≥ RANDDT

- Date of the last assessment of disease progression:

	Table, and selection if necessary	**Variable**
Date of the last assessment of disease progression	Last disease assessment available (time point response and FU)	SDTM.RS.RSDTC where RSDTC> RANDDT

Then, the derivation of the main variables of the ADTTE ADaM dataset:

Variable	**Subjects with a progression event**	**Subjects with no progression event**
PARCAT1N	1	
PARCAT1	PRIMARY ENDPOINT	
PARAMCD	PFS	
PARAM	PROGRESSION FREE SURVIVAL	
AVISITN	AVISITN	
AVISIT	AVISIT	
ADT	min(RSDTC,CMSTDTC1,QSDTC,CMSTDTC2,DSDTC)	RSDTC
AVAL[1]	[min(RSDTC,CMSTDTC1,QSDTC,CMSTDTC2,DSDTC) - Date of randomization) + 1] / 30.4375	[(date of last assessment - Date of randomization) + 1] / 30.4375
STARTDT	RANDDT	
CSNR	0	1
EVNTDESC	- RADIOGRAPHIC DISEASE PROGRESSION if ADT = RSDTC - UNEQUIVOCAL CLINICAL PROGRESSION if ADT in (CMSTDTC1,QSDTC,CMSTDTC2) - DEATH if ADT = DSDTC	NO PROGRESSION

NOTE:
[1] The PFS is defined as the time (in months) from randomization (period 2 week 1) to the earliest progression event.

10.8 Appendix 8: Key Contributors and Approvers

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

Primary author (s)

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Approved by:

PPD

PPD