NCT02485691

STATISTICAL ANALYSIS PLAN

A randomized, open label, multicenter study of Cabazitaxel versus an Androgen Receptor (AR)-targeted agent (abiraterone or enzalutamide) in mCRPC patients previously treated with Docetaxel and who rapidly failed a prior AR-targeted agent

XRP6258-LPS14201

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DATE OF ISSUE: 20-Jun-2019

Total number of pages: 76

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
aMDRD:	abbreviated modification of diet in renal disease
AR:	androgen receptor
AST:	aspartate aminotransferase
ATC:	anatomical therapeutic chemical
BMI:	body mass index
BPI-SF:	brief pain inventory-short form
BSA:	body surface area
BUN:	blood urea nitrogen
CBZ:	cabazitaxel
CI:	confidence interval
CR:	complete response
CTC:	circulating tumor cell
CTCAE:	common terminology criteria for adverse events
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
EOT:	end of treatment
EWB:	emotional well-being
FACT-P:	functional assessment of cancer therapy-prostate
FST:	first subsequent therapy
FWB:	functional well-being
HIFU:	high intensity focused ultrasound
HLGT:	high-level group term
HLT:	high-level term
HR:	hazard ratio
HRQL:	health-related quality of life
IMP:	investigational medicinal product
INR:	international normalized ratio
ITT:	intent-to-treat
IVRS/IWRS:	interactive voice/web response system
LDH:	lactate dehydrogenase
LLN:	lower limit of normal
mCRPC:	metastatic castration-resistant prostate cancer
MedDRA:	Medical Dictionary for Regulatory Activities
PCWG2:	prostate cancer working group criteria 2
PD:	progressive disease
PR:	partial response
PS:	performance status
PSA:	prostate-specific antigen

PSC:	prostate-specific concerns
PT:	preferred term
PWB:	physical well-being
RBC:	red blood cells
RECIST:	response evaluation criteria in solid tumors
rPFS:	radiographic progression-free survival
SAE:	serious adverse event
SC:	steering committee
SD:	stable disease
SOC:	system organ class
SSE:	symptomatic skeletal event
SWB:	social/family well-being
TEAE:	treatment-emergent adverse event
TOI:	trial outcome index
TTPP:	time to PSA progression
TURP:	transurethral resection of prostate
ULN:	upper limit of normal
VAS:	visual analogue scale
WBC:	white blood cell
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This phase IV study is prospective, multicenter, multinational, randomized, stratified, open label, 2-parallel-group.

After a screening phase of up to four weeks, metastatic Castration-Resistant Prostate Cancer (mCRPC) patients, previously treated with Docetaxel and who rapidly failed a prior Androgen Receptor (AR)-targeted agent (Abiraterone acetate or Enzalutamide), will be randomized by an Interactive Voice/Web Response System (IVRS/IWRS) in a 1:1 ratio to one of the two treatment groups: cabazitaxel (CBZ) at 25 mg/m² plus prednisone (or prednisolone) 10 mg daily (Arm A) versus either Enzalutamide at 160 mg once daily or Abiraterone acetate at 1000 mg once daily plus prednisone (or prednisolone) at 5 mg twice daily (Arm B).

The randomization will be stratified by:

- Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-1 versus 2).
- Time from AR targeted agent initiation to progression ([0; 6 months] versus]6; 12 months]).
- Timing of AR targeted agent (before versus after Docetaxel).

A total of 234 patients in 2 arms (117 patients per arm) are anticipated to be needed to reach the targeted 196 number of patients with event. This new target should be achieved for an estimated constant accrual rate equal to 12 until the end of the recruitment expected in June 2018.

The study is event driven and the main cut-off date will be when 196 rPFS events have occurred.

End of trial will occur 30 days after the last patient last cycle. Exposure and safety analyses will be updated at time of the final database lock.

A steering committee (SC), including the Study Chairmen and sponsor representatives, will be responsible for:

- Supervising the progress of the trial towards its overall objectives.
- Reviewing at regular intervals relevant information that may affect the study conduct.

A translational SC will be responsible for supervising the biomarkers part. This committee will include Study Chairmen’s and Sponsor’s representatives.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to compare CBZ plus prednisone versus either Abiraterone plus prednisone or Enzalutamide in term of radiographic Progression-Free Survival (rPFS) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for tumor lesions and Prostate Cancer Working Group criteria 2 (PCWG2) criteria for bone scan lesions or death due to any cause in mCRPC patients who have been treated with Docetaxel and who had disease progression while receiving AR targeted therapy within 12 months of AR treatment initiation (≤12 months) (either before or after docetaxel).

1.2.2 Secondary objectives

Handling multiplicity issues (Section 2.4.4.3) it has been decided to proceed to a hierarchical procedure, providing statistical testing for the four main secondary endpoints (OS, PFS, Prostate-Specific Antigen [PSA] response rate and Objective tumor response) and conducting descriptive analysis for others secondary endpoints.

- To compare efficacy of CBZ plus prednisone to enzalutamide or abiraterone acetate plus prednisone for:
  - Overall Survival (OS),
  - Progression-Free Survival (PFS),
  - PSA response rate,
  - Objective tumor response (RECIST 1.1 criteria in patients with measurable disease).
- To compare efficacy of CBZ plus prednisone to Abiraterone acetate plus prednisone or Enzalutamide for :
  - Time to PSA Progression (TTPP),
  - Duration of tumor response,
  - Pain intensity palliation,
  - Time to pain progression,
  - Symptomatic skeletal events (SSE) rate,
  - Time to occurrence of SSEs.
- To compare Health-Related Quality Of Life (HRQL) according to Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire between arms.
- To compare Health status/utility (EQ-5D-5L) between arms.
- To evaluate the correlation of a signature of resistance to AR targeted agents with clinical outcomes, via the analysis of Circulating Tumor Cells (CTC) phenotypes as well as expression and localization of proteins including AR isoforms in CTCs.
  The description of these analyses will be detailed in a separate Statistical Analysis Plan.
- To evaluate safety in both treatment arms.

1.2.3 Exploratory objectives

- [redacted]
- [redacted]

The description of these analyses will be detailed in a separate Statistical Analysis Plan.

1.3 DETERMINATION OF SAMPLE SIZE

A power reduction from 90% to 80% has been updated in protocol amendment V4, before this amendment, a total of 263 patients with event were needed to achieve 90% power to demonstrate rPFS superiority of CBZ over abiraterone acetate/prednisone or enzalutamide by 2 sided log rank test at 0.05 type I error rate.

Further assuming the accrual is at a constant rate of 18 patients per month, a total of 324 patients in 2 arms (162 patients per arm) are anticipated to be needed to reach the targeted number of patients with event.

Sample size section, has been updated as follow:

In post-docetaxel setting, the HR for rPFS is 0.66 [0.58-0.76] between abiraterone/prednisone and prednisone in COU-AA-301 (1) and 0.40 [0.35-0.47] between enzalutamide and placebo in AFFIRM (2).

In pre-docetaxel setting, the HR for rPFS is 0.53 [0.45 to 0.62] between abiraterone/prednisone and prednisone in COU-AA-302 (3) and 0.19 [0.15-0.23] between enzalutamide and placebo in PREVAIL (4).

We thus consider that a HR of 0.67 should be considered as the smallest effect of clinical interest between cabazitaxel and an AR-targeted agent (abiraterone or enzalutamide).

The following table presents how such a HR translates for a variety of envisaged median rPFS in the abiraterone acetate or enzalutamide group (5, 6).

Table 1 - HR translates for a variety of envisaged median rPFS in the abiraterone acetate or Enzalutamide group

Hazard Ratio	Median rPFS (month)	
	Abiraterone acetate or Enzalutamide group	Cabazitaxel group
0.67	4	6.0
0.67	5	7.5
0.67	6	9.0

A total of 196 patients with event is needed to achieve 80% power to demonstrate rPFS superiority of cabazitaxel over abiraterone acetate/prednisone or enzalutamide by 2 sided log rank test at 0.05 type I error rate.

At the time of the cut-off date, when the primary analysis will be conducted, events will be censored in some patients either by end-of-study or by cut-off date. [redacted]

The observed accrual rates, that have been lower than expected, have been considered for this new sample size calculation using East 6.4:

Table 2 - Accrual period

Period	Starting at time	Accrual rate
1	Mid-November 2015 = M0	3
2	Mid-October 2016 = M11	8
3	Mid-February 2017 = M15	7
4	Mid-August 2017 = M25	12
5	Mid-December 2017 = M29 (up to end of June 2018)	12

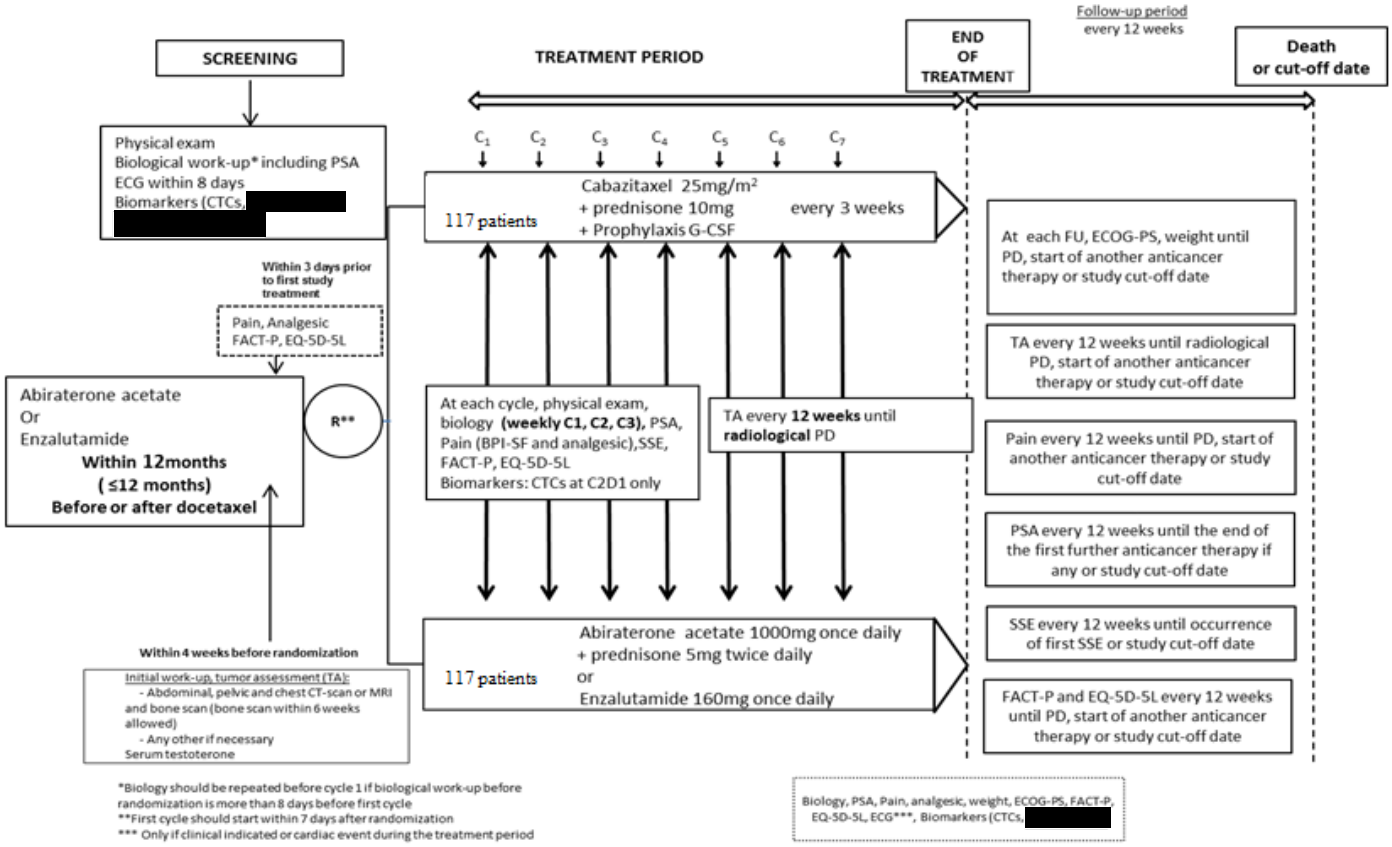
A total of 234 patients in 2 arms (117 patients per arm) are anticipated to be needed to reach the targeted number of patients with event. This new target should be achieved for an estimated constant accrual rate equal to 12 until the end of the recruitment expected in June 2018.

1.4 STUDY PLAN

This study comprises three periods:

- Screening period: up to four weeks before randomization.
- Treatment period: it begins at the first study treatment administration within seven days after randomization and ends 30 days after the last treatment administration. Each patient will be treated until radiographic disease progression, unacceptable toxicity or patient's refusal of further study treatment. Cabazitaxel will be administered intravenously every three weeks. The comparators will be given orally continuously but 3-week cycles are also defined for them.
- Follow-up period: after study treatment's discontinuation, patients will be followed every 12 weeks until death, cut-off date or withdrawal of patient's consent, whichever comes first. During the follow-up period, all SAEs and/or adverse events (AE) related to study treatment and ongoing at the end of the study, or new related to study treatment AE which occur during the follow-up period will be collected and followed until resolution or stabilization of patient's condition. Patients still on study treatment at the cut-off date can continue treatment until at least one treatment discontinuation criterion as defined in the protocol is met.

For each patient, after the screening visit, a visit per cycle is scheduled with three assessments (Day 01, Day 08 and Day 15) for hematology and biochemistry data collection during the three first cycles, an end of treatment (EOT) visit and a follow-up visit every 12 weeks until death, study cut-off date or withdrawal of patients' consent.



PD: progression disease.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The statistical section of the protocol was changed in an amendment dated on 08 November 2018.

- The sample size was calculated based on observed and further expected accrual periods of recruitment and observed, further expected accrual rates, furthermore power has been decreased from 90% to 80% due to recruitment difficulties.

Table 3 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
Protocol amendment V4.0	08-Nov-2018	Sample size section revised due to recruitment difficulties	Sample size section revised (see Section 1.3)

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Table 4 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
Final 2.0	20-Jun-2019	Sample size section revised due to recruitment difficulties	All sample size section following protocol amendment (V4.0) (see Section 1.3).
		Additional important prognostic factors have been identified and included in the SAP.	Baseline definition clarified when assessment was not done prior randomization.
			Disease history and clinically relevant characteristics at inclusion have been updated.
			All analgesic treatments recorded in clinical database to be classified according to the World Health Organization (WHO) analgesic ladder for cancer pain. Based on this update, pain definition has been clarified.
			Type of progression at randomization classified in 3 categories: PSA progression only (no radiological progression, no pain defined by BPI-SF 0-1 and analgesic level in 0-1), radiological progression (± PSA progression), pain progression (BPI-SF>1 and/or analgesic Level 2-3).
			Duration of first ADT has been defined.
		Some analyses planned in prior SAP version have been removed as not planned in the protocol.	Duration in months of pain (intensity and interference) palliation AND Time to symptomatic deterioration have been removed as secondary endpoints were not part of protocol.
		As this analysis is not planned as per protocol, we've decided to remove this and it's been replaced by subgroups analyses to have a whole picture of the impact of prognostic factors on efficacy outcome.	Multivariate cox model for primary endpoint has been removed and replaced by subgroup analyses for each stratification / prognostics factors assessing treatment effect on primary endpoint.
		Due to important decrease of evaluable patient cycle after cycle, decision has been made to restrict the statistical analyses up to the cycles that would contain enough observations.	Analyses made on quality of life questionnaires will be done provide up to the cycle for which at least 20% of evaluable patients will be reached in each treatment group, except end-of treatment evaluation that will be provided anyway. Figures (bar plot) have been removed.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is generally defined as the last available value before randomization.

Furthermore, for laboratory and vital sign assessment, the last available assessment before first intake will be considered as the baseline for randomized treated patients, and the last available assessment before randomization if patients were non-treated.

When CTC, [redacted] and/or QoL evaluations were not done before randomization, baseline might be considered as the last assessment performed before first treatment intake.

All baseline safety and efficacy parameters are presented along with the on-treatment summary statistics in the efficacy and safety sections (Section 2.4.4 and Section 2.4.5).

Demographic characteristics

Demographic variable is:

- Age in years at screening (quantitative and qualitative: <65, [65-70[, [70-75[and ≥75 years).
- Age (years) at prostate cancer diagnosis (quantitative).
- Age (years) at diagnosis of metastatic disease.
- Age (years) at diagnosis of mCRPC (Section 2.5.3 handling of mCRPC missing/partial dates).

Medical or surgical history

Medical or surgical history includes significant prior and concurrent illnesses other than primary prostate tumor cancer surgery.

This information will be coded using the last version available at the time of database lock of Medical Dictionary for Regulatory Activities (MedDRA).

Prior anticancer therapies

- Prior surgery for prostatic carcinoma excluding androgen ablation:
  - Radical prostatectomy,
  - Pelvic lymphadenectomy,
  - Extended lymphadenectomy,
  - Transurethral resection of prostate (TURP),
  - Cryosurgery,
  - High Intensity Focused Ultrasound (HIFU),
  - Other.

- Prior surgery for androgen ablation:
  - Bilateral orchiectomy,
  - Bilateral adrenalectomy,
  - Hypophysectomy,
  - Other.
- Radiation therapy prior treatment except radiopharmaceutical therapies:
  - Location (according to a code list),
  - Intent by location (palliative/curative),
  - Radiation type (internal/external).
- Prior radical prostatectomy or prior radiotherapy of prostate for localized disease (ie, before date of metastatic disease).
- Prior anticancer therapy - Docetaxel:
  - Number of lines (quantitative and by class 1 line, 2 lines, 3 lines and >3 lines),
  - Initial dosage, schedule, cumulative dose, daily Prednisone/Prednisolone, prophylactic G-CSF by therapy type for all docetaxel lines,

    Listings summarizing docetaxel initial dosages other than 75 mg/m² and schedules other than 3-weekly/bi-weekly/weekly will be provided.
  - Reason for discontinuation: AE, patient lost to follow-up, patient's request, disease progression, completed treatment, other reason,
  - Best response: complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD), not applicable/not assessed, not evaluable, unknown,
  - Treatment duration (months) (calculated as end date - start date + 1)/30.4375,
  - Time to disease progression from start date of therapy to date of radiological and/or symptomatic progression (months),
  - For last docetaxel therapy line: progression-free interval since last cycle (time from last cycle to radiological and/or symptomatic progression, whichever comes first):

    Progression during docetaxel treatment,
    Progression <6 months after last docetaxel cycle,
    Progression ≥6 months after last docetaxel cycle, based on end date of last line,
  - Number of patients treated with docetaxel for newly diagnosed metastatic hormone-naive prostate cancer (first cycle of docetaxel given within three months after starting first ADT in patients with M1 disease at diagnosis),
  - Number of patients treated with docetaxel for metastatic castration-resistant prostate cancer (first cycle of docetaxel given at the date of mCRPC diagnosis or after).

- Prior anticancer therapy - new AR-targeted agents and regimens containing Docetaxel excepted:
  - Number of prior hormonal therapies regimen (quantitative if relevant and by class 0 line, 1 line, 2 lines, 3 lines and >3 lines),
  - Number of prior chemotherapy regimens other than docetaxel (by class 0 line, 1 line, 2 lines, 3 lines and >3 lines),
  - Number of prior chemotherapy (docetaxel or not) (quantitative if relevant and by classes 0 line, 1 line, 2 lines, 3 lines and >3 lines),
  - Therapy type:

    Chemotherapy other than docetaxel,
    Hormonotherapy type: orchiectomy, LHRH agonist, LHRH antagonist, anti-androgen, oestrogens, ketoconazole, prednisone for prostate cancer (see Appendix G),
    Immunotherapy,
    Radium 223 (radium RA 223 Dichloride, radium),
    Systemic radiation,
    Other (Gene therapy, Cryotherapy, Biologicals, etc).
- Prior anticancer therapy: novel AR targeted agents (Abiraterone or Enzalutamide)
  - Number of patients with Abiraterone or Enzalutamide,
  - Daily Prednisone/Prednisolone,
  - Reason for discontinuation: AE, patient lost to follow-up, patient's request, disease progression, completed treatment, other reason,
  - Best response: CR, PR, PD, SD, not applicable/not assessed, not evaluable, unknown,
  - Total duration of therapy with novel AR targeted agent (months) calculated as end date - start date + 1)/30.4375,
  - Time from start date of therapy to first relapse/progression date (radiological or symptomatic) (months),
  - Time from last dose of Abiraterone or Enzalutamide to randomization (months),
  - Duration of first ADT (<12 months vs ≥12 months) (ie, time from first intake of ADT to subsequent ADT for which the duration is greater than 3months). All prior anti-cancer therapy, id est orchiectomy, LHRH, another hormonotherapy, or docetaxel, or abiraterone or enzalutamide or radium 223 will be considered to assess this parameter,

    If end date of ADT is missing or ADT is ongoing at time of the randomization (see Section 2.5.3),
  - Total Duration of prior ADT (months) (time from first intake of ADT to screening visit).

Disease characteristics at baseline

- Initial cancer diagnosis:
  - Time between histological diagnosis and screening (months),
  - Time between metastatic disease and mCRPC (months),
  - Time between mCRPC and screening (months),
  - Presence of neuroendocrine component (Yes/No/unknown),
  - Total Gleason Score, in continuous and in classes (≤6, 7 and ≥8),
  - Staging at initial diagnostic（T, N, M）,
    TNM staging according to the following 4 categories, from the best to the worst:
    Localized (T1/T2 & N0),
    Locally advanced (T3/T4 & N0),
    Node-positive (N+ & M0),
    Distant Metastases (M1),
    Unknown.
- Disease status at study entry:
  - Overall criteria on which progression before study entry was diagnosed
    Rising PSA (Yes/No),
    Progression of measurable lesions (Yes/No) [1],
    Progression of non-measurable lesions (except bone) (Yes/No) [2],
    Appearance of new lesions on bone scan (Yes/No) [3],
    Total radiological progression ([1] and/or [2] and/or [3]),
    Total radiological progression and rising PSA,
    Total radiological progression without rising PSA,
  - BPI-SF Item 3 (0-1, 2-3, ≥4),
  - Consumption of analgesics at study entry (ongoing at randomization or within one week prior to randomization) (Section 2.5.3):
    0 (No analgesic),
    1 (mild pain = non-opioid analgesics),
    2 (mild to moderate pain = opioids for moderate pain),
    3 (severe pain = opioids for severe pain).
- Type of progression at randomization:
  - Pain status at study entry (Yes, No):
    No: if BPI-SF in (0, 1) and analgesics level in (0, 1),
    Yes: if BPI-SF >1 and/or analgesics level in (2, 3),
  - Rising PSA only (no radiological progression and no pain) (Yes/No),

- Radiological progression (± rising PSA) and no pain (Yes/No),

  Radiological progression (with rising PSA) and no pain (Yes/No),

  Radiological progression (without rising PSA) and no pain (Yes/No).

- Tumor assessment of target and non-target lesions at baseline:
  - Number of organ involved, continuous and by classes (0, 1, 2, 3, ≥4),
  - Location (from tumor work-up eCFR form),
  - Location category see Table 5 (7).

    Any measurable disease (yes if presence of a target lesion at baseline tumor assessment).

    If any, a listing will be provided for other locations.

    "Visceral disease patients were, in turn, placed in one of the following three categories: any patient with liver metastases was categorized as having liver metastases even if they had other metastatic sites; patients with lung metastases were denoted as having lung metastases, unless they also had liver metastases; and all other patients with visceral disease were categorized as having nonhepatic, nonpulmonary visceral metastases (such as adrenal, kidney, and others). In the nonvisceral disease group, patients were classified as either having LN-only disease or bone metastases with or without nodal involvement." (7).

Table 5 - Classification of site of Metastases by mutually exclusive categories

Sites of Metastases	Presence of LN[a] Metastases[b]	Presence of Bone Metastases[c]	Presence of Visceral Metastases[d]	Category
LN only	Yes	No	No	LN
Bone only	No	Yes	No	Bone
Bone with LN involvement	Yes	Yes	No	Bone
Lung	No/Yes	No	Yes	Lung
Lung	No/Yes	Yes	Yes	Lung
Liver	No/Yes	No	Yes	Liver
Liver	No/Yes	Yes	Yes	Liver

a Abbreviation: LN, Lymph node.

b Presence of LN Metastases defined as Yes for lesion location is Lymph nodes (target and non-target at baseline).

c Presence of Bone Metastases defined as Yes for Lesion Location Bone.

d Presence of Visceral Metastases defined as Yes for all lesions location except LN and Bone (target and non-target at baseline).

- Tumor markers
  - Inclusion PSA (ug/L) value (ie, the last value measured within eight days prior to randomization if collected, or last PSA value prior first IMP administration if not collected prior randomization),
  - Baseline Testosterone (quantitative and <median, ≥median),
  - Baseline hemoglobin (quantitative and <median, ≥median),
  - Baseline LDH (quantitative and >ULN, and <median, ≥median),
  - Baseline Alkaline phosphatase (quantitative, >ULN, and <median, ≥median),
  - Baseline Neutrophil to lymphocyte ratio (quantitative and <median, ≥median),

  - Neutrophils (quantitative and <median , ≥median),
  - Lymphocytes count (quantitative and <median , ≥median),
  - Grade ≥3 neutropenia, n(%).
- Symptomatic Skeletal Event (SSE) evaluation at baseline
  - Total number of patients with SSE,
  - Number of patients with an occurrence of new symptomatic pathological fracture,
  - Number of patients with use of external beam radiation to relieve bone pain,
  - Number of patients with an occurrence of spinal cord compression,
  - Number of patients with tumor -related orthopaedic surgical intervention.

The SSE is given in the SSE evaluation CRF page.

- Brief Pain Inventory-Short Form (BPI-SF) (questionnaire):
  - Pain intensity = worst pain intensity in the last 24 hours (ie, Item 3 of the questionnaire: “pain at its worst”, quantitative) (8),
  - Item “pain at its least” (Item 4),
  - Item “pain at its average” (Item 5),
  - Item “pain at its current” (Item 6),
  - Mean severity score = mean of the four item above if at least two of them are not missing,
  - Pain interference = mean of the seven answers of the ninth item of questionnaire if at least four answers among seven are not missing.
- EQ-5D-5L:
  - 5 Dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression),
  - Global utility index score,
  - The EQ Visual Analogue Scale (VAS).
- Functional Assessment of Cancer Therapy-Prostate (FACT-P):
  - 5 Subscales of the FACT-P:

    Physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), prostate-specific concerns (PSC),
  - HRQL assessed using the FACT-P Total score which combines the PWB (7 items), SWB (7 items), EWB (6 items), FWB (7 items), and prostate cancer scale/prostate specific concerns (12 items),
  - Additional HRQL summary scores include the FACT-G Total (PWB + SWB + EWB + FWB), the FACT-P Trial Outcome Index (TOI) (PWB + FWB + PSC) and the Pain PCS (4 items, P1-P3, GP4).

Vital signs

Vital signs at baseline (before first study product intake, or before randomization for non-treated patients) are:

- Weight (kg).
- Height (cm).
- BMI (kg/m^2) and OMS classes (Underweight <18.5; Normal weight [18.5 to 25[; Pre-obesity [25.0 to 30[; Obesity class I [30.0 to 35[; Obesity class II [35.0 to 40[; Obesity class III >=40).
- Body surface area (BSA) (m^2).
- Blood pressure (systolic and diastolic in mmHg).
- Heart rate (bpm).
- ECOG PS (0, 1, 2, 3, 4).

Technical details related to computation, dates and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications taken within 28 days before randomization or at any time during the study and up to 30 days after the end of study treatment are to be reported in the CRF pages.

All medications will be coded using the last version available at the time of database lock of World Health Organization-Drug Dictionary (WHO-DD).

- Prior medications are those the patient used prior to first investigational medicinal product (IMP) administration. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP from randomization to the EOT + 30 days. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in Section 2.1.4).
- Post-treatment medications are those taken by the patient in the period running from the day after last IMP administration up to the end of the study.

Technical details related to computation, dates or imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy variable will be the rPFS defined as the time in months from randomization to the occurrence of one of the following events:

- Radiological tumor progression using RECIST 1.1 (see Appendix B) except for lymph nodes: if lymph node metastasis is the only evidence of metastasis at baseline, it must be ≥20 mm in diameter when measured by spiral CT or MRI (as defined by PCWG2).
- Progression of bone lesions according to PCWG2 criteria:
  - The first bone scan with ≥2 new lesions compared to baseline is observed <12 weeks from randomization and is confirmed by a second bone scan performed ≥6 weeks later and showing ≥2 additional new lesions compared to previous bone scan (a total of ≥4 new lesions compared to baseline),
  - The first bone scan with ≥2 new lesions compared to baseline is observed ≥12 weeks from randomization and the new lesions are verified on the next bone scan ≥6 weeks later (a total of ≥2 new lesions compared to baseline).
- Death due to any cause from death CRF page.

2.1.3.2 Secondary efficacy endpoint(s)

2.1.3.2.1 Primary secondary efficacy endpoint(s)

Primary secondary efficacy variables will be:

- OS defined as the time interval from the date of randomization to the date of death due to any cause in months. In the absence of confirmation of death, survival time will be censored at the last date patient is known to be alive or at the cut-off date, whichever comes first.

  In case of incomplete date of death, the following rules will be applied to derive time-to death in OS:
  - If the day of death date is missing, it will be imputed to the first day of the month, except if the date of patient's last contact is the same month as death date. In this case, the death date will be imputed to the date of last contact + 1 day,
  - If the day and month of death date are missing, no imputation will be performed. Patient's last contact date will be defined as the latest date corresponding to a follow-up update with survival status "alive" or the latest date of any of the following panels: investigational product administration, laboratory data, PSA assessment, tumor assessment, AE (use New AE start date), and vital signs, whichever comes last,
  - If date of last contact is not available after randomization, then the patient will be censored for OS to the day of randomization (Day 1).

- PFS defined as the time interval between the date of randomization and the date of the first documentation of any of the following events in months:
  - Radiological tumor progression by RECIST 1.1 (see Section 2.1.3.1) except for lymph nodes: if lymph node metastasis is the only evidence of metastasis at baseline, it must be ≥20 mm in diameter when measured by spiral CT or MRI (as defined by PCWG2),
  - Progression of bone lesions using PCWG2 criteria (see Section 2.1.3.1),
  - Symptomatic progression defined as:
    Occurrence of urinary or bowel symptoms related to prostate cancer,
    Need to change anticancer therapy (most commonly need to administer radiation therapy for palliation of an osseous or epidural lesion),
  - Pain intensity progression defined as an increase ≥30% from baseline in the BPI-SF (8) pain intensity score (Item 3) observed at two consecutive evaluations ≥3 weeks apart without decrease in analgesic usage score (defined as a ≥1 point decrease on the WHO analgesic scale),
    World health organization (WHO) analgesic ladder step calculated using the collected analgesic medication (see Section 2.5.1, and the Appendix E).
    Either criterion has to be maintained for two consecutive evaluations at least three weeks apart.
    Early rise in pain (within the first 12 weeks) only indicates progression if it is associated with another sign of disease progression or if it continues beyond 12 weeks. Progression will only be dated prior to 12 weeks if there is continued increase in PSA beyond that time point or if it was associated with another sign of disease progression.
  - Death due to any cause from the death CRF page.
    Patient's last contact date is the latest date corresponding to a follow-up update with survival status "alive" or the latest date of any of the following panels: investigational product administration, laboratory data, PSA assessment, tumor assessment, AE (use New AE start date), and vital signs, whichever comes last.
    If death or progression is not observed, the patient will be censored at the date of last valid tumor assessment (TA) without evidence of progression (meaning with OR equal to CR/PR/SD but not NE) or the study cut-off date whichever comes first, regardless of other antitumor therapies.
- Objective tumor response, in patients with measurable disease, defined as either PR or CR according to the RECIST 1.1 criteria (see Section 2.1.3.1).
- PSA endpoints: For each patient, PSA will be assessed at baseline, every 3 weeks during study treatment, and in case of study treatment discontinuation without PSA progression every 12 weeks until the end of the first further anticancer therapy if any or study cut-off, whichever comes first:
  - PSA response is defined as a reduction from baseline PSA level of at least 50%, confirmed at least three weeks later. It will be calculated among patients with a baseline PSA ≥2 ng/mL. Increases (of any magnitude) in PSA during the first 12 weeks should be ignored in determining PSA response.

2.1.3.2.2 Other secondary efficacy endpoint(s)

Other secondary efficacy variables will be:

- Time to PSA progression defined as the time interval between the date of randomization and the date of first documented PSA progression in months.
  PSA progression is defined as follows (9):
  - If any decline from baseline: record time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend),
  - If no decline from baseline: PCWG2 defines PSA progression as PSA progression ≥25% and 2 ng/mL after 12 weeks.
    Early increase in PSA within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint. Early rise in PSA only indicates progression if it is associated with another sign of disease progression or if it continues beyond 12 weeks. Progression will only be dated prior to 12 weeks if there is continued increase in PSA beyond that time point or if it is associated with another sign of disease progression.
- Duration of tumor response, defined as the time between the first evaluation at which the tumor response criteria are met (PR or CR as per RECIST 1.1 criteria) and the first documentation of tumor progression or death in months.
- Pain intensity and pain interference endpoints

  Pain scores will be assessed in all patients at baseline, before each cycle, at the EOT and then every 12 weeks until disease progression, start of another anticancer therapy or study cut-off, whichever comes first.
  - Pain response (ie, pain intensity palliation evaluable for i/ patients with pain intensity not nul at baseline and analgesic not missing, ii/ patients with pain intensity nul and analgesic not missing nor nul) defined as a decrease by at least 30% from baseline in the average of BPI-SF pain intensity score observed at two consecutive evaluations ≥3 weeks apart without increase in analgesic usage score (defined as an increase ≥1 point on the WHO analgesic score) (10),

    Number of patients evaluable and not evaluable (no pain at baseline and no analgesic used), will be summarized by treatment group.
    Increases in pain during the first 12 weeks should be ignored in determining pain response.
  - Pain intensity progression (see definition in PFS endpoint),
  - Pain interference palliation: mean pain interference score (ie, the mean of the scores for the pain interference items) decreased by 1.25 points or more compared with baseline at two consecutive follow-up visits,

- Pain interference progression: increase of 1.25 points or more in the mean pain interference score at two consecutive follow-up visits,

  Either criterion has to be maintained for two consecutive evaluations at least 3 weeks apart.

  For all analyses, we will judge non-consecutive visits to be consecutive when scores for intervening visits are missing. All patients will be assessed for pain intensity and pain interference progression, but only patients with clinically significant pain at baseline and at least one post-baseline pain score will be assessed for palliation. For the purpose of the pain intensity analyses, we will define clinically significant baseline pain as a score of 4 or more on pain intensity scale and, for the pain interference analyses, as a mean score of 4 or more on the pain interference scale.

- Time to pain progression defined as the time interval between the date of randomization and the date of the first documented pain progression in months.
  Pain progression, in patients with no pain or stable pain at baseline, is defined as:

  - An increase by ≥30% from baseline in the BPI-SF pain intensity score observed at 2 consecutive evaluations ≥3 weeks apart without decrease in analgesic usage score OR increase in analgesic usage score defined as an increase ≥1 point on the WHO analgesic score (see Section 2.5.1, and the Appendix E):

    Either criterion has to be maintained for two consecutive evaluations at least 3 weeks apart.

    Early rise in pain (within the first 12 weeks) only indicates progression if it is associated with another sign of disease progression or if it continues beyond 12 weeks. Progression will only be dated prior to 12 weeks if there is continued increase in pain beyond that time point or if it was associated with another sign of disease progression. In the absence of pain progression at the time of analysis patients will be censored on the last known date the patient was known to have not progressed or at the cut-off date, whichever comes first. Subjects with no on-study assessment or no baseline assessment will be censored at date of randomization.

- Symptomatic Skeletal Event (SSE) endpoints (see Section 2.1.1):

  - Time to first SSE defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SSE in months. For each patient, SSE will be assessed at baseline, every three weeks during study treatment, at the EOT Visit and every 12 weeks during follow-up until occurrence of first SSE or study cut-off, whichever comes first.

- Evaluation of the correlation of a signature of resistance to AR targeted agents with clinical outcomes, via the analysis of CTCs counts and phenotypes as well as expression and localization of proteins including AR isoforms in CTCs.

2.1.4 Safety endpoints

The safety analysis will be based on the reported AEs including death and other safety information, such as clinical laboratory data, vital signs and Electrocardiogram (ECG).

Observation period

The observation period will be divided into three epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to first administration of the IMP.
- The **treatment-emergent adverse event** (TEAE) epoch is defined as the time from the date of first administration of the IMP to the date of last administration of the IMP + 30 days.
- The **post-treatment** epoch is defined as the period of time starting the day after the end of the TEAE period up to the end of the study (defined as last protocol-planned visit, or death or the resolution/stabilization of all serious adverse events (SAE), related AEs and AEs with overdose).

The on-study observation period is defined as the time from the first study treatment administration until the end of the study (defined as last protocol-planned visit or the resolution/stabilization of all SAEs, related AEs and AEs with overdose.

2.1.4.1 Adverse events variables

Adverse event observation period

- Pre-treatment AEs are any AE reported from the signed informed consent date up to the day before the first administration of IMP.
- Treatment-emergent AEs (TEAEs) are defined as any AE that is new, gets worse, or becomes serious during the treatment period.
- Post-treatment AEs are AEs reported during the post-treatment period.

All AEs (including SAEs and AEs with overdose) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT) and associated primary system organ class (SOC) using the last version of MedDRA at the time of database lock.

Record the occurrence of AEs from the time of signed informed consent until the end of the study.

AEs with pre specified monitoring include overdose:

An overdose with the IP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as increase of at least 30% of the highest dose of CBZ (ie, 30% of 25 mg/m²) to be administered.

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period.
- Death on-treatment: deaths occurring during the TEAE period.
- Death post-treatment: deaths occurring 30 days after the last dose of treatment.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, endocrinological, tumor markers and dipstick urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken within eight days prior Day 1 Cycle 1, weekly (D8 and D15) during the first three cycles (±1 day window is allowed for hematology) and then within further cycles in case of fever or infection.

The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells (RBC) and platelets and coagulation**: hemoglobin (g/dL), platelet count (10^9/L), international normalized ratio (INR),
  - **White blood cells (WBC):** leucocytes (10^9/L), neutrophils (10^9/L), lymphocytes (10^9/L), monocytes (10^9/L), basophils (10^9/L), eosinophils (10^9/L).
- When expressed in %, all parameters derived from WBC will be converted in Giga/l (see Section 2.5.1). Clinical chemistry:
  - **Metabolism:** glucose (mmol/L), total protein (g/L), albumin (g/L),
  - **Electrolytes**: sodium (mmol/L), potassium (mmol/L), calcium (mmol/L), phosphorus (mmol/L), magnesium (mmol/L),
  - **Renal function**: creatinine (µmol/L), urea (mmol/L, mg/dl, umol/L, other) or blood urea nitrogen (BUN) (mmol/L), CrCl categories (mL/min/1.73m²) (Section 2.4.5.5),
  - **Liver function**: alanine aminotransferase (ALT) (IU/L), aspartate aminotransferase (AST) (IU/L), alkaline phosphatase (ALP) (IU/L), lactate dehydrogenase (LDH) (IU/L), total bilirubin (µmol/L).
- Endocrinological: Chromogranin A (µg/L), testosterone (ng/mL) at baseline.
- Tumor markers:
  - NLR Neutrophils Lymphocyte Ratio (NLR), evaluation of the influence of NLR (<median, ≥median), neutrophilia (neutrophil count ≥median) and grade ≥3 neutropenia on outcome and evaluation of NLR,
  - Changes during treatment period,

- Hb <median, ≥median at baseline,
- LDH>ULN at baseline,
- Alkaline phosphatase >ULN at baseline.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: heart rate (bpm), systolic and diastolic blood pressure (mmHg), weight (kg), BMI (kg/m²), BSA (m²) and ECOG PS when post baseline assessments are available.

2.1.4.5 Electrocardiogram variables

ECGs will be recorded automatically by the device at the investigator site. ECG results (normal, abnormal and if abnormal clinically significant or not) will be collected within eight days before randomization and at the EOT Visit only if clinically indicated or cardiac event during the treatment period.

2.1.4.6 Other safety endpoints

Not applicable.

2.1.5 Pharmacokinetic variables

Not applicable.

2.1.6 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.7 Quality-of-life endpoints

- Health-related quality of life (HRQL) evaluation will be performed using the FACT-P questionnaire (Version 4), a disease-specific instrument that measures the concerns of patients with prostate cancer.

  The FACT-P will be assessed 3 days prior to the first study treatment, on the first day of each cycle prior to treatment administration, at the EOT and every 12 weeks during the follow-up period until disease progression, the start of another anticancer therapy or study cut off, whichever comes first.

  The FACT-P consists of the FACT-G 4 general/core domains/subscales (11) plus 1 prostate specific domain/subscale (12).

  Each item is rated on a 0 to 4 Likert type scale (0 = Not at all, 1 = A little bit, 2 = Somewhat, 3 = Quite a bit, 4 = Very much).

The FACT-P is summed from 39 items to give a total score in the range of 0-156, where higher values represent better HRQL. To achieve this, the FACT-P scoring guide (Appendix C) identifies those items which must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from "4" (ie, 4 - item score). After reversing proper items, all subscale items are summed to a total, which is the subscale score.

The MCID has been proposed as the 'smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management' (13).

- The 5 subscales of the FACT-P with their corresponding MCID's are as follows (11):
  - physical well-being: 7 questions (Items GP1 to GP7); range 0-28, MCID = 3,
  - social/family well-being: 7 questions (Items GS1 to GS7): range = 0-28; MCID = 3,
  - emotional well-being: 6 questions (Items GE1 to GE6): range = 0-24; MCID = 3,
  - functional well-being: 7 questions (Items GF1 to GF7): range = 0-28; MCID = 3,
  - prostate-specific concerns: 12 questions (Items C2, C6, P1, P2, P3, P4, P5, P6, P7, BL2, P8 and BL5): range = 0-48; MCID = 3.

  Scoring details on the FACT-P can be found in Section 2.4.7.

  HRQL will be assessed using the FACT-P Total score which combines the PWB (7 items), SWB (7 items), EWB (6 items), FWB (7 items), and prostate cancer scale/prostate specific concerns (12 items).

  Additional HRQL summary scores include the FACT-G Total (PWB + SWB + EWB + FWB), the FACT-P TOI (PWB + FWB + PSC) and the Pain PCS (4 items, P1-P3, GP4).

- Health status will be evaluate using EuroQol Group 5-Dimension, 5-Level (EQ-5D-5L) questionnaire.

  The EQ-5D-5L is a standardized HRQL questionnaire that provides a simple, generic measure of health for clinical and economic appraisal (EuroQol 1990).

  The EQ-5D-5L will be evaluated within 3 days before Randomization, on the first day of each cycle prior to treatment administration, at the EOT Visit and every 12 weeks during the follow-up period until disease progression, start of another anticancer therapy or study cut-off, whichever comes first (see Appendix D).

  The EQ-5D-5L consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) is rated from 1 to 5 likert scale where 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems (14). A global utility index score will be calculated per EQ-5D utility index scoring in Section 2.4.7.

  The EQ VAS will record the respondent's self-rated health on a 20 cm vertical, VAS with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents

2.1.8 Health economic endpoints

Not applicable.

2.1.9 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapies after discontinuation of IMP include chemotherapy, hormonotherapy, gene therapy, immunotherapy, cryotherapy, biologicals, systemic radiation, surgery for prostate cancer etc. (see Section 2.4.8).

2.1.10 Other endpoints

Additional exploratory collaborative endpoints will be detailed in a dedicated separate SAP.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as patients with a date of screening visit and a signed informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used.

For patient study status, the total number of patients in each one of the following categories will be presented in the clinical study report using a summary table:

- Screened patients.
- Nonrandomized but treated patients.
- Randomized patients before protocol amendment.
- Randomized patients after protocol amendment.
- Randomized patients by stratification factors distribution:
  - ECOG PS (0-1 versus 2),
  - Time from AR targeted agent initiation to progression ([0; 6 months] versus]6; 12 months],
  - Timing of AR targeted agent (before versus after docetaxel).
- Distribution of randomized patients across the 8 level of strata combinations.
- Randomized but not treated patients.
- Randomized and treated patients.
- Patients still on treatment (ie, patients who did not discontinue study treatment).
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation.
- Status at last study contact.
- Main Reason for Stopping Study.

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group. In addition, all categories of randomized patients will be split by stratification factors.

Number of screened patients, randomized patients, treated patients and patients who discontinued study treatment will be displayed by country and by site.

A listing of other reason for permanent study treatment discontinuation will also be provided.

All critical or major deviations potentially impacting efficacy analyses, randomization and drug-dispensing irregularities and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group. Listings for critical or major deviations will be provided.

Additionally, the analyzed populations for safety and efficacy will be **summarized** in a table by number of patients on the randomized population.

Efficacy population: intent-to-treat (ITT) population and evaluable populations (see Section 2.3.1) and health related quality of life population and health status population (see Section 2.3.3).

Safety population: see Section 2.3.2.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

- A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice.

  OR

- A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a non-randomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Non randomized and treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IVRS transaction
Erroneous kit dispensation
Kit not available
Randomization by error
Patient randomized twice
Stratification error
Patient switched to another site

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population.

Patients allocated outside the IVRS/IWRS, who are dispensed at the first call study drug without calling the IRT or before calling the IRT, are considered nonrandomized patients. They are excluded from any population for analysis, including safety. However, if these patients experienced any significant safety event, they should be documented separately in the clinical study report.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately and these patients will not be in the safety population.

2.3.1 Efficacy populations

2.3.1.1 Intent–to-treat population

The primary efficacy analysis population will be the ITT population, as defined in the protocol.

The ITT population is the randomized population analyzed according to the treatment group allocated by randomization.

2.3.1.2 Per-protocol population

Not applicable.

2.3.1.3 Other efficacy population

The following evaluable patient populations are defined for some selected efficacy endpoints.

- Tumor response will be evaluated in patients with measurable disease at baseline (defined by the presence of at least one measurable target lesion at baseline), with at least one post baseline assessment.
- PSA response will be evaluated in patients with PSA level of at least 2 ng/mL at baseline, with at least two post-baseline assessments separated by at least 3 weeks.
- PSA response on first subsequent therapy (FST) will be evaluated in patients with PSA level of at least 2 ng/mL before the first further therapy intake, with at least one assessment during the first subsequent therapy administration (15).
- Duration of first subsequent therapy will be evaluated in patients with a FST.
- Pain response will be evaluated in patients using BPI-SF score and WHO Analgesic Ladder at baseline, with at least one post baseline assessment.

Those populations are subsets of the ITT population and patients are considered in the group "as randomized".

2.3.2 Safety population

This population includes all randomized patients who received at least one of the study drugs (CBZ, or Abiraterone or Enzalutamide). This population is for all safety analyses. All analyses using this population will be based on the treatment actually received (ie, "as treated").

In addition:

- Non randomized but treated patients will not be part of the safety population; however, their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized.
- For patients receiving more than one study treatment during the trial, patients will belong to the first treatment group and observation of AEs will be followed till 30 days of last dose of that treatment or start date of second treatment, whichever starts earlier.

2.3.3 Other analysis population (Health related Quality of Life and Health status population)

The health related quality of life population based on the ITT population, taking into account patients who have at least one evaluable subscale of FACT-P questionnaire at baseline and at least one post baseline evaluable FACT-P.

The health status population is based on the ITT population, taking into account patients who have at least one evaluable utility index of EQ-5D-5L at baseline and with at least one post-baseline evaluable EQ-5D-5L.

Those populations are a subset of the ITT population, and patients are considered in the group "as randomized".

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Standard demographic and baseline characteristics (including age), medical history, disease characteristics at baseline and prior anticancer therapy will be collected at baseline. Baseline efficacy variables, eg, tumor assessment, pain, PSA, and other prognostic variables will be assessed as well. Baseline value defined see Section 2.1.1.

Continuous data will be summarized using the number of available data, mean, standard deviation, median, Q1, Q3, minimum, maximum and missing data for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized on the ITT. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the ITT population for any treatment group.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

Medical and surgical history at baseline will be presented by descriptive statistics on patients of the safety population (number and percentage of patients having a given medical or surgical history).

2.4.2 Prior or concomitant medications (other than anticancer therapies)

The prior and concomitant medications will be presented for the ITT population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the Anatomical Therapeutic Chemical (ATC) (anatomic category) and the first three digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior, concomitant and post-treatment medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequencies regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and dose information will be assessed and summarized by actual treatment within the safety population (see Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of exposure will be assessed by the duration of exposure within the safety population.

The number of patients treated, number of cycles administered, duration of dosing (weeks), cumulative dose (mg/m²), dose intensity (mg/m²/week) and relative dose intensity (%) will be presented by treatment group.

Duration of exposure is defined as:

- Last dose date - first dose date + 21 days for cabazitaxel.
- Last dose date - first dose date + 1 day for abiraterone or enzalutamide.
  Regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data). The first and the last study administration is any dose of first and last administration of CBZ or AR-target agent (abiraterone or enzalutamide).

The overall extent of exposure will be assessed for each patient as by using Total number of cycles (K), determined by the longest duration of each individual drug.

The duration of treatment exposure (weeks) and number of cycles will also be provided for the two subsets of patients below:

- Patients without any first subsequent therapy, OR with a first subsequent therapy and without any PSA assessment during the first subsequent therapy.
- Patients with any first subsequent therapy and with evaluable PSA during the first subsequent therapy.

The average (%) of cycles with G-CSF prophylaxis during the whole treatment exposure and the number of patients receiving G-CSF as curative intent during treatment exposure n(%) will be summarized by treatment group.

If any G-CSF used as curative intent, number of patients with G-CSF used as curative for neutropenia (and/or neutrophil blood decrease) and number of patients with G-CSF used as curative for Febrile neutropenia or neutropenic infection will be summarized by treatment group if at least 10% of safety population, otherwise a listing will be provided.

For CBZ arm:

Dose information will be assessed by the following variables:

- The actual dose received (mg/m²) by cycle is defined as (actual dose [mg] collected in the CRF/BSA [m²]).
- Cumulative dose (mg/m²): the cumulative dose for a time period (a given cycle or during the study) is the sum of all “actual” doses received during this time period.
- Overall duration of dosing (weeks) is defined as (last IMP administration - first IMP administration + 21)/7.
- The actual dose intensity (ADI) (mg/m²/3 weeks) is defined as the cumulative dose during the study divided by overall duration of dosing multiplied by 3.

- The relative dose intensity (RDI) (%) is defined as the ratio of the ADI to the planned dose intensity. The planned dose intensity (mg/m²/3 weeks) is defined as (theoretical dose of 25 mg/m² x number of cycles x 3 / overall duration of dosing).
- Dose reduction: a patient with dose reduction is defined as a patient received less than about 80% of the original planned study drug dose level at any administration of any cycle. Dose reduction event at a cycle will be derived by using the definition provided in Table 6. The original planned study drug dose level is taken from the planned dose level at Cycle 1 and will be compared with actual received dose for dose reduction event at Cycle 1. For the second and subsequent cycles, a dose is deemed to have been reduced if the dose level a patient receives is lower than the previous actual dose level.

There are two reductions allowed for CBZ.

Table 6 - Cabazitaxel dose reduction levels

Actual dose level	Corresponding dose level (mg/m²)	Dose limits
Over dose	>32.5	>32.5
Upper dose	NA	NA
Planned dose	25	≥21.25 to <32.5
Reduced dose Level 1	20	≥16 to <21.25
Reduced dose Level 2	15	≥12.75 to <16
Reduced dose Level 3	12	≥9.6 to <12.75
Low dose	<12	>0 to <9.6
No dose administered	0	0

- Dose delays: A cycle is deemed to have been delayed if (start date of the current cycle - start date of previous cycle) - 21>3 days.
- Dose interruption: if dose is interrupted for IP at a given cycle, multiple start time and end time will be reported in the case report form.

Number of patients receiving G-CSF as prophylaxis during the 3 first cycles and at all cycles [n(%)] will be summarized. The actual dose received, the cumulative dose, the overall duration of dosing, the actual dose intensity and the relative dose intensity will be summarized descriptively (number, mean, standard deviation, median, Q1, Q3, minimum, maximum and missing data) while the dose reduction (respectively delay) will be described by occurrences' number and the number of patients with at least one dose reduction (respectively delay) during the study.

For comparator arm:

Dose information will be assessed for each treatment Abiraterone and Enzalutamide and the pool both by the following variables:

- Total intended dose is the sum of intended daily dose during the treatment intake period.
- Average actual dose received (mg) per cycle during the whole treatment period.

- Total number of patients with at least one dose reduction, a patient with dose reduction is defined as a patient received less than about 80% of the original planned study drug dose level at any administration of any cycle. Dose reduction event at a cycle will be derived by using the definition provided in Table 7. The original planned study drug dose level is taken from the planned dose level at Cycle 1 and will be compared with actual received dose for dose reduction event at Cycle 1. For the second and subsequent cycles, a dose is deemed to have been reduced if the dose level a patient receives is lower than the previous actual dose level.

  Quantitative parameters will be summarized descriptively (number, mean, standard deviation, median, Q1, Q3, minimum, maximum and missing data).

Table 7 - Abiraterone / Enzalutamide dose reduction levels

AR-target therapy	Initial daily dose mg (tablets/capsules)	Initial dose per cycle mg (tablets/capsules)	Dose reduction 1 mg (tablets/capsules)	Dose reduction 2 mg (tablets/capsules)
Abiraterone	1000 (4 tablets - 250 mg)	21000 (84)	<16750 (<67 tablets)	<13250 (<53 tablets)
(or) Abiraterone	1000 (2 tablets -500 mg)	21000 (42)	<16500 (<33 tablets)	<13000 (<26 tablets)
Enzalutamide	160 (4 capsules)	3360 (84)	<2680 (<67 capsules)	<2120 (<53 capsules)

- Total number of dose reduction.
- Summary of Prednisone/prednisolone will also be given. Details on the average per cycle, of number of days taken and number of days not taken.

2.4.3.2 Compliance

Dose information will be assessed for AR-targeted agent and specifically within AR-targeted agent (ie, AR-targeted agent [abiraterone or enzalutamide], abiraterone and enzalutamide) by the following variables:

- Compliance is defined as the total actual dose divided by the total intended dose.
  The summaries will consist of the number and percentage of patients in each class of compliance, starting at ≤75% to a maximum of 100% in increments of 5%, and summarized as quantitative as well.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

Analyses of the primary efficacy endpoint will be performed on the ITT population.

2.4.4.1.1 Primary analysis

The primary analysis will consist of rPFS comparison between Abiraterone acetate or Enzalutamide group and CBZ group through a 2-sided 5% log rank test procedure stratified by the stratification factors recorded at randomization:

Eastern Cooperative Oncology Group performance status (0-1 versus 2), time from AR targeted agent initiation to progression ([0; 6 months] versus [6; 12 months]), timing of AR targeted agent (before versus after docetaxel).

When applicable, for all efficacy endpoints, if some strata event rates are too low, we might have to consider to pool some strata with others strata in a blinded way depending rPFS events distribution within strata, this will be determined before database lock.

If radiological progression or death is not observed during the study, data on rPFS will be censored at the last valid tumor assessment or at the cut-off date (see Section 1.1), whichever comes first.

The survival curves will be estimated using Kaplan-Meier estimates. Median survival times and associated 95% CIs will also be provided by treatment arm.

Reasons for censoring will be summarized by treatment arm, if any lost to follow up, Time from last contact to cutoff date (months) will be summarized.

Date of last valid tumor assessment:

If several scans are performed at different dates for a given tumor evaluation reported on the eCRF, the date of the last valid tumor assessment is the date of latest scan. A patient without event (death or progression) and without any valid post baseline tumor assessment will be censored for PFS on the day of randomization (Day 1).

Non evaluable cases:

Missing scans: if one lesion is not evaluated/missing for a given tumor assessment, the OR should generally be NE unless there is clear evidence of progression (independently of the missing lesion). For the primary analysis of rPFS, progression or death occurring after a tumor evaluation with an OR equal to NE will be considered as an event in the analysis.

2.4.4.1.2 Secondary analyses

The primary efficacy endpoint will also be analyzed as follows:

The survival curves will be estimated using Kaplan-Meier estimates and Median survival times and associated 95% CIs will also be provided by treatment arm for the following analyses:

- Further anticancer treatments after stop of investigational product are very common. Patients on the CBZ group are likely to receive AR-targeted agent treatment that could be confounded with the treatment effect of CBZ. Patients on the AR-targeted agent group are also likely to receive CBZ treatment that could be confounded with the treatment effect of AR-targeted agent. A time-dependent variable (time-to the first post-study treatment anticancer therapy from randomization) will be added in the Cox hazard proportional model stratified by the stratification factor at randomization to check its impact on rPFS.

  Moreover if radiological progression or death is not observed during the study, data on rPFS will be censored at the last valid tumor assessment or the start date of another anti-cancer therapy, or at the cut-off date (see Section 1.1), whichever comes first.
- Within each stratification factor level, the treatment effect hazard ratio (HR) and its (1-α)% confidence intervals (CI) will be estimated using a Cox Proportional Hazard model stratified by the same stratification factors as those used for primary analyses,
  PH assumption will be checked. For each stratification factor level and for the overall population, HRs and (1-α)% CI will be displayed using forest plots.

If radiological progression or death is not observed during the study, data on rPFS will be censored at the last valid tumor assessment or the start date of another anti-cancer therapy, or at the cut-off date (see Section 1.1), whichever comes first.

- Subgroup analyses of rPFS:

  The consistency of the treatment effect on rPFS will be evaluated with respect to stratification and prognostic factors as defined in Table 8.

  For each parameter, a Cox Proportional Hazard Model will be used for the overall population, including the parameter and all or others stratification factors (if subgroup analyses made by stratification factor subgroups), treatment effect and the treatment by parameter interaction (only pvalue for the interaction term will be provided for descriptive purpose only).

  In addition, Kaplan-Meier curves of rPFS and summary statistics showing number of patients, number (%) of rPFS, median rPFS and (1-α)% confidence limits may be provided for each treatment arm in previously selected subgroups defined by the stratification /prognostic factors.

  Within each selected subgroup, the treatment effect hazard ratio and its (1-α)% confidence intervals will be estimated using a Cox Proportional Hazard model on patients of this subgroup. For each subgroup and for the overall population, hazard ratios and (1-α)% will be displayed using forest plots for the following stratification and prognostic factors defined in the Table 8.

Table 8 - Potential Stratification/Prognostic factors

Stratification factor	Description (coding)
ECOG performance status	0, 1 (ref) vs 2
Time to progression with AR targeted agent	[0 ; 6 months] (ref) vs]6 ; 12 months]
Timing of AR targeted agent	Before (ref) vs after docetaxel
Prognostic factor	**Description (coding)**
Duration of first ADT	<12 months (ref) vs ≥12 months
Neutrophils to Lymphocyte Ratio (NLR)[a]	<median (ref) vs ≥median
Neutrophil count	<median (ref) vs ≥median
Age (years)	<70 (ref) vs ≥70 years
Visceral mets[a] (see Table 5)	Yes vs No (ref)
Gleason 8-10 at diagnosis	Yes vs No (ref)
Prior therapy with curative intent (radical prostatectomy or radiation therapy of prostate) for localized disease (TNM staging Localized, Locally advanced or Node-positive)	Yes (ref) vs No
M1 disease at diagnosis	Yes vs No (ref)

Stratification factor	Description (coding)
Type of progression at randomization	PSA only (no radiological, no pain) (ref) vs Radiological (± rising PSA), no pain AND Pain (± radiological, ± rising PSA) vs PSA only (no radiological, no pain) (ref)
Hemoglobin[a] at randomization	<median (ref) vs ≥median
Alkaline phosphatase[a] at randomization	<median (ref) vs ≥median
LDH[a] at randomization	<median (ref) vs ≥median
Testosterone at randomization	<median (ref) vs ≥median
PSA value (log 10) at randomization[a]	<median (ref) vs ≥median

a Last available measure before randomization

2.4.4.1.3 Sensitivity analysis

Finally, the two arms will also be compared using a 2-sided 5% stratified log-rank test when considering the non-compliance tumor assessment evaluation below.

Data on rPFS will be censored:

- At the last valid tumor assessment if documented radiological progression or death occurs more than 18* weeks after the last valid tumor assessment without progression.
  And
- At the start of further anticancer therapy if patients do not have a PD documented before start of further anticancer therapies.
- Or at the cut-off date (see Section 1.1), whichever comes first.

  *The 18-week threshold corresponds to 1.5 the time interval between two tumor assessments (every 12 weeks), as defined in the protocol.

2.4.4.2 Analyses of secondary efficacy endpoints

Unless otherwise stated, secondary efficacy endpoints defined in Section 2.1.3.2 will be analyzed on the ITT population.

2.4.4.2.1 Primary analyses for secondary endpoints

Time to event endpoints (OS, PFS) will be compared between treatment arms a 2-sided 5% log rank test procedure stratified by the stratification factors recorded at randomization.

The survival curves will be estimated using Kaplan-Meier estimates.

The estimates of the HR and corresponding 95% CI will be provided using a Cox proportional hazard model stratified by the same stratification factors as those used for the log-rank test described above, PH assumption will be checked. Median times and associated 95% CIs will also be provided by treatment arm using a forest plot.

For both OS and PFS, reasons for censoring will be summarized by treatment arm.

Categorical data (Objective tumor and PSA responses rates) will be summarized using number and percentage of patients by treatment with their 95% CI estimated by Normal approximation (patients with missing data will not be included in the percentage calculation). The two arms will be compared using Cochran-Mantel-Haenszel chi-square test stratified by stratification factors at the randomization. Objective tumor response and PSA will be analyzed on their respective evaluable population, taking into account assessments made during the on-treatment period, ie, until starts of first subsequent therapy.

A waterfall plot of PSA response at Cycle 2 Day 1, at 12 weeks and best PSA response at any time during treatment exposure will be provided.

2.4.4.2.2 Others analysis for others secondary endpoints

Time to event endpoints (TTPP, duration of tumor response, times to pain progression, time to occurrence of SSE) will be summarized by treatment arms.

Median times and associated 95% CIs will also be provided by treatment.

If no event for TTPP is observed, patients will be censored at the last valid tumor assessment (meaning with OR equal to CR/PR/SD but not NE) date (whatever the start or not another anti-cancer therapy) or the study cutoff date, whichever is first.

In the absence of skeletal-related events, events will be censored at the last assessment (physical exam) in the study. Patients with no such assessment on-study will be censored at randomization.

If no pain palliation/progression is observed during the study, data on pain palliation/progression will be censored at the last pain evaluation date.

If no symptomatic deterioration is observed during the study, data on decision of the clinical progression will be censored at the last assessment (physical exam) in the study or the study cutoff date, whichever is first.

For all, reasons for censoring will be summarized by treatment arm.

Continuous data will be summarized using the number of available data, mean, standard deviation, median, Q1, Q3, minimum, maximum and missing data for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group (patients with missing data will not be included in the percentage calculation).

Time to PSA Progression (PSA), tumor response, pain and SSE endpoints will be analyzed on their respective evaluable population.

2.4.4.3 Multiplicity issues

2.4.4.3.1 Primary endpoint

Not applicable for primary endpoint (16).

2.4.4.3.2 Main secondary endpoints

To control the type I error, a hierarchical step-down testing procedure (17) is applied.

Only if a significant difference in the rPFS of Abiraterone acetate or Enzalutamide group and CBZ has been demonstrated for the primary endpoint, the testing procedure is performed confirmatory to test the following main secondary efficacy endpoints by prioritized order (OS, PFS, PSA responses rates and Objective tumor response). The tests will stop as soon as an endpoint is found not statistically significant at two-sided α=0.05 level.

2.4.4.3.3 Other secondary endpoint

No multiplicity adjustment is made on other secondary and exploratory efficacy variables than those mentioned above.

2.4.4.4 Additional efficacy analysis(es)

Not applicable.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group and specifically within AR-targeted agent (ie, CBZ, AR-targeted agent [Abiraterone or Enzalutamide], Abiraterone and Enzalutamide).

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately.
- The baseline value is defined as the last value or measurement taken up to the first dose in the study.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.
- Selected safety analyses will be summarized by age or any pertinent subgroups (Age at inclusion (<65, [65-75 [or ≥75), ECOG at inclusion ([0; 1], ≥2), Number of prior chemotherapy lines ([0, 1]; >1 lines).

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAEs. Pretreatment and post-treatment AEs will be described separately.

If an AE date/time of onset (occurrence, worsening or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pretreatment, treatment-emergent or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of AEs with missing or partial onset dates are provided in Section 2.5.3.

The grade and cycle will be taken into account in the summary. For patients with multiple occurrences of the same event, the maximum grade is used. The denominator used for the summary by cycle is the total number of cycles administered in a treatment group. For a given event, a patient contributes one to the numerator for each cycle in which an episode occurred. An episode occurs during a cycle if the date of onset is on or after the first day of the cycle but prior to the first day of the next cycle.

Sorting within tables ensures the same presentation for the set of all AEs within the observation period (pretreatment, treatment-emergent and post-treatment). For that purpose, the table of all TEAEs will present the number (n) and percentage (%) of patients experiencing an AE by SOC (sorted by internationally agreed order), HLGT, HLT and PT (sorted in alphabetical order) for each treatment group.

All tables below are applicable by adding worst NCI grade in the selection.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE,
  - Grade 3-4 TEAE,
  - Grade 3-4 related TEAE,
  - Serious TEAE,
  - Serious related TEAE,
  - TEAE leading to death (fatal outcome),
  - TEAE leading to permanent treatment discontinuation.

The same overview will be provided by patient/cycle (except fatal outcome and permanent treatment discontinuation).

- All TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of patients with at least one TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.

- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least one TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- Summary of common TEAEs will also be provided by demographic factors including: age categories (<65, [65-75 [or ≥75) and subgroups of interest if appropriate.
- All TEAEs regardless of relationship and related to IMP, by primary SOC, HLGT, HLT and PT.
- All TEAEs related to IMP, by primary SOC, HLGT, HLT and PT.

Analysis of all treatment emergent serious adverse event(s)

- All serious TEAEs by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least one serious TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.
- All serious TEAEs regardless of relationship and related to IMP, by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least one serious TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.

Analysis of all treatment emergent non-serious adverse event(s)

- All non-serious TEAEs by primary SOC, HLGT, HLT and PT, using the threshold of ≥5%, showing the number (%) of patients with at least one serious TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.

Analysis of all treatment-emergent adverse event(s) leading to dose modification

- All TEAEs leading to dose modification, by primary SOC and PT (worst grade by patient), showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to dose reduction, by primary SOC and PT (worst grade by patient), showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to dose interruption, by primary SOC and PT (worst grade by patient), showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to dose delay , by primary SOC and PT (worst grade by patient), showing the number (%) of patients, sorted by the sorting order defined above.

Analysis of adverse events with pre-specified monitoring AEs (overdose):

- All treatment emergent of pre-specified monitoring AEs, by PT, showing number (%) of patients, sorted by decreasing incidence of PT will be presented.

Analysis of pretreatment and post-treatment adverse events

- All pre-treatment AEs by primary SOC and PT (worst grade by patient), showing the number (%) of patients with at least one pretreatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All pre-treatment AEs leading to study discontinuation by primary SOC and PT (worst grade by patient), showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All post-treatment AEs by primary SOC and PT (worst grade by patient), showing the number (%) of patients with at least one post-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All post-treatment SAEs by primary SOC and PT (worst grade by patient), showing the number (%) of patients with at least one post-treatment SAE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population:

- Number (%) of patients who died by study period (on-study, on-treatment, post-study) and cause of death.
- TEAEs leading to death by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT and PT presented in alphabetical order within each SOC.
- All TEAEs leading to death and related TEAEs leading to death will be also summarized in one table. This table will include a tabular summary of all TEAEs leading to death with a column for the related TEAEs leading to death.
- All pre-treatment AEs leading to death by primary SOC and PT, showing number (%) of patients, sorted by SOC internationally agreed order and decreasing incidence of PTs within SOC.
- All post-treatment AEs leading to death by primary SOC and PT, showing number (%) of patients, sorted by SOC internationally agreed order and decreasing incidence of PTs within SOC.

Furthermore a listing of deaths in non-randomized patients or randomized but not treated patients.

2.4.5.3 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum, maximum and missing data) of vital signs variables (raw values and changes from baseline) will be calculated for each cycle by treatment group for weight, systolic and diastolic blood pressure and heart rate. For ECOG PS, a shift table will be provided for the last and worst evaluations respectively relative to baseline.

2.4.5.4 Analyses of electrocardiogram variables

Interpretation of ECG will be described at the screening and EoT (if available) visits by treatment group. The frequency will be presented on ECG parameter: Normal vs Abnormal using a shift table that will be provided for the EoT evaluation respectively relative to baseline.

2.4.5.5 Analyses of other safety endpoints (laboratory variables)

All laboratory toxicities will be summarized by treatment group and specifically within AR-targeted agent (ie, CBZ, AR-targeted agent [abiraterone or enzalutamide], abiraterone and enzalutamide).

Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI CTCAE (Version 4.0) using the standards lower and upper ranges defined by the sponsor when exist (see Appendix H) whatever they have been collected or not in the eCRF. For AST, ALT, Bilirubin, Alkaline phosphatase, LDH and creatinine the lower and/or upper ranges when collected in the eCRF will be used.

In addition to creatinine levels, estimations of the renal function will be made by calculating the glomerular filtration rate (GFR) using the abbreviated Modification of Diet in Renal Disease (aMDRD) formula if the creatinine at baseline is 1.0-1.5 x ULN:

$$GFR(mL/min/1.73m^2) = k \times 186 \times [SCR]^{-1.154} \times [age]^{-0.203}$$
with k=1 (men) and SCR=Serum creatinine

CrCl categories (≥90, [60 to 90[, [45 to 60[, [30 to 45[and, [15 to 30[, <15 mL/min/1.73m²) and number of patients with renal function abnormalities on Creatinine clearance will be splitted and provided for both, when creatinine ≤1 x ULN and when creatinine >1 x ULN.

Hematological and biochemistry toxicities will be assessed from laboratory parameters. Worst NCI CTCAE grades, whenever applicable will be calculated according to the NCI common terminology criteria.

The number of patients with abnormal laboratory tests at baseline (all grades, Grade 1, Grade 2, Grade 3 and Grade 4) will be presented by grade. The frequency of patients in each grade (all grades, Grade 1, Grade 2, Grade 3 and Grade 4) of laboratory tests during treatment will be summarized. For patients with multiple occurrences of the same laboratory variable during the treatment, the maximum grade (worst) per patient will be used. When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade 3-4 abnormal laboratory tests.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

Not applicable.

2.4.7 Analyses of quality of life/health economics variables

2.4.7.1 Health-Related Quality of Life

HRQL analysis will be performed on the HRQL population.

The FACT-P is summed to give a FACT-P total score in the range of 0-156, where higher values represent better HRQL (18).

To achieve this, the FACT-P scoring guide (see Appendix C) identifies those items which must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from "4" (ie, 4 - Item score). After reversing proper items, all subscale items are summed to a total, which is the subscale score (18).

Handling missing items is detailed in Section 2.5.3.

For all FACT-G see Appendix C - Scoring guide and FACT-P subscale scores and symptom indices, the higher the score the better the HRQL.

The FACT-P total score is calculated as the sum of the un-weighted subscale scores and is evaluable when more than 80% of the items are answered (eg, at least 22 of 27 FACT-G items completed, at least 21 of 26 TOI items completed). This is not to be confused with individual subscale item response rates, which allows a subscale score to be prorated for missing items if greater than 50% of items are answered. Additionally a subscale score should be completed if the component subscales have valid scores.

Analyses by cycles will be done up to the cycle (or follow-up visit) for which at least 20% of HRQL population will be reached in each treatment group, end-of treatment summary will be provided anyway.

Descriptive summary of the FACT-P evaluable scores (each subscale score from a domain, FACT-G, TOI, Pain PCS and total FACT-P scores will be calculated) for each visit and change from baseline at each visit will be provided.

The comparison of change from baseline on health-related quality-of-life scores (FACT-P total scores, subscale scores, summary measure scores: TOI and FACT-G total score and Pain PCS) between treatment arms will be performed by using MIXED linear repeated measures model where treatment is a fixed effect variable and subject is a random effect variable. The baseline stratification variables will be included in the model as covariates as well as the interaction treatment*visit. The least square means by treatment group with their 95% CIs obtained from mixed model will be presented graphically. These analyses will be conduct up to the cycle (or follow-up visit) for which at least 20% of HRQL population will be reached in each treatment group, and will include the end-of treatment visit.

The "robust" empirical estimator will be used to estimate the covariance structure for the estimator of model parameters. Compound symmetry will be the assumed covariance structure based on periods for the error terms.

The HRQL secondary analysis will include 4 main FACT-P responder analyses:

For those who improve and for those who deteriorate across 5 categories of FACT-P scales/summary scores (1. FACT-P total; 2. FACT-P subscales summary scale; 3. Pain PCS and 4. FACT-G and FACT TOI). These analyses are based on the MIDs for the FACT-P. The MIDS for each scale and summary score of the FACT-P can be found in Appendix C.

The first responder analysis is for the FACT-P total score responders.

- Improvement in ***FACT-P total scores*** is defined as an increase of ≥10-points in FACT-P total scores from baseline on 2 consecutive evaluations ≥3 weeks apart during on-treatment period.
- Deterioration in ***FACT-P total scores*** is defined as a decrease of ≥10-points in FACT-P total scores from baseline on 2 consecutive evaluations ≥3 weeks apart during on-treatment period.

The 2nd responder analysis is for the physical, social, emotional, and functional well-being (*PWB, SWB, EWB and FWB*) *scales* responders.

- Improvement in ***PWB, SWB, EWB and FWB scales*** is defined as an increase of ≥3 points in FACT-P *PWB, SWB, EWB, FWB subscale scores* from baseline on 2 consecutive evaluations ≥3 weeks apart.
- Deterioration in PWB, SWB, EWB and FWB scales scores is defined as a decrease of ≥3 points in FACT-P PWB, SWB, EWB, FWB subscales scores from baseline on 2 consecutive evaluations ≥3 weeks apart.

The 3rd responder analysis is for Pain PCS summary score responders.

- Improvement in Pain *PCS summary score* is defined as an increase ≥2 points from baseline in Pain PCS scores observed at 2 consecutive evaluations ≥3 weeks apart.
- Deterioration Pain PCS summary score is defined as a decrease of at least 2 points from baseline Pain PCS scores observed at 2 consecutive evaluations ≥3 weeks apart.

The fourth and final responder analysis is for the ***FACT-G Total*** and ***FACT-P TOI responders.***

- Improvement in *FACT-G Total* and *FACT-P TOI scores* is defined as an increase of ≥9 points from baseline in the FACT-G Total and the FACT-P TOI summary scores observed at 2 consecutive evaluations ≥3 weeks apart.
- Deterioration in FACT-G Total and FACT-P TOI summary scores is defined as a decrease of ≥9 points from baseline in the FACT-G Total and the FACT-P TOI summary scores observed at 2 consecutive evaluations ≥3 weeks apart.

For all four types of responder analyses the response rate during on-treatment will be descriptively summarized up to the cycle (or follow-up visit) for which at least 20% of HRQL population will be reached in each treatment group, end-of treatment summary will be provided anyway.

The time to definitive deterioration (in months), will be analyzed by using a Cox proportional hazard model adjusted for the stratification factors. HRs and corresponding 95% confidence intervals will be provided. Kaplan-Meier estimates and the log-rank test will be performed if appropriate.

Deterioration was considered to be definitive if there was no subsequent improvement above the defined threshold before further anticancer therapy was administered. If a definitive deterioration was observed after a scheduled visit with a missing value, it was assumed that the deterioration occurred at the time of the missing value.

Death was considered an event in the absence of definitive deterioration if it occurred within 30 days of the last assessment. Otherwise, the patient was considered lost to follow-up and censored at the date of last assessment. Patients receiving further antitumor therapy before definitive deterioration were censored at the date of their last assessment before therapy.

2.4.7.2 Health status

EQ-5D analysis will be performed on the health status population. Analyses by cycles will be done up to the cycle (or follow-up visit) for which at least 20% of health status population will be reached in each treatment group, end-of treatment summary will be provided anyway.

Each dimension of EQ-5D-5L will be summarized at each visit using number and percentage of patients by treatment (patients with missing data will not be included in the percentage calculation).

The comparison of change from baseline on health-related quality-of-life scores EQ-5D-5L utility index scores and EQ-5D-5L VAS between treatment arms will be performed by using MIXED linear repeated measures model where treatment is a fixed effect variable and subject is a random effect variable. The baseline stratification variables will be included in the model as covariates. The least square means by treatment group with their 95% CIs obtained from mixed model will be presented graphically. These analyses will be conduct up to the cycle (or follow-up visit) for which at least 20% of health status population will be reached in each treatment group, and will include the end-of treatment visit.

Change from baseline to each visit will also be provided. For qualitative parameters (each dimension of EQ-5D-5L) change will be assessed in terms of number of patient with worsening, no change and improvement.

EQ-5D-5L VAS and utility index score will be summarized using the number of available data, mean, standard deviation, median, Q1, Q3, minimum, maximum and missing data by treatment at each visit as well as change from baseline to each visit.

EQ VAS score at each time points will be described graphically by treatment groups. Mean value of Index utility score and corresponding 95% CIs will also be described graphically by treatment groups for each time points. Those graphical approach will be done up to the cycle (or follow-up visit) for which at least 20% of health status population will be reached in each treatment group, and will include the end-of treatment visit.

The utility index will be derived according to Euroqol specific country algorithms provided to the Sponsor. In case a specific country algorithm is missing the value sets based on the UK population will be used to generate health utility scores.

The MID which will be used for the EQ-5D-5L utility index is .14 while the MID which will be used for the VAS is 11 (19).

2.4.8 Further anti-cancer therapy after discontinuation of investigational medicinal product administration during the study

A summary table will be provided for further therapies based on WHO-DD coding. Similar analysis will be performed for further RT and further surgery.

Time to subsequent therapy for prostate cancer defined as time interval from the date of randomization to the date of initiation of subsequent therapy for prostate cancer. Patients who have no subsequent therapy at the time of the analysis will be censored at the last known alive date

The type of post-study treatment will be described by treatment group.

All analyses below will be performed by type of subsequent therapy.

Descriptive statistics (or listing if relevant) for reason for discontinuation and best response will be provided based on population of patients with further anticancer therapy.

The PSA response during the first subsequent therapy will be calculated using the last PSA assessment before the start of the further therapy as baseline value (if enough patients to be considered).

A waterfall plot will be provided for best PSA change by treatment group and type of subsequent therapy.

Duration of subsequent therapy will be summarized on the ITT population with any first subsequent therapy.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computations of parameters.

Demographic formulas

Age (years) = Integer [(Date of screening visit - Date of birth)/365.25]

In case of missing data apply these rules:

- Missing Day: assume = 15.
- Missing Month: assume = 6.
- Missing Year: calculations cannot be done.

In case of incomplete dates, see Section 2.5.3.

$$BSA\ (m^2) = 0.007184 \times Height\ (cm)^{0.725} \times Weight\ (kg)^{0.425}$$

(the variation of DuBois and DuBois formula),

Time between diagnosis and screening (months) = [(Date of screening visit - Date of initial diagnosis to be confirmed)/30.4375],

Time to event (months) = [(Date of event or censure - Date of randomization)/30.4375].

Tumor markers

Nadir value of PSA is defined as the lowest value of PSA from baseline.

Laboratory data

Conversion of laboratory data from used units to international units will be done, if necessary (see Appendix F) containing conversion factors for all parameters mentioned in this SAP.

The NCI CTCAE grade of laboratory data will be calculated using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and upper limit of normal (ULN) and lower limit of normal (LLN) (20). The standards lower and upper ranges defined by the sponsor when exist (see Appendix H) whatever they have been collected or not in the eCRF will be used.

For AST, ALT, Bilirubin, Alkaline phosphatase, LDH and creatinine the lower and upper ranges collected in the eCRF will be used.

For all WBC laboratory parameters, when expressed in %, and when possible (ie, if WBC is not missing and expressed in Giga/l) then laboratory parameters expressed in % will be derived and expressed in Giga/l as well using the formula below:

Laboratory parameter(Giga/L)= Laboratory parameters (%)*WBC (Giga/l).

Tumor response

See Appendix B.

WHO analgesic score

The WHO analgesic score will be derived from the pre-treatment and the on-treatment medications mentioned in the CRF using the 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).
The correspondence between the medications and the scale will be classified appropriately according to the Appendix E (21).

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the last cycle performed. If this date is missing, the exposure duration should be left as missing.

The last dose administration should be clearly identified in the CRF and should not be approximated by the last returned package date.

Handling of CRPC and/or mCRPC missing/partial dates

For Age at prostate cancer diagnosis, age at metastatic disease and age at mCRPC diagnosis, when date of birth is missing, the age at randomization will be used for the derivation.

If dates are partially missing, the missing day will be imputed to 15 and the missing month will be imputed to June if imputed date are still consistent (mCRPC is after date of metastatic disease, except if there was a date for CRPC , and both prior histological diagnosis).

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered as a prior, concomitant and post-treatment medication.

When prior-therapy duration needed, if start date is partially missing then date should be imputed to the 15th day of the month, except if the end date is completed and the month and year are the same as the start date (then the day of the start date should be imputed to the 1st day of the month). If end date is partially missing then date should be imputed to the 1st day of the month, except if the month and year are the same as the start date in which case end date will be imputed to start date.

For the first ADT duration calculation [in month and <12 months vs ≥12 months)], when applicable if patient has an hormonotherapy ongoing at time of randomization, the end date of the first hormonotherapy will be the start date of the next therapy (another hormonotherapy or docetaxel or abiraterone or enzalutamide or radium 223).

For the consumption of analgesics at study entry, if not ongoing at randomization, and end date partially missing, if the end is the same month and year than randomization data then the treatment intake is considered to be taken within one week prior to randomization.

Handling of adverse events with missing or partial date of onset

Missing or partial AE onset dates will be imputed so that if the partial AE onset date information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent. No imputation of AE end dates will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date of AE resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all AEs that occurred on or after the day of randomization should be considered as TEAEs. The exposure duration should be kept as missing.

The last dose administration should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the AE considered as such in the frequency tables of possibly related AEs, but no imputation should be done at the data level.

Handling of missing severity/grades of adverse events

If the severity/grade is missing for one of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of missing dates for times calculations

Not applicable.

Handling of missing data for FACT-P

If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. When there are missing data, prorating by subscale is acceptable as long as more than 50% of the items in a domain were answered (eg, a minimum of 4 of 7 items, 4 of 6 items, 7 of 12 items, etc) (18).

This can be done by using the formula below:

Prorated subscale score = [Sum of item scores] x [N of items in subscale] ÷ [N of items answered].

2.5.4 Windows for time points

Summaries by cycle focusing on AEs, exposure and tumor assessments will be tabulated based on cycles as recorded in the CRF.

No time windows will be defined except for blood chemistry performed at D8 and D15 during the 3 first cycles for which 1 day window is allowed.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs and ECG will be used for computation of baseline and worst values and/or grades.

2.5.6 Pooling of centers for statistical analyses

Each parameter will be described globally pooling all centers of all countries.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

The study is event driven and the cut-off date will be when 196 rPFS events have occurred. The end of clinical trial will be last patient last visit.

So the main database lock will be driven by the cutoff date and the final DBL driven by the LPLV, likely to occur in Q3-2019.

The final database is planned to be locked at 30 days after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS Version 9.2.

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7 LIST OF APPENDICES

Appendix A Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
rPFS	ITT	A 2-sided 5% log-rank test stratified by the stratification factors. Survival curves using Kaplan-Meier estimates.	Yes HR estimation using Cox proportional hazard model stratified by stratification factors and its 95% CI with time-dependent variable. HR estimation within each stratification factor using Cox proportional hazard model by each stratification factors and its 95% CI and forest plot. A 2-sided 5% stratified log-rank test considered the start date of another anti-cancer therapy. Survival curves using Kaplan-Meier estimates. Sensitivity analysis (Section 2.4.4.1.3) A 2-sided 5% stratified log-rank test when considering the non-compliance tumor assessment. Survival curves using Kaplan-Meier estimates evaluation.	Yes Subgroups analyses (Section 2.4.4.1.2) with respect to stratification factors, for each prognostics factors (mentioned in Table 8) that would be considered as subgroups. Forest plot for subgroup analyses.	

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Secondary endpoints					
OS	ITT	A 2-sided 5% log-rank test stratified by the stratification factors and survival curve.	Cox proportional hazard model stratified by stratification factors and forest plot.	No	No
PFS	ITT	A 2-sided 5% log-rank test stratified by the stratification factors and survival curve.	Cox proportional hazard model stratified by stratification factors and forest plot.	No	No
PSA response during study treatment	Concerned evaluable population	Number and percentage of patients by treatment and a CMH chi-square test stratified comparing the 2 arms.	Waterfall plots for PSA response at Cycle 2 Day 1, at 12 weeks abd best PSA response at any time during treatment exposure.	No	No
Tumor response	Concerned evaluable population	Number and percentage of patients by treatment and a CMH chi-square test stratified comparing the 2 arms.	No	No	No
TTPP	ITT	Summarized by treatment arm.	No	No	No
Duration of tumor response	ITT	Summarized by treatment arm.	No	No	No
Time to pain progression	Concerned evaluable population	Summarized by treatment arm.	No	No	No
Number of SSE	ITT	Number and percentage of patients with any SSE by treatment group (new symptomatic pathological fracture, use of external beam radiation to relieve bone pain, spinal cord compression, Tumor-related orthopaedic surgical intervention) and a chi-square test comparing the 2 arms (at baseline, each cycle, EOT and FUP visits) for each cycle and on the on treatment period.	No	No	No
Time to occurrence of SSE	ITT	Summarized by treatment arm.		No	No
PSA response during the first subsequent therapy	Concerned evaluable population	A 2-sided 5% log-rank test and Survival curves using Kaplan-Meier estimates.	A waterfall plot will be provided for best PSA change by treatment group and type of subsequent therapy.	No	No
Duration of first subsequent therapy	Concerned evaluable population	A 2-sided 5% log-rank test and Survival curves using Kaplan-Meier estimates.	No	No	No

SAFETY ANALYSES

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Adverse events	Safety	Follow safety guidelines.	No	No	No
Laboratory Data	Safety	Descriptive analysis at baseline and each cycle (worst value).	No	No	No
Vital Signs (except PS ECOG) PS ECOG	Safety	Descriptive analysis at each cycle (raw value and change from baseline). Value at baseline and worst post-baseline value during the study according to baseline value.	No	No	No
ECG	Safety	Descriptive analysis at baseline and EOT Visit if available according to baseline value.	No	No	No

QUALITY OF LIFE ANALYSES

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
FACT-P	Concerned evaluable population	Descriptive analyses at baseline, each cycle, EOT and follow-up visits and change from baseline (at each cycles, EOT and F-UP visits) for each subscales, TOI and total score. Change from baseline analyzed by a mixed linear repeated measures model with the stratification factors as covariates + graphical representation of LS means at each timepoints for TOI score and FACT-P total score.	Rate of responders by treatment group for deterioration and improvement for all 5 responders' classes (see Section 2.4.7).	No	Responder analyses: time to definitive deterioration of score by 3-points, 2-points, 9, or 10 (according to the sub-domains, sub-scores specific MID definition) points will be analyzed using Kaplan Meier results and Cox model adjusted on stratification factors.
EQ-5D-5L	Concerned evaluable population	Descriptive analyses at baseline, each cycle, EOT and follow-up visits for each dimension, VAS and Index utility index. The comparison of change from baseline on health-related quality-of-life scores EQ-5D-5L utility index scores and EQ-5D-5L VAS between treatment arms will be performed by using MIXED linear repeated measures model where treatment is a fixed effect variable and subject is a random effect variable. The baseline stratification variables will be included in the model as covariates. The least square means by treatment group with their 95% CIs obtained from mixed model will be presented graphically.	Change from baseline to each visit will also be provided. For qualitative parameters (each dimension of EQ-5D-5L) change will be assessed in terms of number of patient with worsening, no change and improvement. Graphical approach (up to the cycle for which at least 20% of the concerned evaluable population will be reached in the treatment group, End of treatment visit included, will be used for AQ-VAS and Index utility score description.	No	No

Appendix B Tumor response evaluation

Table 9 - Target lesions and non-target lesions evaluation

	Evaluation of target lesions	Evaluation of non-target lesions
CR	Disappearance of all TLs. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.	Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.	
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Although a clear progression of "non-trarget" lesions only is exceptionnal, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Table 10 - Time point response: patients with target (± non-target) disease

Target lesions	Non-Target lesions	New lesion(s)	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = Non evaluable.

With 35 days as the minimum number of days after study entry to confirm a SD cycle response not preceded by an evaluable assessment.

Table 11 - Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR).

Best response would depend on whether minimum duration for SD was met.

However, sometimes ‘CR’ may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix C FACT-P Scoring guidelines

FACT-P Scoring Guidelines (Version 4) – Page 1

Instructions:*
1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-P).
5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL WELL-BEING (PWB)	GP1	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
				Divide by number of items answered: _____	=PWB subscale score
SOCIAL/FAMILY WELL-BEING (SWB)	GS1	0	+	_____	=_____
	GS2	0	+	_____	=_____
	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
				Divide by number of items answered: _____	=SWB subscale score
EMOTIONAL WELL-BEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____
				Sum individual item scores: _____	
				Multiply by 6: _____	
				Divide by number of items answered: _____	=EWB subscale score
FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
				Divide by number of items answered: _____	=FWB subscale score

FACT-P scoring template 05.21.03

FACT-P Scoring Guidelines (Version 4) – Page 2

Subscale	Item Code	Reverse item?		Item response	Item Score
PROSTATE CANCER SUBSCALE (PCS)	C2	4	-	_____	=_____
	C6	0	+	_____	=_____
	P1	4	-	_____	=_____
	P2	4	-	_____	=_____
	P3	4	-	_____	=_____
Score range: 0-48	P4	0	+	_____	=_____
	P5	0	+	_____	=_____
	P6	4	-	_____	=_____
	P7	4	-	_____	=_____
	BL2	4	-	_____	=_____
	P8	4	-	_____	=_____
	BL5	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 12: _____
Divide by number of items answered: _____ =PC Subscale score

To derive a FACT-P Trial Outcome Index (TOI):
Score range: 0-104

_____ (PWB score) + _____ (FWB score) + _____ (PCS score) = _____ =FACT-P TOI

To Derive a FACT-G total score:
Score range: 0-108

_____ (PWB score) + _____ (SWB score) + _____ (EWB score) + _____ (FWB score) = _____ =FACT-G Total score

To Derive a FACT-P total score:
Score range: 0-156

_____ (PWB score) + _____ (SWB score) + _____ (EWB score) + _____ (FWB score) + _____ (PCS score) = _____ =FACT-P Total score

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

FACT-P scoring template 05.21.03

FACT-P Scoring Information and MIDs for each Scale and Summary Score

5 Scales 5 Summary Scores	# of items	Scoring range	MID
PWB	7	0-28	3
SWB	7	0-28	3
EWB	6	0-24	3
FWB	7	0-28	3
PCS	12	0-48	3
FACT-P Total	PWB + SWB + EWB + FWB + PCS	0-156	10
FACT-G Total	PWB + SWB + EWB + FWB	0-108	9
FACT-P TOI	PWB + FWB + PCS	0-104	9
PCS-Pain	4 items (P1, P2, P3, GP4)	0-16	2

Appendix D EQ-5D-5L user guide

https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Appendix E World Health Organization analgesic ladder for cancer pain

Analgesic medication has been classified as below:

- 0 (No analgesic).
- 1 (mild pain = non-opioid analgesics).
- 2 (mild to moderate pain = opioids for moderate pain).
- 3 (severe pain = opioids for severe pain).

WHO analgesic ladder step	Score on numerical rating scale	Analgesics of choice
1 (mild pain)	<3 out of 10	Paracetamol and NSAIDs
2 (mild to moderate pain)	3 to 6 out of 10	Weak opiods (eg codein or dihydrocoideine) plus paracetamol and NSAIDs;
3 (severe pain)	>6 out of 10	Strong opiods (eg, morphine, alfentanil, diamorphine, fentanyl, hydromorphone or oxycodone) plus paractemol and NSAIDs.

Table 12 - Analgesic treatment classification

0 (No analgesic)	1 (mild pain = non-opioid analgesics)	2 (mild to moderate pain = opioids for moderate pain)	3 (severe pain = opioids for severe pain)
ACETYLSALICYLIC ACID (if indication Other : used as anticoagulant)	ACETYLSALICYLIC ACID (if indication Adverse event)	CAFFEINE; CODEINE PHOSPHATE; PARACETAMOL	BUPRENORPHINE
AMITRIPTYLINE HYDROCHLORIDE	ACETYLSALICYLIC ACID; CAFFEINE; ORPHENADRINE CITRATE; PHENACETIN	CODEINE	BUPRENORPHINE HYDROCHLORIDE
CANNABIS SATIVA	ANTIINFLAMMATORY AGENTS, NON-STEROIDS	CODEINE PHOSPHATE HEMIHYDRATE; PARACETAMOL	FENTANYL
CAPSAICIN	ASCORBIC ACID; PARACETAMOL	CODEINE PHOSPHATE; DICLOFENAC SODIUM	FENTANYL CITRATE
CARBIDOPA; LEVODOPA	CAFFEINE; GUAIFENESIN; PARACETAMOL	CODEINE PHOSPHATE; PARACETAMOL	HYDROMORPHONE
DEXAMETHASONE	CAFFEINE; PAPAVER SOMNIFERUM LATEX; PARACETAMOL	CODEINE; PARACETAMOL	HYDROMORPHONE HYDROCHLORIDE
DEXAMETHASONE SODIUM PHOSPHATE	CAFFEINE; PARACETAMOL	DEXTROPROPOXYPHENE; METAMIZOLE MAGNESIUM	KETOBEMIDONE HYDROCHLORIDE
DOXEPIN	CAFFEINE; PARACETAMOL; PROPYPHENAZONE	DIHYDROCODEINE BITARTRATE	MORPHINE

0 (No analgesic)	1 (mild pain = non-opioid analgesics)	2 (mild to moderate pain = opioids for moderate pain)	3 (severe pain = opioids for severe pain)
DRONABINOL	CELECOXIB	LEVOMETHADONE	MORPHINE HYDROCHLORIDE
GABAPENTIN	DEXAMETHASONE; DICLOFENAC	LEVOMETHADONE HYDROCHLORIDE	MORPHINE SULFATE
HYOSCINE BUTYLBROMIDE	DEXIBUPROFEN	METHADONE HYDROCHLORIDE	MORPHINE SULFATE PENTAHYDRATE
LIDOCAINE	DEXKETOPROFEN	PARACETAMOL; TRAMADOL HYDROCHLORIDE	NALOXONE HYDROCHLORIDE; OXYCODONE HYDROCHLORIDE
MAGNESIUM SALICYLATE	DEXKETOPROFEN TROMETAMOL	TRAMADOL	NALOXONE HYDROCHLORIDE; TILIDINE HYDROCHLORIDE
MIDAZOLAM	DICLOFENAC	TRAMADOL HYDROCHLORIDE	OXYCODONE
NALOXONE	DICLOFENAC DIETHYLAMINE		OXYCODONE HYDROCHLORIDE
NALOXONE HYDROCHLORIDE	DICLOFENAC POTASSIUM		OXYCODONE HYDROCHLORIDE; PARACETAMOL
PREDNISOLONE	DICLOFENAC SODIUM		PIRITRAMIDE
PREDNISONE	DICLOFENAC SODIUM; ORPHENADRINE CITRATE		TAPENTADOL
PREGABALIN	ETORICOXIB		TAPENTADOL HYDROCHLORIDE
PROCHLORPERAZINE	IBUPROFEN		
TIZANIDINE HYDROCHLORIDE	KETOPROFEN		
	KETOPROFEN LYSINE		
	KETOROLAC		
	MEFENAMIC ACID		
	METAMIZOLE		
	METAMIZOLE MAGNESIUM		
	METAMIZOLE SODIUM		
	NAPROXEN		
	NEFOPAM		
	NEFOPAM HYDROCHLORIDE		
	NIMESULIDE		
	OXACEPROL		
	PARACETAMOL		

Appendix F GMA rfactor file

LBTESTCD	LBTEST	LBSPEC	CDISCID	LBORRESU	SI_FLAG	LBSTRESU	LBCONV	USSTRESU	USCONV	LBCAT
ALT	Alanine Aminotransferase		C64433	IU/L	X	IU/L	1	U/L	1	CHEMISTRY
ALB	Albumin	CEREBROSPINAL FLUID	C64431	g/L		mg/L	1000	g/dL	0,1	CHEMISTRY
ALP	Alkaline Phosphatase		C64432	IU/L	X	IU/L	1	U/L	1	CHEMISTRY
AST	Aspartate Aminotransferase		C64467	IU/L	X	IU/L	1	U/L	1	CHEMISTRY
BILI	Bilirubin	URINE	C38037	umol/L		mg/dL	0,0585	mg/dL	0,05847	
BUN	Blood Urea Nitrogen		C61019	mmol/L	X	mmol/L	1	mg/dL	2,8011205	CHEMISTRY
CA	Calcium		C64488	mmol/L	X	mmol/L	1	mg/dL	4	
CGA	Chromogranin A		C122108	nmol/L		ug/L	48,918	ng/mL	48,918	
CGA	Chromogranin A		C122108	ug/L	X	ug/L	1	ng/mL	1	
CREAT	Creatinine		C64547	umol/L		umol/L	1	mg/dL	0,0113122	CHEMISTRY
GLU	Glucose	PLASMA	C105585	mmol/L	X	mmol/L	1	mg/dL	18,014772	CHEMISTRY
HB	Hemoglobin		C64848	g/L	X	g/L	1	g/dL	0,1	HEMATOLOGY
LDH	Lactate Dehydrogenase		C64855	IU/L	X	IU/L	1	U/L	1	~~CHEMISTRY~~
MG	Magnesium		C64840	mmol/L	X	mmol/L	1	mg/dL	2,4307244	
PLAT	Platelets		C51951	10^9/L	X	10^9/L	1	10^3/uL	1	~~HEMATOLOGY~~
K	Potassium		C64853	mmol/L	X	mmol/L	1	mEq/L	1	CHEMISTRY
PROT	Protein	SERUM	C64858	g/L	X	g/L	1	g/dL	0,1	
NAUR	Sodium		C64809	mmol/L	X	mmol/L	1	mEq/L	1	~~CHEMISTRY~~
TESTO	Testosterone		C74793	ng/l		nmol/L	3,467	ng/dL	100	
UREA	Urea		C64815	mg/dL		mmol/L	0,1665	mg/dL	1	~~CHEMISTRY~~

LBTESTCD	LBTEST	LBSPEC	CDISCID	LBORRESU	SI_FLAG	LBSTRESU	LBCONV	USSTRESU	USCONV	LBCAT
UREA	Urea		C64815	umol/L		mmol/L	0,001	mg/dL	0,006006	CHEMISTRY
UREA	Urea		C64815	mmol/L	X	mmol/L	1	mg/dL	6,006006	CHEMISTRY
BASOLE	Basophils/Leukocytes		C64471	%	X	%	1	%	1	
EOSLE	Eosinophils/Leukocytes		C64604	%	X	%	1	%	1	
LYMLE	Lymphocytes/Leukocytes		C64820	%	X	%	1	%	1	
MONOLE	Monocytes/Leukocytes		C64824	%	X	%	1	%	1	
NEUTLE	Neutrophils/Leukocytes		C64827	%	X	%	1	%	1	

Appendix G Prior anti-cancer therapy type classification

LH-RH ANTAGONISTS		
cdgname	**termcd**	**termlbl**
CDG00005	014536	CETRORELIX
CDG00005	014536	CETRORELIX ACETATE
CDG00005	014536	CETRORELIX PAMOATE
CDG00005	014537	GANIRELIX
CDG00005	014537	GANIRELIX ACETATE
CDG00005	014795	ITURELIX
CDG00005	014812	ABARELIX
CDG00005	017648	DEGARELIX
CDG00005	017648	DEGARELIX ACETATE
CDG00005	022345	FOLLISTIM/ANTAGON
CDG00005	062979	ELAGOLIX
CDG00005	105696	FOLLITROPIN BETA; GANIRELIX

LH-RH AGONISTS		
cdgname	**termcd**	**termlbl**
CDG00006	901147	GONADOTROPIN RELEASING HORMONES AND ANALOGUES
CDG00006	901157	GONADOTROPIN RELEASING HORMONE ANALOGUES
CDG00006	004865	GONADORELIN
CDG00006	004865	GONADORELIN HYDROCHLORIDE
CDG00006	004865	GONADORELIN DIACETATE
CDG00006	004865	GONADORELIN DIACETATE TETRAHYDRATE
CDG00006	007269	LEUPRORELIN
CDG00006	007269	LEUPRORELIN ACETATE
CDG00006	007321	GOSERELIN
CDG00006	007321	GOSERELIN ACETATE
CDG00006	007716	BUSERELIN
CDG00006	007716	BUSERELIN ACETATE
CDG00006	009759	TRIPTORELIN
CDG00006	009759	TRIPTORELIN ACETATE
CDG00006	009759	TRIPTORELIN EMBONATE
CDG00006	009852	NAFARELIN
CDG00006	009852	NAFARELIN ACETATE
CDG00006	012465	HISTRELIN
CDG00006	012465	HISTRELIN ACETATE
CDG00006	017025	CASODEX W/ZOLADEX
CDG00006	018521	RELEFACT LH/RH/TRH
CDG00006	063648	ZOLACOS CP
CDG00006	067603	DESLORELIN
CDG00006	067603	DESLORELIN ACETATE
CDG00006	086980	LEUPRORELIN ACETATE W/NORETHISTERONE ACETATE
CDG00006	126257	LEUPRORELIN; NORETHISTERONE

ANTI-ANDROGEN HORMONAL

RECNO	SEQ1	SEQ2	ENGLISH_DR
000054	01	001	ACONCEN
002372	01	001	CYPROTERONE
002372	02	001	CYPROTERONE ACETATE
005419	01	001	DIANE
011161	01	001	CLIMEN /01116101/
012608	01	001	FEMILAR
071240	01	001	CYPROTERONE W/ETHINYLESTRADIOL
076934	01	001	CYPROTERONE W/ESTROGEN NOS
084315	01	001	CYPROTERONE W/ESTRADIOL VALERATE
900249	01	001	ANTIANDROGENS
900250	01	001	ANTIANDROGENS AND ESTROGENS
900879	01	001	ANTIANDROGENS, PLAIN
006529	01	001	FLUTAMIDE
008517	01	001	NILUTAMIDE
012711	01	001	BICALUTAMIDE
064485	01	001	ABIRATERONE ACETATE W/PREDNISOLONE
073193	01	001	GALETERONE
078429	01	001	ENZALUTAMIDE
089166	01	001	APALUTAMIDE
089563	01	001	TAS 3681
093046	01	001	DAROLUTAMIDE
110431	01	001	ABIRATERONE; PREDNISOLONE
143072	01	001	AZD 3514
143213	01	001	BMS 641988
145052	01	001	RALANITEN ACETATE
900554	01	001	ANTI-ANDROGENS
011300	01	001	FINASTERIDE
015898	01	001	DUTASTERIDE
017025	01	001	CASODEX W/ZOLADEX
035979	01	001	EPRISTERIDE
062095	01	001	DUTAS-T
062951	01	001	ABIRATERONE
062951	02	001	ABIRATERONE ACETATE

ANTI-ANDROGEN HORMONAL

RECNO	SEQ1	SEQ2	ENGLISH_DR
063648	01	001	ZOLACOS CP
063976	01	001	GESTONORONE
066493	01	001	PROSTASAX PLUS
080330	01	001	MINSCALP F
087221	01	001	ALFUZOSIN HYDROCHLORIDE W/FINASTERIDE
087346	01	001	DUTASTERIDE W/SILODOSIN
124910	01	001	DOXAZOSIN; FINASTERIDE
125031	01	001	FINASTERIDE; TAMSULOSIN
125064	01	001	DUTASTERIDE; TAMSULOSIN
126370	01	001	ALFUZOSIN; FINASTERIDE

Appendix H Sponsor standards LLN and ULN for laboratory parameters

Analyte	LowValue	HighValue	LabUnit	From Age	From Age_AGEU	To Age	To Age_AGEU	Sex
Basophils	0	0.15	10^9/L	18	Year	150	Year	
Eosinophils	0	0.4	10^9/L	18	Year	150	Year	
Hemoglobin	135	175	g/L	18	Year	100	Year	Male
Hemoglobin	120	160	g/L	18	Year	100	Year	Female
Leukocytes	4.5	11	10^9/L	18	Year	150	Year	
Lymphocytes	1	2	10^9/L	18	Year	150	Year	
Monocytes	0.18	0.5	10^9/L	18	Year	150	Year	
Neutrophils	1.8	3.15	10^9/L	18	Year	150	Year	
Platelets	150	350	10^9/L	18	Year	150	Year	
INR	0.8	1.2	Ratio	18	Year	150	Year	
Albumin	35	55	g/L	18	Year	100	Year	
Blood Urea Nitrogen (BUN)	3.6	7.1	mmol/L	18	Year	100	Year	
Calcium	2.2	2.6	mmol/L	18	Year	100	Year	
Glucose	3.900001	6.999999	mmol/L	18	Year	100	Year	
Potassium	3.5	5	mmol/L	18	Year	100	Year	
Magnesium	0,8	1,2	mmol/L	18	Year	100	Year	
Sodium	136	145	mmol/L	18	Year	100	Year	
Phosphate	1	1.4	mmol/L	18	Year	100	Year	
Protein	55	80	g/L	18	Year	100	Year	
Urea	3.6	7.1	mmol/L	18	Year	100	Year	

Signature Page

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Approve & eSign	[redacted]