NCT02379390

AMENDED CLINICAL TRIAL PROTOCOL 01

COMPOUND: Jevtana®/cabazitaxel/XRP6258

Phase II, randomized, open label, multicenter study in chemotherapy-naïve metastatic Castration-Resistant Prostate Cancer (mCRPC) patients who have PRIMary resistance to abiraterone acetate or Enzalutamide treatment comparing the anti-tumor effect of CABazitaxel to alternative Androgen Receptors (AR) targeted therapy.

STUDY NUMBER: XRP6258-LPS14022

STUDY NAME: PRIMCAB

VERSION DATE / STATUS: 22-Feb-2016 / Approved

CLINICAL STUDY DIRECTOR: [redacted]

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: XRP6258 **Jevtana®/cabazitaxel**	**STUDY No: XRP6258-LPS14022** **STUDY NAME: PRIMCAB**
TITLE	Phase II, randomized, open label, multicenter study in chemotherapy-naïve metastatic Castration-Resistant Prostate Cancer (mCRPC) patients who have PRIMary resistance to abiraterone acetate or Enzalutamide treatment comparing the anti-tumor effect of CABazitaxel to alternative Androgen Receptors (AR) targeted therapy
INVESTIGATOR/TRIAL LOCATION	Multicenter/ International
PHASE OF DEVELOPMENT	Phase II
STUDY OBJECTIVE(S)	**Primary objective** To demonstrate the superiority in term of radiographic Progression-Free Survival (rPFS) [using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 and PCWG2] (1)(2) of cabazitaxel at 25 mg/m² plus prednisone (Arm A) versus either enzalutamide at 160 mg once daily or abiraterone acetate at 1000 mg once daily plus prednisone (Arm B) in chemotherapy-naïve patients with metastatic Castration-Resistant Prostate Cancer (mCRPC) who have disease progression while receiving AR targeted therapy (abiraterone plus prednisone or enzalutamide) within 12 months of treatment initiation (≤12 months). **Secondary objectives** • To compare efficacy of cabazitaxel plus prednisone to enzalutamide or abiraterone acetate plus prednisone for: - PSA response rate, - Progression Free Survival (PFS), - Overall Survival (OS), - Time To PSA Progression (TTPP), - Tumor response rate in patients with measurable disease (RECIST 1.1), - Duration of tumor response, - Pain response, - Time To Pain Progression, - Symptomatic skeletal events (SSE) rate, - Time to occurrence of any symptomatic skeletal events (SSE) • To analyze messenger RNAs including androgen-receptor splice variant 7 messenger RNA (AR-V7) at baseline and post-treatment in Circulating Tumor Cells (CTCs). • To evaluate safety in the 2 treatment arms [redacted] • To analyze Circulating Tumor Cells (CTCs) phenotypes as well as expression and localization of proteins including androgen receptors

	(AR) isoforms in CTCs at baseline. • To collect circulating free nucleic acids (cfDNA and cfRNA) derived from plasma at baseline, on treatment and post-treatment for biomarker studies. • To collect germline DNA derived from whole blood at baseline for biomarker studies and subtractive mutation analysis.
STUDY DESIGN	This is a prospective, multicenter, multinational, randomized, open label study, comparing the efficacy of cabazitaxel at 25 mg/m² plus prednisone (Arm A) versus either enzalutamide at 160 mg once daily or abiraterone acetate at 1000 mg once daily plus prednisone (Arm B) in term of rPFS [using RECIST 1.1] in chemotherapy-naïve patients with mCRPC who have primary resistance to abiraterone acetate or enzalutamide. Resistant population is defined as patients who have disease progression while receiving AR targeted therapy within 12 months of AR treatment initiation (≤12 months) (3) Each patient will be treated until disease progression, unacceptable toxicity, or patient's refusal of further study treatment. A Steering Committee will be responsible for supervising the progress of the trial. This committee will include the 3 Study Chairmen's and Sponsor's representatives. Treatment allocation will be performed by an Interactive Voice/Web Response System (IVRS/IWRS). All eligible patients will be randomly assigned to either arm A or B in a 1:1 proportion. Randomization will be stratified by: extra nodal visceral metastases (yes, no), level of PSA decline within 12 months of initiation of AR targeted therapy (no decline, decline 1% to <50%, decline ≥50%) and time from AR targeted agent initiation to progression ([0 ; 6 months],]6 ; 12 months].
STUDY POPULATION **Main selection criteria**	**Inclusion criteria** I 01. Diagnosis of histologically or cytologically confirmed prostate adenocarcinoma. I 02. Metastatic disease. I 03. Progressive disease (PD) while receiving AR targeted therapy with abiraterone acetate or enzalutamide within 12 months of treatment initiation (≤12 months) by at least one of the following: a) Progression in measurable disease (RECIST 1.1 criteria). Patient with measurable disease must have at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be at least 10 mm when measured by computed tomography (CT) [CT scan thickness no greater than 5 mm] or magnetic resonance imaging (MRI). Lymph nodes should be ≥15 mm in short axis. As defined by PCWG2 (2), if lymph node metastasis is the only evidence of metastasis, it must be ≥20 mm in diameter when measured by spiral CT or MRI. Previously irradiated lesions, primary prostate lesion and bone lesions will be considered non-measurable disease, and/or b) Appearance of 2 or more new bone lesions. They must be confirmed by other imaging modalities (CT; MRI) if ambiguous

	results (PCWG2) , and/or c) Rising PSA defined (PCWG2) as at least two consecutive rises in PSA to be documented over a reference value (measure 1) taken at least one week apart. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2nd beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the 2nd measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than the 2nd measure. The third (or the fourth) confirmatory PSA should be taken within 4 weeks prior to randomization (Appendix A). In case of progression based on rising PSA only, the first rising PSA (measure 2) must be obtained within 6 months of initiation of AR targeted therapy (≤6 months). Duration of the first AR targeted agent treatment should not exceed 12 months for patients with PD within 6 months and should not exceed 18 months for those with PD between 6 and 12 months. I 04. A PSA value of at least 2 ng/mL is required at study entry. I 05. Effective castration (serum testosterone levels <0.5 ng/mL). I 06. Prior AR targeted therapy (abiraterone acetate or enzalutamide) must be stopped at least 2 weeks before study treatment. I 07. Signed written informed consent. **Exclusion criteria** **Related to methodology:** E 01. Prior chemotherapy for prostate cancer, except estramustine and except adjuvant/neoadjuvant treatment completed >3 years ago. No further anti-cancer therapy after the previous AR targeted therapy and before inclusion. Prior docetaxel in hormone sensitive setting is allowed if completed >1 year before randomization (4). Prior immunotherapy is allowed. E 02. Less than 28 days elapsed from prior treatment with immunotherapy, radiotherapy or surgery to the time of randomization. E 03. Adverse events (excluding alopecia and those listed in the specific exclusion criteria) from any prior anticancer therapy of grade >1 (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v4.0) at the time of randomization. E 04. Less than 18 years (or country's legal age of majority if the legal age is >18 years). E 05. Eastern Cooperative Oncology Group (ECOG) performance status >1. E 06. History of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis or new evidence of brain or leptomeningeal disease. E 07. Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) bladder cancer are allowed, as well as any other cancer for which treatment has been completed ≥5 years ago and from which the patient has been disease-free for

	≥5 years. E 08. Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization. E 09. Acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral treatment. E 10. Any severe acute or chronic medical condition including uncontrolled diabetes mellitus, severe renal impairment, history of cardiovascular disease (uncontrolled hypertension, arterial thrombotic events in the past 6 months, congestive heart failure, severe or unstable angina pectoris, recent myocardial infraction within last 6 months or uncontrolled cardiac arrhythmia), which could impair the ability of the patient to participate to the study or interfere with interpretation of study results, or patient unable to comply with the study procedures. E 11. Patients with reproductive potential who do not agree to use accepted and effective method of contraception during the study treatment period and up to 6 months after the last administered dose. The definition of "effective method of contraception" will be based on the investigator's judgment **Related to study treatment:** E 12. Known allergies, hypersensitivity or intolerance to prednisone or excipients of abiraterone acetate or enzalutamide. History of hypersensitivity to docetaxel or polysorbate 80. E 13. Known history of mineralocorticoid excess or deficiency (not applicable to patients who have already been treated with abiraterone acetate in first line before inclusion). E 14. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain arteriovenous malformation or the use of concomitant medications that may lower the seizure threshold (not applicable to patients who have already been treated with enzalutamide in first line before inclusion). E 15. Unable to swallow a whole tablet or capsule E 16. Inadequate organ and bone marrow function as evidenced by: a) Hemoglobin <10.0 g/dL b) Absolute neutrophil count <1.5 x 109/L c) Platelet count <100 x 109/L d) AST/SGOT and/or ALT/SGPT >1.5 x ULN; e) Total bilirubin >1.0 x ULN f) Potassium <3.5 mmol/L g) Serum albumin <3.0 g/dL h) Child-Pugh Class B and C E 17. Contraindications to the use of corticosteroid treatment. E 18. Symptomatic peripheral neuropathy grade ≥2 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.0). E 19. Concomitant vaccination with yellow fever vaccine.

Total expected number of patients	Approximately 206
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	**Arm A:** **Cabazitaxel (XRP6258)** Cabazitaxel is supplied as a sterile, non-pyrogenic, non-aqueous yellowish to brownish yellow solution contained in a 15 mL clear glass vial, stoppered with a chlorobutyl rubber closure coated with a transparent ETFE coating. The rubber closure is crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap. Single-dose vial, containing a total of 60 mg of cabazitaxel expressed as anhydrous and solvent-free basis, per 1.5 mL of solution. The fill volume has been established to include an overfill, (ie, 1.5 mL [nominal volume] + 0.33 mL). This overfill was determined to ensure that a 10 mg/mL concentration is obtained in the premix and that 60 mg dose can be extracted **Solvent:** The diluent used for the preparation of the premix is a sterile, non pyrogenic solution containing a 13% w/w ethanol solution in water for injection. This solution is contained in a 15 mL clear glass vial, stoppered with a chlorobutyl rubber closure coated with a transparent ETFE coating. The rubber closure is crimped to the vial with either an aluminum cap covered with a light grey plastic flip-off cap or a gold-color aluminum cap covered with a clear plastic flip-off cap. Each vial of solvent is overfilled to ensure that a 10 mg/mL concentration is obtained in the Premix and that 60 mg dose can be extracted. (ie, 4.5 mL (nominal volume) + 1.17 mL]. Each vial of cabazitaxel must be diluted with the ENTIRE content of one solvent vial. The solution is a clear colorless liquid. **Arm B:** **Abiraterone acetate OR Enzalutamide** **Abiraterone acetate** 250 mg tablets, white to off-white, oval tablets debossed with AA250 on one side. Abiraterone acetate 250 mg tablets are available in high-density polyethylene bottles of 120 tablets. OR **Enzalutamide** 40 mg capsules, white to off-white oblong soft capsules (approximately 20 mm x 9 mm) imprinted with “ENZ” in black ink on one side. Commercially available formulations will be used for the comparators (abiraterone acetate and enzalutamide).
Route(s) of administration	Cabazitaxel will be administered by IV route. Abiraterone acetate and enzalutamide will be administered by oral route
Dose regimen	**Arm A:** Cabazitaxel 25 mg/m² intravenously in 1 hour (Day 1) every 3 weeks, plus prednisone 10 mg orally given daily. A cycle is defined as a 3-weeks period

	Arm B: **Abiraterone acetate**: Patients who were treated with enzalutamide before study entry, will receive abiraterone acetate at the dose of 1000 mg (4 tablets) orally (PO) continuously once daily from D1 to D21. It must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose is taken and at least 1 hour after the dose is taken. The tablets should be swallowed whole with water, plus prednisone 5 mg orally twice daily. A cycle is defined as a 3-weeks period. **OR** **Enzalutamide:** Patients who were treated with abiraterone acetate before study entry, will receive enzalutamide at the dose of 160 mg (4 capsules) orally (PO) continuously once daily from D1 to D21, with or without food, capsules should be swallowed whole. A cycle is defined as a 3-weeks period
Non-Investigational medicinal product(s) (IMP)	Prednisone or Prednisolone: Commercially available product will be used. Prednisone or Prednisolone will be administered by oral route.

ENDPOINT(S)	**Primary endpoint**
	Radiographic Progression-Free Survival (rPFS) defined as the time from randomization to the occurrence of one of the following:
	• Radiological tumor progressions using RECIST 1.1
	• Progression of bone lesions using PCWG2 criteria
	• Death due to any cause
	Secondary endpoint(s)
	Efficacy
	• **PSA response** defined as a reduction from baseline PSA level of at least 50%, maintained for at least 3 weeks.
	• **Progression-free survival** defined as the time interval between the date of randomization and the date of the first documentation of any of the following events (1)(2) :
	  • Radiological tumor progression by RECIST 1.1 and PCWG2,
	  • PSA progression,
	  • Pain progression,
	  • Death due to any cause.
	• **Overall Survival** defined as the time interval from the date of randomization to the date of death due to any cause
	• **Time to PSA progression (TTPP)** defined as the time interval between the date of randomization and the date of first documented PSA progression. PSA progression is defined as (2)(Appendix A):
	  • **Decline from baseline:** an increase of ≥25% (at least 2ng/mL) over the nadir value, confirmed by a second PSA value at least 3 weeks apart.
	  • **No decline from baseline:** an increase of ≥25% (at least 2ng/mL) over the baseline value after 12 weeks of treatment, confirmed by a second PSA value at least 3 weeks apart.

Early increase in PSA within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint.

- **Tumor response** in patients with measurable disease (RECIST 1.1).
- **Duration of tumor response** in patients with measurable disease, defined as the time between the first evaluation at which the tumor response criteria are met and the first documentation of tumor progression.
- **Pain response** defined as a decrease by <30% from baseline in the average of Brief Pain Inventory-Short Form (BPI-SF) pain intensity score observed at 2 consecutive evaluations ≥3 weeks apart without increase in analgesic usage score (defined as a ≥1 point increase on the WHO analgesic scale).
- **Time to Pain progression** defined as the time interval between the date of randomization and the date of the first documented pain progression. Pain Progression will be defined as increase by ≥30% from baseline in the average of BPI-SF pain intensity observed at 2 consecutive evaluations ≥3 weeks apart without decrease in analgesic usage score OR increase in analgesic usage score of 30% or greater.

Early increase in BPI-SF or analgesic usage within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint.

- **Symptomatic Skeletal Events (SSE) rate**, occurrence of SSE (by clinical evaluation) is defined (5) as:
  - The occurrence of a new symptomatic pathological fracture, or
  - The use of external beam radiation to relieve bone pain, or
  - The occurrence of spinal cord compression, or
  - Tumor-related orthopeadic surgical intervention
- **Time to occurrence of SSE** defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SSE, whichever is earlier.
- **Analysis of messenger RNAs** including androgen-receptor splice variant 7 messenger RNA (AR-V7) at baseline and post-treatment in Circulating Tumor Cells (CTCs).

Safety:

- **Treatment Emergent Adverse Events (TEAE):** Type according to MedDRA (Medical Dictionary for Regulatory Activities), frequency, severity according to NCI CTCAE V4.0, seriousness, and relationship of study treatment will be assessed. Laboratory abnormalities will be assessed according to the NCI CTCAE v.4.0.

[redacted]

Biomarkers:

- Analysis of Circulating Tumor Cells (CTCs) phenotypes as well as expression and localization of proteins including AR isoforms in CTCs at baseline.
- Analysis of tumoral genetic and genomic variations in circulating free nucleic acids derived from plasma at baseline, on treatment and post-treatment. Subtractive mutation analysis will be performed

	with germline DNA data to identify tumoral specific variations.
ASSESSMENT SCHEDULE	Screening will be performed within 4 weeks before randomization. Clinical examinations (including height at baseline only, weight, ECOG PS and vital signs), laboratory tests (including complete blood counts, and serum chemistry), concomitant medications and AEs (NCI CTCAE v.4.0) will be obtained prior to drug administration, every cycle before treatment administration and up to 30 days after the last study treatment administration. Weight and ECOG PS will be collected until disease progression, start of another anticancer therapy or study cut-off date, whichever comes first. ECG will be obtained within 8 days prior to first drug administration and at the end of treatment visit only if clinically indicated or cardiac event during the treatment period. Serum testosterone will be measured at baseline. PSA will be determined at baseline, every 3 weeks at each visit before study treatment administration, at the end of treatment visit, every 12 weeks at each follow-up until the end of the first further anticancer therapy if any or study cut-off whichever comes first. Patient's diary to be used by all patients to record the consumption of abiraterone acetate or enzalutamide (in Arm B) and/or prednisone or prednisolone. Completion of Pain, and analgesic diary and SSE assessment will be obtained at baseline, every 3 weeks at each visit before study treatment administration, at the end of treatment visit, and then completion pain and analgesic scale will be done every 12 weeks at each follow-up until disease progression, death or study cut-off whichever comes first SSE will be assessed every 12 weeks until occurrence of first SSE or study cut-off, whichever comes first. Tumor radiological evaluation by computerized tomography (CT) or magnetic resonance imaging (MRI) of the whole body (chest, abdomen, and pelvis) and by bone scan for all patients at baseline, every 9 weeks for the first 6 months (27 weeks), then every 12 weeks until radiological tumor progression is documented, start of another cancer therapy or study cut-off, whichever comes first, using the same method for each assessment. Blood samples for CTCs analysis will be collected in patients at screening (24h apart before first cycle administration) and at relapse or EOT. Blood samples for cfDNA/cfRNA analysis will be collected in patients at screening, at C4D1 and at relapse or EOT. Blood samples for germline DNA collection will be done in patients at screening. After study treatment discontinuation, patients will be followed every 12 weeks until death, study cut-off date or withdrawal of patients' consent. Details of any further anticancer-therapy will be collected
STATISTICAL CONSIDERATIONS	[redacted] Based on bibliographic references (6)(7)(8)(9)(10), a Hazard Ratio of 0.67 is targeted as the smallest effect of clinical interest. The following table presents how such a Hazard Ratio (HR) translates for a variety of envisaged median rPFS in the abiraterone acetate or Enzalutamide group (11)(12).

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 155 patients with event are needed to achieve 80% power to demonstrate rPFS superiority of Cabazitaxel over abiraterone acetate or Enzalutamide by one-sided log rank test at 0.05 type I error rate. Further assuming the accrual is at a constant rate of 4 patients per month for 5 months and then 11 patients per month, a total of 206 patients in 2 arms (103 patients per arm) is anticipated to be needed to reach the targeted number of patients with event.

Analysis population:

Intent-to-Treat (ITT) population: This population includes all randomized patients. It is the primary population for all efficacy parameters. All analyses using this population will be based on the treatment assigned by randomization.

Safety population: This population includes all patients who will take at least one dose of the study drug. This population is for safety analyses. All analyses using this population will be based on the treatment actually received.

Evaluable population: tumor response will be evaluated in patients with measurable disease at baseline. PSA response will be evaluated in patients with >10 ng/dL. Pain response will be evaluated in patients using BPI-SF and WHO Analgesic Ladder.

Primary analysis:

Primary analysis will consist of rPFS comparison between abiraterone acetate or enzalutamide group and Cabazitaxel group through a one-sided 5% log-rank adjusted for the stratification factors (extra nodal visceral metastases, time from AR targeted agent initiation to progression and level of PSA decline) as specified at the time of randomization. This analysis will be performed on the ITT population. If radiological progression or death is not observed during the study, data on rPFS will be censored at the date patient is known to be alive or at the cut-off date, whichever comes first.

The estimates of the hazard ratio and corresponding 90% and 95% confidence interval will also be provided using Cox model adjusted for the stratification factors. Medians survival times and 95% confidence intervals will also be provided by treatment arm. The survival curves will be estimated using Kaplan-Meier estimates.

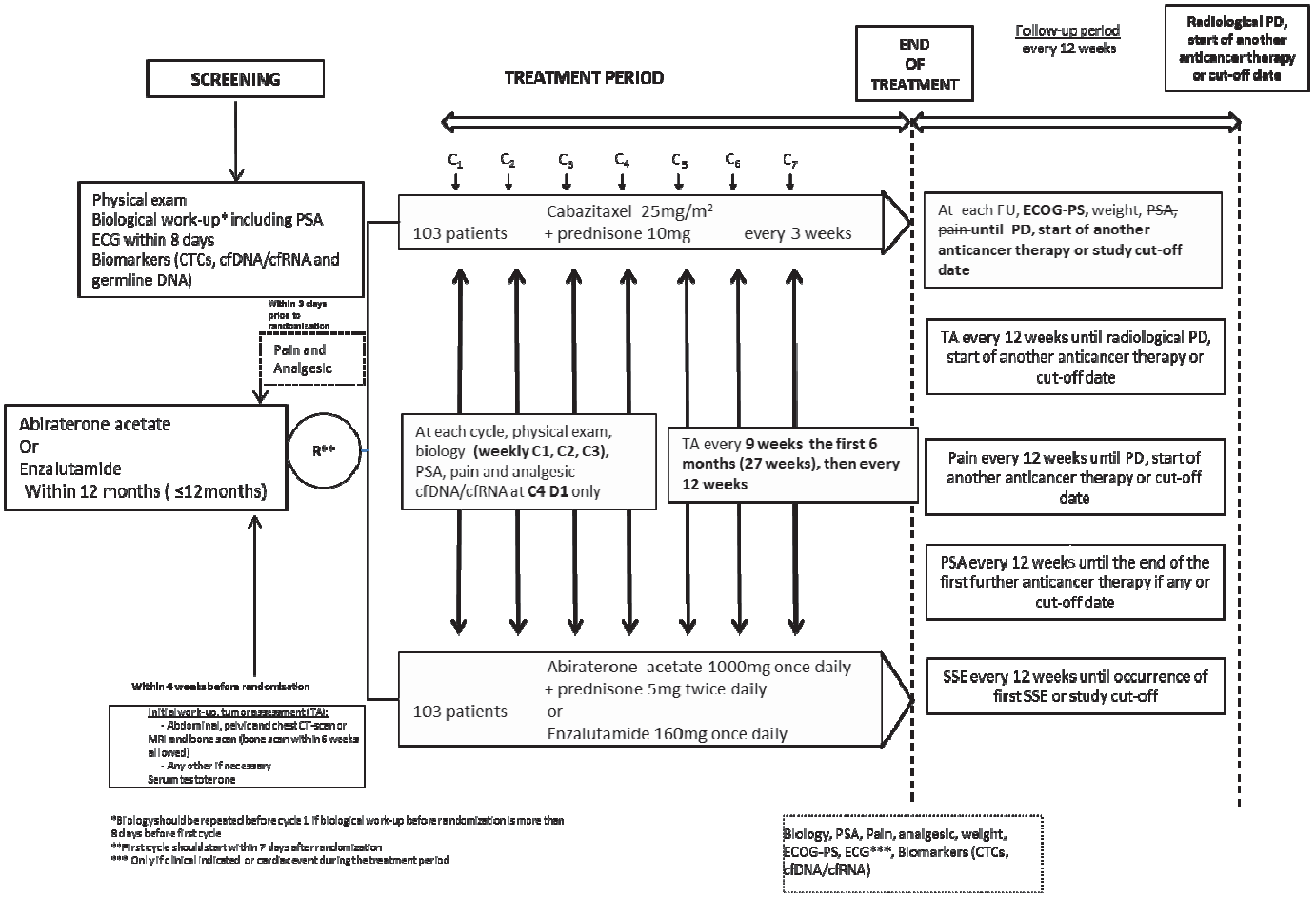
Analysis of secondary endpoints:

Time To event data will be compared between the 2 treatment arms by the log-rank test procedure. Medians and 95% confidence intervals will also be

	provided by treatment arm. Hazard ratios and 95% confidence intervals will be provided using a Cox proportional hazard model. PSA response will be compared between groups using chi-square tests under evaluable population. Safety endpoints will be summarized by the frequency in patients and by toxicity grade.
DURATION OF STUDY PERIOD (per patient)	Patients will be treated until radiographic progressive disease, unacceptable toxicity, patient's refusal of further study treatment. All patients will be followed when on study treatment and after completion of study treatment during follow up period until death, the study cutoff date, or withdrawal of patients' consent whichever comes first.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

Evaluation	Baseline		Treatment period First cycle within 7 days after randomization		Post- treatment follow-up period
	Prior to randomization		Every cycle	End of treatment (30 days after last treatment)	Every 12 weeks
Informed Consent	Before any study procedures				
Inclusion/Exclusion Criteria	Within 8 days				
Patient demography	Within 4 weeks				
Prior Medical/Surgical & Cancer History[a]	Within 4 weeks				
Physical Examination[b]	Within 8 days		X	X	X (ECOG and weight only)
Laboratory Studies [c]*	Within 8 days		X (Hematology/Biochemistry weekly during 3 first cycles)	X	
12 lead Electrocardiogram [d]*	Within 8 days			X	
Study drug Administration [e]			X		
Adverse Events [f]			X	X	X
Prior/ Concomitant/ Post Medications [g]	Within 4 weeks		X	X	X(if indicated)
Other investigations	As clinically indicated		X	X	X
Skeletal Related Event [h]	Within 8 days		X	X	X
Tumor Assessment [i]	Within 4 weeks		every 9 weeks the first 6 months (27 weeks) then every 12 weeks	X	X
Serum Testosterone Measurement [j]	Within 4 weeks				
PSA Measurement [k]**	Within 8 days		X	X	X
Analgesic & Pain [l]	Within 3 days		X	X	X
Patient's diary[m]			X		
Circulating Tumor Cells (CTCs)[n]	Within 8 days			X	
cfDNA/cfRNA [o]	Within 8 days		D1 of cycle 4	X	
Germline DNA [o]	Within 8 days				
Further anticancer therapy [p]					X
Survival status[q]					X

RANDOMIZATION [r]

Evaluation	Baseline		Treatment period First cycle within 7 days after randomization	Post- treatment follow-up period

* To be repeated if performed more than 8 days before the 1st infusion. ** Must be performed prior to registration for eligibility assessment.

a **Prior Medical/Surgical & Cancer History** Includes cancer diagnosis (primary tumor characteristics and metastatic sites), prior surgery for cancer, radiotherapy, systemic anticancer therapy, and concurrent illness.

b **Physical Examination:** Includes examination of major body systems (height (at baseline only), body weight, ECOG PS and vital signs). During the follow-up period, ECOG PS, weight will be collected every 12 weeks from end of study treatment until disease progression, start of other anticancer therapy or study cut-off, whichever comes first.

c **Laboratory Studies** Includes, prior each cycle, hematology (WBC with differential count, ANC, hemoglobin, platelet count). **Blood biochemistry** (sodium, potassium, calcium, phosphorus, blood urea nitrogen (BUN), magnesium, LDH, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose. In addition, hematology and biochemistry will be performed every week (D8 and D15) during the 3 first cycles and then within further cycles in case of fever or infection. During treatment, creatinine clearance (CLcr) should be performed if creatinine >1 x ULN. Coagulation (prothrombin time expressed as international normalized ratio) at baseline. In addition and only at baseline: serum Chromogranin A (CgA).

d **12-lead ECG** to be performed at baseline, and at end of study treatment only if clinically indicated or cardiac event during the treatment period.

e **Study drug Administration** Arm A: Cabazitaxel 25 mg/m² will be administered on Days 1 of each 21-day cycle + prednisone 10 mg daily per os (in countries where prednisone is not commercially available prednisolone 10 mg daily per os may be used). Cycle administration will start within 7 calendar days of randomization, and then repeated every 3 weeks. Arm B: abiraterone acetate 1000 mg (4 tablets) orally once daily plus prednisone 5 mg orally twice daily, continuously or enzalutamide 160 mg (4 capsules) orally once daily continuously.

f **Adverse Events** The period of safety observation starts from the time the patient gives informed consent. All adverse events will be recorded until 30 days after the last administration of study drugs. During the follow-up period, only ongoing related or new related adverse events will be recorded. Serious adverse events ongoing at the end of the study treatment will be followed during the follow-up period until resolution or stabilization regardless of relationship with study drugs. Adverse events will be recorded according to NCI-CTCAE version 4.0.

g **Prior/ Concomitant/ Post Medications** Concomitant medications and treatments will be recorded from 4 weeks prior to the start of study drug, before every cycle during the study treatment period, and up to 30 days after the final dose of study drug. Once the patient has withdrawn from study treatment, concomitant medication should only be recorded if used to treat new or unresolved study treatment related adverse events.

h **Symptomatic Skeletal Event**: The use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture, or occurrence of spinal cord compression, or tumor-related orthopeadic surgical intervention until the occurrence of the first SSE or study cut-off date.

i **Tumor Assessment** Chest, abdomen, and pelvic CT-scan or MRI, bone scan and all other exams as clinically indicated (e.g. brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to be performed to assess disease status at baseline within 4 weeks prior randomization (bone scan performed within 6 weeks prior to randomization is allowed), then every 9 weeks for the first 6 months (27 weeks), then every 12 weeks until radiological tumor progression, whenever disease progression is suspected, using the same method for each assessment to follow all target and/ or non-target lesions present at baseline, start of another anticancer therapy or study cut-off, whichever comes first. In addition, bone scan will be repeated to confirm progression (6 weeks after initial documentation of progression); In case of doubtful lesions on bone scan, bone-centered X-ray or MRI scan should be performed to determine the nature of those lesions (metastatic or not). In post treatment follow up period, patients that have not progressed or started another anticancer therapy, tumor assessment to be performed every 12 weeks.

j **Serum testosterone measurement,** to be performed at baseline only

k **PSA measurements** to be performed at baseline and then repeated on pre dose of Day 1 of each cycle, approximately 30 days after the last study treatment administration (end of treatment visit), every 12 weeks during the follow-up period until the end of the first further anticancer therapy if any or the study cutoff date, whichever comes first.

l **Analgesic and pain** diary information should be collected (at baseline, and before each cycle, at the end of treatment and every 12 weeks until disease progression, start of another anticancer therapy or study cut off, whichever comes first.

m Patient's diary to be used by all patients to record the consumption of abiraterone acetate or enzalutamide (in Arm B) and/or prednisone or prednisolone.

n **Circulating Tumor Cells (CTCs)** – CTCs assays will be done by 2 central laboratories. 3 samples will be taken prior randomization and 2 of them at least 24h apart before first cycle administration at screening (within 8 days during abiraterone acetate or enzalutamide washout) and at relapse or EOT if any other reason of discontinuation.

o **Samples for cfDNA/cfRNA/germline DNA:** 3 samples will be taken prior randomization and 2 of them at least 24h apart before first cycle administration at screening (within 8 days during abiraterone acetate or enzalutamide washout)/at C4D1/ and at relapse or EOT if any other reason of discontinuation and stored for future exploratory biomarkers.

p **Further anticancer therapy** if any will be collected after patient treatment discontinuation.

q **Survival status:** During the follow-up period, patients who went off study treatment prior to documented disease progression will be evaluated for tumor progression, ECOG, weight, PS, Pain and HRQL every 12 weeks from end of study treatment until disease progression or start of other anticancer therapy. Further anticancer therapy data will be collected until death or study cutoff date.

r **Randomization** All eligible patients will be randomly assigned to one of the 2 treatment groups using an Interactive Voice/Web Response System (IVRSIWRS). Study treatment should be started within 7 calendar days from randomization.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

ACTH:	Adrenocorticotropic hormone
ADT:	Androgen Deprivation Therapy
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
AR:	androgen receptor
AST:	aspartate aminotransferase
AUC:	area under curve
BUN:	blood urea nitrogen
CBZ:	cabazitaxel
cfDNA:	circulating free Deoxyribonucleic Acid
cfRNA:	circulating free Ribonucleic acid
CRF:	Case Report Form
CRPC:	castration-resistant prostate cancer
CTC:	circulating tumor cells
DLT:	dose limiting toxicity
DNA:	Deoxyribonucleic acid
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
EMA:	European Medicines Agency
EOT:	end of treatment
FDA:	Food and Drug Administration
GCP:	Good clinical practice
HLGT:	high group level term
HLT:	high level term
HR:	hazard ratio
ICH:	International Conference on Harmonisation
IMP:	investigational medicinal product
IRB/IEC:	Institutional Review Board/Independent Ethics Committee
ITT:	intent to treat
LDH:	lactate deshydrogenase
LH-RH:	luteinizing hormone-releasing hormone
mCRPC:	metastatic Castration Resistant Prostate Cancer
MTX:	mitoxantrone
NCI CTCAE:	National Cancer Institute Common Terminology Criteria of Adverse Events
OS:	overall survival
PCWG2:	Prostate Cancer Working Group 2
PD:	progressive disease
PSA:	Prostate-Specific antigen

PT:	preferred term
RECIST:	Response Evaluation Criteria In Solid Tumors
rPFS:	radiographic Progression-Free Survival
SAE:	Serious Adverse Event
SGOT:	Serum Glutamooxaloacétate Transférase
SGPT:	Serum Glutamo-Pyruvate Transferase
SOC:	System organ class
SSE:	symptomatic skeletal event
TEAE:	Treatment Emergent Adverse Events
ULN:	upper limit of normal
WBC:	white blood cell
WHO:	World Health Organization

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Prostate cancer is a major worldwide health problem and is the most frequently diagnosed male malignancy after lung cancer. Worldwide, there were 903,452 new cases and 258,381deaths due to prostate cancer alone during the year 2008 (13). Prostate cancer is associated with extensive morbidity, as most patients experience significant pain as the result of osseous metastases. Patients with advanced disease usually receive treatment with hormonal agents (orchiectomy, luteinizing hormone-releasing hormone [LH-RH] agonists and/or anti-androgens). However, the effect of ADT (Androgen Deprivation Therapy) is temporary, and most patients experience disease progression after 18 months of treatment.

Although chemotherapy has historically been showed as modestly effective for the treatment of hormone resistant metastatic prostate cancer (HRMPC), recent studies have suggested that this may be changing. In 1990's, randomized Phase III clinical trials comparing mitoxantrone plus corticosteroids to corticosteroids alone showed that mitoxantrone significantly increased the palliative effect of corticosteroid therapy ($p = 0.01$)(14)(15). Mitoxantrone became the first chemotherapy agent to be approved for the treatment of prostate cancer. However, there was no difference in survival between the treatment arms.

Taxotere® in combination with prednisone was approved in 2004 for the treatment of androgen independent metastatic prostate cancer patients and demonstrated a 2.9 month survival benefit compared to mitoxantrone plus prednisone, prolonging survival from 16.5 months to 18.9 months (16). Standard of care in second line prostate evolved following the adoption of Taxotere® as standard first line therapy for Hormone Refractory Prostate Cancer (HRPC).

A rapid evolution in the understanding of disease biology, combined with approvals of new therapies including immunotherapy, novel chemotherapy, hormonal agents and a bone calcium matrix-targeted radionuclide, along with further drugs in development, have made treatment decisions for metastatic castration-resistant prostate cancer (mCRPC) increasingly complex and challenging. At the individual tumor level, the cellular states are dynamic (ie, one or all cell types may exist simultaneously within a tumor and their activity may evolve through adaptation or genomic events as the disease progresses). Optimal treatment of CRPC, therefore, will involve identification of ligand-dependent versus -independent states, and individualization of therapies for different clinical states. Thus, distinguishing between patients with CRPC with preserved Androgen Receptor (AR) activity from those without AR activity has the potential to guide therapy for patients with advanced disease and may improve overall patient outcome. Furthermore, there is a paucity of evidence on how to better select the right patient for the right treatment and the manual for how to integrate these newly approved drugs for CRPC management needs to be investigated as a matter of urgency.

Cabazitaxel is a next-generation taxane that has preclinical activity against docetaxel resistance tumor models, the ability to cross the blood–brain barrier and a tolerable safety profile consistent

with other approved chemotherapies. In the phase III TROPIC trial, cabazitaxel plus prednisone or prednisolone significantly improved overall survival (OS) in patients with mCRPC versus mitoxantrone plus prednisone or prednisolone, with a 30% reduction in the risk of death [hazard ratio (HR) 0.70; 95% confidence interval (CI) 0.59–0.83; P <0.0001; data cut-off 25 September 2009] (10). Based on the results of the TROPIC trial, cabazitaxel (25 mg/m2 once every 3 weeks) plus prednisone was approved by the European Medicines Agency (EMA), Food and Drug Administration (FDA) and other national health authorities for the treatment of men with metastatic 'hormone-refractory' prostate cancer whose disease has progressed after receiving a docetaxel-containing regimen.

The recognition of AR gene expression in CRPC in 2004 refocused research in the continued role of AR in CRPC. This discovery changed the paradigm of treatment from the previous standard that all patients with disease progression on ADT were hormone-refractory. It was recognized that even in castration-resistant disease, the AR remains a driver of tumor proliferation in some patients (17)(18)(19).

Following this basic science breakthrough, several new AR targeted compounds entered into late phase clinical development for the treatment of advanced prostate cancer. Abiraterone acetate and Enzalutamide have successfully demonstrated efficacy and safety in both chemo-naïve and post chemotherapy mCRPC patients (6)(7)(8)(9). These data led to the FDA and EMA approval of using abiraterone acetate for both chemo-naïve and post chemotherapy mCRPC patients and enzalutamide for mCRPC patient post docetaxel treatment. It is also expected that the recent positive interim analysis from the PREVAIL study (9) which showed overall survival benefit of enzalutamide comparing to placebo will likely support the approval of enzalutamide for the chemo-naïve mCRPC patients in 2014. Thus, the mCRPC treatment landscape for chemo-naïve mCRPC patients is going through a significant change for the coming years.

4.2 INVESTIGATIONAL MEDICINAL PRODUCT

4.2.1 Preclinical data

Cabazitaxel (also known as XRP6258, RPR116258A) is a semisynthetic compound derived from the 10-deacetyl Baccatin III, which is extracted from European yew needles. This new taxoid which promotes the tubulin assembly in vitro and stabilizes microtubules against cold-induced depolymerization as efficiently as docetaxel was selected for development based on a better antiproliferative activity on resistant cell lines than docetaxel. Using cell lines with acquired resistance to doxorubicin, vincristine, vinblastine, paclitaxel and docetaxel, the resistance factors ranged from 1.8 to 10 and 4.8 to 59, for cabazitaxel and for docetaxel, respectively. Cabazitaxel exhibited a broad spectrum of in vivo antitumor activity, not only in docetaxel -sensitive tumor models, but also in tumors models in which docetaxel was either poorly active or not active. A trend for schedule-dependency was observed with maximum tolerated dosages 4.8-fold higher with an intermittent schedule than with a split dose schedule. The best antitumor efficacy was obtained with the schedules allowing the administration of the highest amount of drug. In addition, this compound was found to penetrate the blood brain barrier and marked antitumor activity was obtained in nude mice bearing intracranial glioblastomas.

More information on the preclinical data is available in the clinical Investigator's brochure (20).

4.2.2 Summary of clinical data

In single agent, 3 Phase I studies were conducted to determine the schedule and the recommended dose, one study investigating the disposition of radiolabeled cabazitaxel, one Phase 2 study in patients with metastatic breast cancer (MBC), and one Phase 3 study in patients with mCRPC. One Phase I/II study has been conducted with cabazitaxel plus prednisone in combination with capecitabine.

4.2.2.1 Phase 1

The 3 Phase 1 studies in solid tumors (TED6188, TED6189, TED6190) have been completed. There were 2 partial responses in patients with prostate cancer in Phase 1 studies evaluating the every 3 week schedule; 2 PR out of 8 patients with metastatic HRPC in TED6190 at 25 mg/m2 suggesting potential biological and clinical activity in patients with prostate cancer.

The safety profile was comparable in TED6188 and TED6190, with the intermittent schedule (1-hour infusion every 3 weeks). The dose limiting toxicity (DLT) of cabazitaxel was neutropenia and its infectious complications at the highest dose tested, 30 mg/m² in TED6188 and 25 mg/m² in TED6190.

As a result, the dose levels of 20 mg/m² and 25 mg/m² every 3 weeks were defined as the recommended doses for further clinical development with the intermittent schedule.

In TED6189 with the weekly schedule, the maximum tolerated dose (MTD) was reached at 12 mg/m², at which the DLT was diarrhea. As a result, the dose level of 10 mg/m² was defined as the recommended dose for further clinical development with this weekly schedule.

In TCD6945 the recommended dose was defined as cabazitaxel 20 mg/m² on D1 and capecitabine 1000 mg/m² twice daily from D1 to D14, every 3 weeks. DLT were all grade 4 neutropenia lasting more than 7 days.

4.2.2.2 Phase 2

One Phase 2 study in patients with taxane- and/or anthracycline-resistant metastatic breast cancer has been completed (ARD6191). In this study patients were treated with a starting dose of 20 mg/m2 cabazitaxel every 3 weeks with the option to dose-escalate cabazitaxel based on favorable tolerability at Cycle 1. In 20 of 71 patients, the cabazitaxel dose was escalated from 20 to 25 mg/m2 after the first cycle. The most frequently occurring toxicities overall were Grade 3 and 4 neutropenia (73.2%), fatigue (50.7%), nausea (43.7%), diarrhea (39.4%), myalgia (25.4%), anorexia (25.4%), weight loss (25.4%), and vomiting (23.9%). The overall response rate was 14.1% with 2 complete responses (CR) and 8 partial responses (PR).

4.2.2.3 Phase 3

One Phase 3 study was conducted in mCRPC patients previously treated with docetaxel containing regimen. This study compared cabazitaxel (CBZ) plus prednisone to mitoxantrone (MTX) plus prednisone (EFC6193). A total of 755 patients were randomized (378 patients in CBZ arm and 377 patients in MTX arm). A statistically significant increase in OS was observed in patients treated with CBZ plus prednisone compared to patients treated with MTX plus prednisone, with a HR of 0.70 (95%CI: 0.59 – 0.83), a log-rank p-value of 0.0001. The median OS was 15.1 months (95%CI: 14.1 – 16.3) in CBZ arm versus 12.7 months (95%CI: 11.6–13.7) in MTX arm.

The secondary endpoints also demonstrated a net benefit in favor of CBZ treated patients compared with MTX treated patients. Progression-free survival, defined as the earliest date of radiological tumor progression, PSA progression, pain progression, or symptom deterioration or death due to any cause, was statistically significantly longer in the CBZ group compared with the MTX group ($p<0.0001$, HR = 0.74 [95% CI, 0.64-0.86]), and median progression-free survival was 2.8 months versus 1.4 months. Response rates for PSA and tumor assessments, as well as the time to PSA and tumor progression when defined as radiological progression or death were statistically significant in favor of CBZ. Pain response and time to pain progression were not statistically different between CBZ and MTX, for which the primary basis for approval was pain relief and control.

Treatment emergent AEs were experienced by 95.7% of patients in the CBZ group and 88.4% of patients in the MTX group; 57.4% of patients in the CBZ group and 39.4% of patients in the MTX group had at least one Grade 3-4 TEAE. In the CBZ group 39.1% of patients had at least 1 Serious Adverse Event (SAE) compared with 20.8% of patients in the MTX group. Study treatment discontinuation due to a TEAE was reported in 18.3% of patients in the CBZ group and 8.4% of patients in the MTX group.

The most frequent toxicity in the CBZ group were neutropenia and its clinical consequences of febrile neutropenia and infections. Based on laboratory assessments, 81.7% of patients in the CBZ group and 58.0% of patients in the MTX group had grade 3-4 neutropenia. Patients treated with CBZ also had higher rates of infections Grade 3-4 with or without concomitant severe neutropenia (10.2% CBZ, 5.1% MTX) and febrile neutropenia (7.5% CBZ, 1.3% MTX).

Gastrointestinal disorders of all types (Grade 3-4) were more common in the CBZ group (12.4% CBZ, 1.6% MTX). Notably, Grade 3-4 diarrhea was more common on CBZ (6.2%) compared with MTX (0.3%). Incidence of Grade 3-4 stomatitis (0% in both groups) and mucositis (0.3% in both groups) was similar in both treatment groups.

Adverse events in the renal and urinary disorders System Organ Class (SOC) (Grade 3-4) also were more common in the CBZ group (8.6% CBZ, 2.4% MTX). These events consisted of renal failure and impairment (3.2% CBZ, 0.3% MTX) as well as renal obstructive disorders (0.8% CBZ, 0.5% MTX). In the CBZ group, 15 patients were reported to have acute renal Adverse Events (AEs) Grade 3-4, the etiology of which was multifactorial consisting of pre-renal, renal, or obstructive causes. According to laboratory values, the incidence of all grade /grade 3-4 creatinine increase was 15.6%/1.3% in CBZ arm and 11.6%/0.5% in MTX. In addition, more hematuria was

reported in CBZ arm versus MTX arm (62 patients/16.7% versus 14 patients/3.8%). In CBZ arm, no clear possible explanation such as local infection/obstruction/progression, or anticoagulation/aspirin therapy, or thrombocytopenia was found for 21 patients. In prior studies conducted in metastatic breast cancer, a total of 6 patients (2 in the ARD6191 and 4 in the TCD6945) experienced cystitis without local infection including 5 hemorrhagic cystitis (3 cystitis were documented with biopsy). Of note, in human the urinary excretion of cabazitaxel is about 3.7% of the dose with 2.3% excreted as unchanged drug.

Death within 30 days due to AE occurred in 18 patients (4.9%) in the CBZ group and 3 patients (<1.0%) in the MTX group. Of the 18 deaths in the CBZ group, 7 were the result of neutropenia and/or infection, 5 were due to cardiac events (2 cardiac arrest, 1 cardiac failure, 1 dyspnea and 1 ventricular fibrillation), 1 was due to dehydration and hydro-electrolyte imbalance, 3 were pre- or post-renal events leading to renal failure, and 2 were due to other causes, including a death of unknown etiology and a death from a cerebral hemorrhage following a fall in a patient taking concomitant clopidrogrel.

Based on the results of this study, a dossier to register cabazitaxel in hormone refractory metastatic prostate cancer patients previously treated with Taxotere® containing regimen has been submitted in several countries worldwide Cabazitaxel in combination with prednisone or prednisolone is currently approved in the United States, the European Union, Canada, Switzerland, and numerous other countries in Latin America, Asia, and the Middle East.

4.3 STUDY RATIONALE

While abiraterone acetate in association with prednisone or enzalutamide provided significant improvements in the mCRPC patients, not all patients treated with the AR-targeted agents responded to the treatments. Early radiological progression within the first 3 months, was noted in about 1 of every 4 patients treated with enzalutamide in the AFFIRM study (Phase III study of enzalutamide in post-chemo setting) (8). Similarly, in the COU-AA-301 phase 3 study of abiraterone acetate conducted in mCRPC patients with prior exposure to docetaxel, early progression was noted in about 1 of every 3 patients (6). Moreover, almost 50% of patients experienced disease progression at month 6. Recently, two large randomized Phase 3 trials have demonstrated the clinical benefit of treating chemo-naive mCRPC patients with abiraterone (COU-AA-302) (7) or enzalutamide (PREVAIL) (9). Despite of earlier treatment with potent novel AR targeted therapies, around 20-25% of the patients experienced early progression of the disease within first 6 month which clearly suggested the ligand independent nature of a subset of the CRPC and confirmed the heterogeneity of the CRPC.

Interestingly, in a separate study of abiraterone acetate in association with prednisone in 57 patients with CRPC and bone metastases, a subgroup of patients 14 patients (25%) experienced no clinical benefit. These patients, who had no symptomatic improvement and no objective evidence of tumor regression, were considered to exhibit primary resistance to abiraterone acetate. The further examination of the bone marrow biopsies of these patients revealed that a lack of nuclear AR and cytoplasmic CYP17 in bone marrow were associated with primary resistance. Thus, these data support the tumor biological differences between different mCRPC patients and warrant further exploration of alternative treatment options (21).

More recently, Emmanuel Antonarakis from Johns Hopkins Universty, published data about AR-V7 and resistance to abiraterone acetate and enzalutamide (22). Detection of AR-V7 in CTCs from patients with CRPC may be associated with resistance to enzalutamide and abiraterone.

A total of 31 enzalutamide-treated patients and 31 abiraterone-treated patients were enrolled, of whom 39% and 19%, respectively, had detectable AR-V7 in CTCs. Among men receiving enzalutamide, AR-V7 positive patients had lower PSA response rates than AR-V7 negative patients (0% vs. 53%, P = 0.004) and shorter PSA progression-free survival (median, 1.4 months vs. 6.0 months; P<0.001), clinical or radiographic progression-free survival (median, 2.1 months vs. 6.1 months; P<0.001), and overall survival (median, 5.5 months vs. not reached; P = 0.002). Similarly, among men receiving abiraterone, AR-V7 positive patients had lower PSA response rates than AR-V7 negative patients (0% vs. 68%, P = 0.004) and shorter PSA progression-free survival (median, 1.3 months vs. not reached; P<0.001), clinical or radiographic progression-free survival (median, 2.3 months vs. not reached; P<0.001), and overall survival (median, 10.6months vs. not reached, P = 0.006).

The biological heterogeneity of the CRPC and the adaptation of the tumor cells to the microenvironment clearly indicate the needs for an effective AR independent tumor targeting strategy and the importance of distinguish these patients with primary resistance to AR targeted therapy with appropriate monitoring during the treatment.

COU-AA-302 study is the pivotal study of studying abiraterone acetate's activity in the chemo-naïve mCRPC patient population and subsequently led to the approval by the FDA for using abiraterone for the treatment of mCRPC patients prior to docetaxel treatment. Additional analyses were also performed including the response. Although treatment decisions for COU-AA-302 were not made on the basis of PSA alterations, other studies have suggested a prognostic value of PSA declines of 50% or greater from baseline in relation to survival with a variety of therapies in patients with mCRPC. In an exploratory analysis of COU-AA-302, Ryan et al. examined the relationship between baseline PSA and degree of PSA decline with radiographic Progression-Free Survival (rPFS) and other clinical efficacy outcomes in patients with mCRPC treated with abiraterone acetate (23). This analysis found that PSA decline rates were greater and the degree of decline higher in the abiraterone acetate treatment arm compared with the prednisone arm. Interesting, they also found that rPFS, OS, and TTPP were positively associated with the magnitude of PSA decline and inversely associated with baseline PSA in a step-wise fashion. Importantly, the patient group who has not achieved a PSA response as defined by ≥50% decline from the baseline in response to treatment was associated with no or limited improvements in clinical outcomes compared to patients who had a PSA response. Thus it is important to investigate the PSA kinetics in patients treated with AR targeted therapy to quickly identify the patients who might have limited benefit from AR targeted therapy. In addition, Rathkopf published data suggesting that the median TTPP is 11.1 months for patients treated with abiraterone Acetate in chemo-naïve patients (24).

Hormonal intra-class cross resistance has been reported recently. While the mechanisms of action of enzalutamide and abiraterone acetate differ by either direct inhibition of AR or inhibition of extragonadal androgen synthesis, both target AR signaling. Two retrospective studies evaluating the antitumor activity of abiraterone acetate in patients with CRPC who progressed following

treatment with enzalutamide have documented lower PSA response rates and smaller decreases in PSA.

In these studies, a small population of patients sequentially treated with abiraterone acetate after having received docetaxel and enzalutamide, both studies reported that only a small subset of patients showed significant benefit from sequential treatment. In the first study (25), among 38 patients, abiraterone acetate resulted in ≥50% decrease in PSA in only 3 patients (1 who failed to respond to enzalutamide and 2 with prior response to enzalutamide) suggesting clinical cross resistance between the AR-targeted agents. These findings mirror the second study of a multicenter review of 30 patients treated with enzalutamide followed by abiraterone acetate treatment. In the second study, abiraterone acetate, administered for a median of 13 weeks, resulted in no objective radiographic responses. Best response to enzalutamide was 90%, 50% and 30% decrease in PSA in 23%, 63% and 70% of patients, respectively. In contrast, the best response to abiraterone acetate was 90%, 50% and 30% decrease in PSA in 0%, 3% and 11% of patients, respectively. Among the 21 patients with prior ≥30% decrease in PSA on enzalutamide, only one patient had a >30% decline in PSA with abiraterone acetate (26).

Similar to the observation of switching from enzalutamide to abiraterone acetate, the reduced response rate was also observed when patients received enzalutamide treatment post abiraterone acetate therapy from several retrospective studies. A pilot study evaluated the biochemical response to enzalutamide in 35 patients with CRPC who had previously received docetaxel followed by abiraterone acetate. A decrease in PSA >50% was achieved by 10 (28.6%) patients. Patients with >50% response in PSA had a significantly longer mean duration of enzalutamide than those who did not (7.8 months versus 3.8 months; P=0.001). The patients with failure to respond to enzalutamide had higher Gleason scores (8-10). A significant decline in PSA (>50%) was observed in 7 of 16 patients who had shown a similar response to abiraterone acetate in and in 3 of 19 patients (15.8%) who had no significant response to abiraterone acetate. Clinical response or stabilization of condition was observed in 19 (54.3%) of patients including six patients who had no biochemical response (27).

In a second retrospective study of enzalutamide, conducted in post-docetaxel patients also treated with prior abiraterone acetate, 39 patients were treated and 22 (56%) had no PSA decline as their best response. A total of 9 patients (23%) had a PSA decline of >50% but only 5 of these patients had a confirmed >50% PSA decline. Thus many of the reported declines in PSA were short-lived. Of the 15 patients with a >50% PSA response after abiraterone acetate, 2 had >50% PSA response to enzalutamide. Of the 22 patients without a response to abiraterone acetate, 2 had a >50% PSA response to enzalutamide. The median duration of treatment was only 2.9 months and median time to progression was 2.8 months. This compares to a median time to progression of 8.3 months in the phase III post-docetaxel AFFIRM trial. In the AFFIRM trial the RECIST response rate was 29% as compared to a RECIST response rate of 4% in this retrospective analysis (28).

More recently, the post hoc analysis of the COU-AA-302 study revealed that 88 patients who have received a second AR targeted treatment post abiraterone experienced modest clinical response rates and short treatment duration (2.8 to 3.8 month) (12).

Thus, although the data are minimal and mainly from retrospective reports, there is a strong suggestion of cross-resistance between abiraterone acetate and enzalutamide although one could

not exclude a response to enzalutamide by looking at an individual's prior data while taking abiraterone acetate. More importantly, the duration of enzalutamide treatment in the third line setting is relatively short, measuring less than 3 months.

Several retrospective studies have evaluated clinical response to the taxanes in relation to AR-targeted agents. Preliminary demonstration of possible cross-resistance between AR-targeted agents and taxanes was reported by Mezynski in a retrospective evaluation of the activity of docetaxel in CRPC patients previously treated with abiraterone acetate (29). Among the 35 patients who received docetaxel post-abiraterone acetate, the eight patients who were abiraterone acetate refractory (failed to achieve PSA decrease) were also refractory to docetaxel. In 24 patients with radiologically evaluable disease, partial responses were reported in only four patients (11%), none of whom were abiraterone acetate refractory. Of 27 patients with a ≥50% PSA decrease with abiraterone acetate, nine had a similar decrease in PSA with docetaxel and 18 did not. Translational research has shed some light for the potential biological mechanisms of this finding. An in vitro assessment showed that the taxanes, docetaxel and cabazitaxel, inhibited AR nuclear translocation (21% and 34%, respectively), albeit at lower rates than abiraterone acetate or enzalutamide (58% and 100%, respectively). These data point to a role for microtubule inhibitors in AR transport, an additional mechanism of taxane activity in CRPC, and provide insight into a potential mechanism of cross-resistance between taxanes and AR-targeted agents (30).

Furthermore, there is some evidence that cross-resistance with the AR-targeted agents may be more specific to docetaxel than to cabazitaxel. One retrospective study of cabazitaxel in 89 mCRPC patients and progressive disease after docetaxel and abiraterone acetate reported ≥50% decline in PSA in 44 patients (49%) (31). A second study evaluated response following cabazitaxel in 125 mCRPC patients. Cabazitaxel was administered after AR-targeting agents in 33% of patients and before AR-targeting agents in 16% of patients. The median overall survival from first dose of docetaxel was 65 months in the patients who received cabazitaxel before AR-targeting agents versus 39 months in those who received the AR-targeting agents before cabazitaxel (32).

While these observations require confirmation in prospective clinical trials, the data suggest that there may be less cross-resistance between cabazitaxel and the AR-targeting agents and that there may be a population of mCRPC patients who would benefit from treatment with cabazitaxel following abiraterone acetate or enzalutamide rather than rechallenge with alternative AR targeted agents.

5 STUDY OBJECTIVES

5.1 PRIMARY

To demonstrate the superiority in term of radiographic Progression-Free Survival (rPFS) [using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 and PCWG2 (1)(2) of cabazitaxel at 25 mg/m² plus prednisone (Arm A) versus either enzalutamide at 160 mg once daily or abiraterone acetate at 1000 mg once daily plus prednisone (Arm B) in chemotherapy-naïve patients with mCRPC who have disease progression while receiving AR targeted therapy (abiraterone plus prednisone or enzalutamide) within 12 months of treatment initiation (≤12 months).

5.2 SECONDARY

- To compare efficacy of cabazitaxel plus prednisone to enzalutamide or abiraterone acetate plus prednisone for:
  - PSA response rate,
  - Progression Free Survival (PFS),
  - Overall Survival (OS),
  - Time To PSA Progression (TTPP),
  - Tumor response rate in patients with measurable disease (RECIST 1.1),
  - Duration of tumor response,
  - Pain response,
  - Time To Pain Progression,
  - Symptomatic skeletal events (SSE) rate,
  - Time to occurrence of any SSE,
- To analyze messenger RNAs including androgen-receptor splice variant 7 messenger RNA (AR-V7) at baseline and post-treatment in Circulating Tumor Cells (CTCs).
- To evaluate safety in the 2 treatment arms

5.3 [redacted]

- To analyze Circulating Tumor Cells (CTCs) phenotypes as well as expression and localization of proteins including androgen receptors (AR) isoforms in CTCs at baseline.
- To collect circulating free nucleic acids (cfDNA and cfRNA) derived from plasma at baseline, on treatment and post-treatment for biomarker studies.
- To collect germline DNA derived from whole blood at baseline for biomarker studies and subtractive mutation analysis.

6 STUDY DESIGN

This is a prospective, multicenter, multinational, randomized, open label study, comparing the efficacy of cabazitaxel at 25 mg/m² plus prednisone (Arm A) versus either enzalutamide at 160 mg once daily or abiraterone acetate at 1000 mg once daily plus prednisone (Arm B). Resistant population is defined as patients who have disease progression while receiving AR targeted therapy within 12 months of treatment (≤12 months) (3).

6.1 DESCRIPTION OF THE PROTOCOL

Treatment allocation will be performed by an Interactive Voice/Web Response System (IVRS/IWRS). All eligible patients will be randomly assigned to either arm A or B in a 1:1 proportion.

Randomization will be stratified by: extra nodal visceral metastases (yes, no), and level of PSA decline within 12 months of initiation of AR targeted therapy (no decline, decline 1% to <50%, decline ≥50%) and time from AR targeted agent initiation to progression ([0; 6 months],]6; 12 months]).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Each patient will be treated until radiographic disease progression, unacceptable toxicity, or patient's refusal of further study treatment. The study period will include the screening phase, the study treatment period (until 30 days after last cabazitaxel or abiraterone acetate or enzalutamide administration) and the follow-up period. Cabazitaxel will be administered every 3 weeks. The comparators will be given orally continuously. The first study treatment should be administered within 7 calendar days after randomization. The time between biological work-up and first cycle should not exceed 8 days. If it is the case, hematology and biochemistry should be done again before first cycle in order to check that eligibility criteria are still met. After study treatment discontinuation, patient 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, ongoing related AEs at end of treatment and all (serious or non-serious) new adverse events related to study treatment will be collected and followed until resolution or stabilization.

Patients still on study treatment at the cut-off date can continue treatment until at least 1 treatment permanent discontinuation criterion as defined in Section 10.3.2 is met.

If a patient discontinues study treatment due to reason other than radiographic progressive disease, investigator may consider not initiating further anticancer therapy before radiographic progression is documented. In case it occurs within the 4 first cycles, initiation or not of further anticancer therapy before radiographic progression is documented, is left to the investigator decision.

6.2.2 Determination of end of clinical trial (all patients)

The study is event driven and the final cut-off date will be when 155 disease progression events have occurred (expected to occur around 30 months from first patient in).

End of trial will occur 30 days after the last patient last cycle.

6.3 INTERIM ANALYSIS

No Interim analysis is planned.

6.4 STUDY COMMITTEES

A Steering Committee (SC), including the 3 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,

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

Patients meeting all the following criteria will be considered eligible for enrolment into the study:

I 01. Diagnosis of histologically or cytologically confirmed prostate adenocarcinoma

I 02. Metastatic disease

I 03. Progressive disease (PD) while receiving AR targeted therapy with abiraterone acetate or enzalutamide within 12 months of treatment initiation (≤12 months) by at least one of the following:

a) Progression in measurable disease (RECIST 1.1 criteria). Patient with measurable disease must have at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be at least 10 mm when measured by computed tomography (CT) [CT scan thickness no greater than 5 mm] or magnetic resonance imaging (MRI). Lymph nodes should be ≥15 mm in short axis. As defined by PCWG2, if lymph node metastasis is the only evidence of metastasis, it must be ≥20 mm in diameter when measured by spiral CT or MRI. Previously irradiated lesions, primary prostate lesion and bone lesions will be considered non-measurable disease, and/or

b) Appearance of 2 or more new bone lesions. They must be confirmed by other imaging modalities (CT; MRI) if ambiguous results (PCWG2), and/or

c) Rising PSA defined (PCWG2) as at least two consecutive rises in PSA to be documented over a reference value (measure 1) taken at least one week apart. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2nd beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the 2nd measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than the 2nd measure. The third (or the fourth) confirmatory PSA should be taken within 4 weeks prior to randomization Appendix A. In case of progression based on rising PSA only, the first rising PSA (measure 2) must be obtained within 6 months of initiation of AR targeted therapy (≤6 months).

Duration of the first AR targeted agent treatment should not exceed 12 months for patients with PD within 6 months and should not exceed 18 months for those with PD between 6 and 12 months.

I 04. A PSA value of at least 2 ng/mL is required at study entry.

I 05. Effective castration (serum testosterone levels <0.5 ng/mL).

I 06. Prior AR targeted therapy (abiraterone acetate or enzalutamide) must be stopped at least 2 weeks before study treatment.

I 07. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 2 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Prior chemotherapy for prostate cancer, except estramustine and except adjuvant/neoadjuvant treatment completed >3 years ago. No further anti-cancer therapy after the previous AR targeted therapy and before inclusion. Prior docetaxel in hormone sensitive setting is allowed if completed >1 year before randomization (4). Prior immunotherapy is allowed.

E 02. Less than 28 days elapsed from prior treatment with immunotherapy, radiotherapy or surgery to the time of randomization.

E 03. Adverse events (excluding alopecia and those listed in the specific exclusion criteria) from any prior anticancer therapy of grade >1 (National Cancer Institute Common Terminology Criteria of Adverse Events [NCI CTCAE] v4.0) at the time of randomization.

E 04. Less than 18 years (or country's legal age of majority if the legal age is >18 years).

E 05. Eastern Cooperative Oncology Group (ECOG) performance status >1.

E 06. History of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis or new evidence of brain or leptomeningeal disease.

E 07. Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) bladder cancer are allowed, as well as any other cancer for which treatment has been completed ≥5 years ago and from which the patient has been disease-free for ≥5 years.

E 08. Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization.

E 09. Acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral treatment.

E 10. Any severe acute or chronic medical condition including uncontrolled diabetes mellitus, severe renal impairment, history of cardiovascular disease (uncontrolled hypertension, arterial thrombotic events in the past 6 months , congestive heart failure, severe or unstable angina pectoris, recent myocardial infraction within last 6 months or uncontrolled cardiac

arrhythmia), which could impair the ability of the patient to participate to the study or interfere with interpretation of study results, or patient unable to comply with the study procedures.

E 11. Patients with reproductive potential who do not agree to use accepted and effective method of contraception during the study treatment period and up to 6 months after the last administered dose. The definition of "effective method of contraception" will be based on the investigator's judgment.

7.2.2 Exclusion criteria related to study treatment

E 12. Known allergies, hypersensitivity or intolerance to prednisone or excipients of abiraterone acetate or enzalutamide. History of hypersensitivity to docetaxel or polysorbate 80.

E 13. Known history of mineralocorticoid excess or deficiency (not applicable to patients who have already been treated with abiraterone acetate in first line before inclusion).

E 14. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain arteriovenous malformation or the use of concomitant medications that may lower the seizure threshold (not applicable to patients who have already been treated with enzalutamide in first line before inclusion).

E 15. Unable to swallow a whole tablet or capsule.

E 16. Inadequate organ and bone marrow function as evidenced by:

a) Hemoglobin <10.0 g/dL
b) Absolute neutrophil count <1.5 x 109/L
c) Platelet count <100 x 109/L
d) AST/SGOT and/or ALT/SGPT >1.5 x ULN;
e) Total bilirubin >1.0 x ULN
f) Potassium <3.5 mmol/L
g) Serum albumin <3.0 g/dL
h) Child-Pugh Class B and C

E 17. Contraindications to the use of corticosteroid treatment.

E 18. Symptomatic peripheral neuropathy grade ≥2 (National Cancer Institute Common Terminology Criteria of Adverse Events [NCI CTCAE] v4.0).

E 19. Concomitant vaccination with yellow fever vaccine.

8 STUDY TREATMENTS

Name and formulation details of drugs used in study are summarized in Table 1 below.

Table 1 - Study treatments

Drug code	**XRP6258**	**-**
INN	**cabazitaxel**	**prednisone or prednisolone**
Formulation	Cabazitaxel is supplied as a sterile, non-pyrogenic, non-aqueous yellowish to brownish yellow solution contained in a 15 mL clear glass vial, stoppered with a chlorobutyl rubber closure coated with a transparent ETFE coating. The rubber closure is crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap. Single-dose vial, containing a total of 60 mg of cabazitaxel expressed as anhydrous and solvent-free basis, per 1.5 mL of solution. The fill volume has been established to include an overfill [ie, 1.5 mL (nominal volume) + 0.33 mL]. This overfill was determined to ensure that a 10 mg/mL concentration is obtained in the premix and that 60 mg dose can be extracted. The solvent used for the preparation of the premix is a sterile, non-pyrogenic solution containing a 13% w/w ethanol solution in water for injection. This solution is contained in a 15 mL clear glass vial, stoppered with a chlorobutyl rubber closure coated with a transparent ETFE coating. The rubber closure is crimped to the vial with either an aluminum cap covered with a light grey plastic flip-off cap or a gold-color aluminum cap covered with a clear plastic flip-off cap. Each vial of solvent is overfilled to ensure that a 10 mg/mL concentration is obtained in the Premix and that 60 mg dose can be extracted. [ie, 4.5 mL (nominal volume) + 1.17 mL]. The solution is a clear colorless liquid.	Commercially available formulation (refer to the local labeling)
Storage conditions	Store at 25°C (77°F); excursions permitted between 15°-30°C (59°- 86°F). Do not refrigerate. The solvent was also shown to be stable under these conditions. All vials must be kept in their box until use.	Refer to the local labeling.

8.1 INVESTIGATIONAL MEDICINAL PRODUCTA

CABAZITAXEL

8.1.1 Preparation and administration of cabazitaxel

The preparation of the cabazitaxel (XRP6258) infusion solution for administration requires the preparation of a premix solution at 60 mg/6 mL (nominal concentration). This must be done with a 13% w/w ethanol solution in water for injection (the "solvent") supplied with the cabazitaxel concentrate for solution for infusion ("preparation of the premix solution"). Then the premix

solution must be diluted in an infusion vehicle ("preparation of the infusion solution") prior to administration.

8.1.1.1 Preparation of the premix solution under aseptic conditions

Set aside the required number of solvent vials (one solvent vial for each vial of cabazitaxel). For each cabazitaxel vial:

- Using a syringe fitted with a needle, withdraw the ENTIRE CONTENTS of the solvent vial and inject it into the corresponding vial of cabazitaxel.
- The addition of the ENTIRE CONTENTS of 1 solvent vial ensures a minimal extractable volume of the premix solution of 6 mL, containing 10 mg/mL of cabazitaxel.
- Remove the syringe and needle and gently mix the reconstituted solution by repeated inversions for at least 45 seconds. Do not shake.
- Allow the premix solution to stand for 5 minutes at room temperature to allow foam to dissipate. The solution is homogeneous and contains no visible particulate matter. It is normal for foam to persist after this time period.

The premix solution contains 10 mg/mL of cabazitaxel. Then the premix solution must be diluted in an infusion vehicle so as to obtain the required dose for administration.

8.1.1.2 Preparation of the infusion solution under aseptic conditions

WARNING: Since foam is normally present, the required dose must be accurately adjusted using a graduated syringe.

- Aseptically, with a syringe and needle, withdraw the volume of the premix solution containing 10 mg/mL of cabazitaxel that corresponds to the required dose (mg) for administration of cabazitaxel
- Inject the required premix volume into a 125 or 250 or 500 mL infusion container (containing either 5% glucose solution or 0.9% sodium chloride solution).

The concentration of the infusion should be between 0.10 mg/mL and 0.26 mg/mL (based on Maximum Tolerated Dose of 30 mg/m² and a Body Surface Area [BSA] of 2.1 m²).

Mix the contents of the infusion container manually by gently inverting the bag or bottle.

8.1.1.3 Infusion conditions

The recommended infusion duration is 1 hour. The infusion solution should be used within 8 hours at ambient temperature (including the one hour infusion time) or within a total of 48 hours if refrigerated (including the 1 hour infusion time).

The infusion solution should be administered at room temperature under normal lighting conditions.

Do not use PVC infusion containers or polyurethane infusion sets for cabazitaxel preparation and administration.

Glass bottles could also be used.

Use and in-line filter of 0.22 µm nominal pore size (also referred to as 0.2 µm) during cabazitaxel administration.

8.1.1.4 Storage period of premix and infusion solution

The premix solution of cabazitaxel should be used immediately after preparation and within 1 hour at ambient temperature.

The infusion solution is stable for 8 hours at ambient conditions (including the 1 hour infusion time) or a total of 48 hours if refrigerated, from preparation to end of infusion.

8.1.1.5 Recommendation for safe handling

Cabazitaxel is an anti-neoplastic agent and, like other potentially toxic compounds, caution should be exercised in handling and preparing cabazitaxel solutions. The use of gloves is recommended.

If cabazitaxel concentrate, premix solution, or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If cabazitaxel concentrate, premix solution, or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

8.1.2 DOSAGE AND SCHEDULE

BSA will be calculated prior to each treatment cycle from body weight in kg, recorded prior to each treatment cycle, and height in cm, recorded at baseline. The preferred Dubois and Dubois equation is: BSA in units of m2 = wgt in kg 0.425 x hgt. in cm 0.725 x 0.007184.

The treatment should continue for at least 12 weeks (4 cycles) in the absence of radiological evidence of disease progression defined in Section 9.1 or unacceptable toxicity or patient refusal of further treatment. Subsequently, no decision of treatment discontinuation should be made in case of PSA increase ALONE or pain increase ALONE, within the first 12 weeks see Sections 9.2.1.2 and 9.2.5.2.

Each patient will be treated until radiographic progressive disease, unacceptable toxicity, patient's refusal of further study treatment or any other discontinuation criteria as defined in Section 10.3.2.

In case of patient discontinues study treatment due to reason other than radiological progressive disease, the investigator may consider not to initiate further anticancer therapy before radiological progression is documented (as defined in Section 9.1), in case study treatment discontinuation occurs within the 4 first cycles the decision is left to investigator judgment.

Dose adjustment will be permitted for subsequent treatment cycles based on individual patient tolerance (see Section 8.1.2.3) Treatment will continue unless any of the Withdrawal Criteria are met as described in Section 10.3.2.

8.1.2.1 STUDY TREATMENTS

Cabazitaxel 25 mg/m² in dextrose 5% or NaCl 0.9% (for volume see Section 8.1.1.2) intravenously on day 1 every 3 weeks, plus prednisone (or prednisolone) 10 mg orally given daily.

8.1.2.2 Premedication

For cabazitaxel premedication will include an antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or other antihistamine), steroid (dexamethasone 8 mg or equivalent steroid), and H2 antagonist (ranitidine 50 mg or other H2 antagonist). These premedications will be administered by IV infusion, at least 30 minutes prior to each dose of cabazitaxel. For countries where IV antihistamines are not available, oral instead of IV antihistamines can be used according to the local practice.

For cabazitaxel appropriate prophylactic antiemetic therapy is left to current hospital practices.

Primary prophylactic with G-CSF should be considered in patients with high-risk clinical features (age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status or other serious comorbidities) according to ASCO guidelines (33) and it is left to the investigator's judgment.

8.1.2.3 [redacted]

8.1.2.3.1 [redacted]

[redacted]

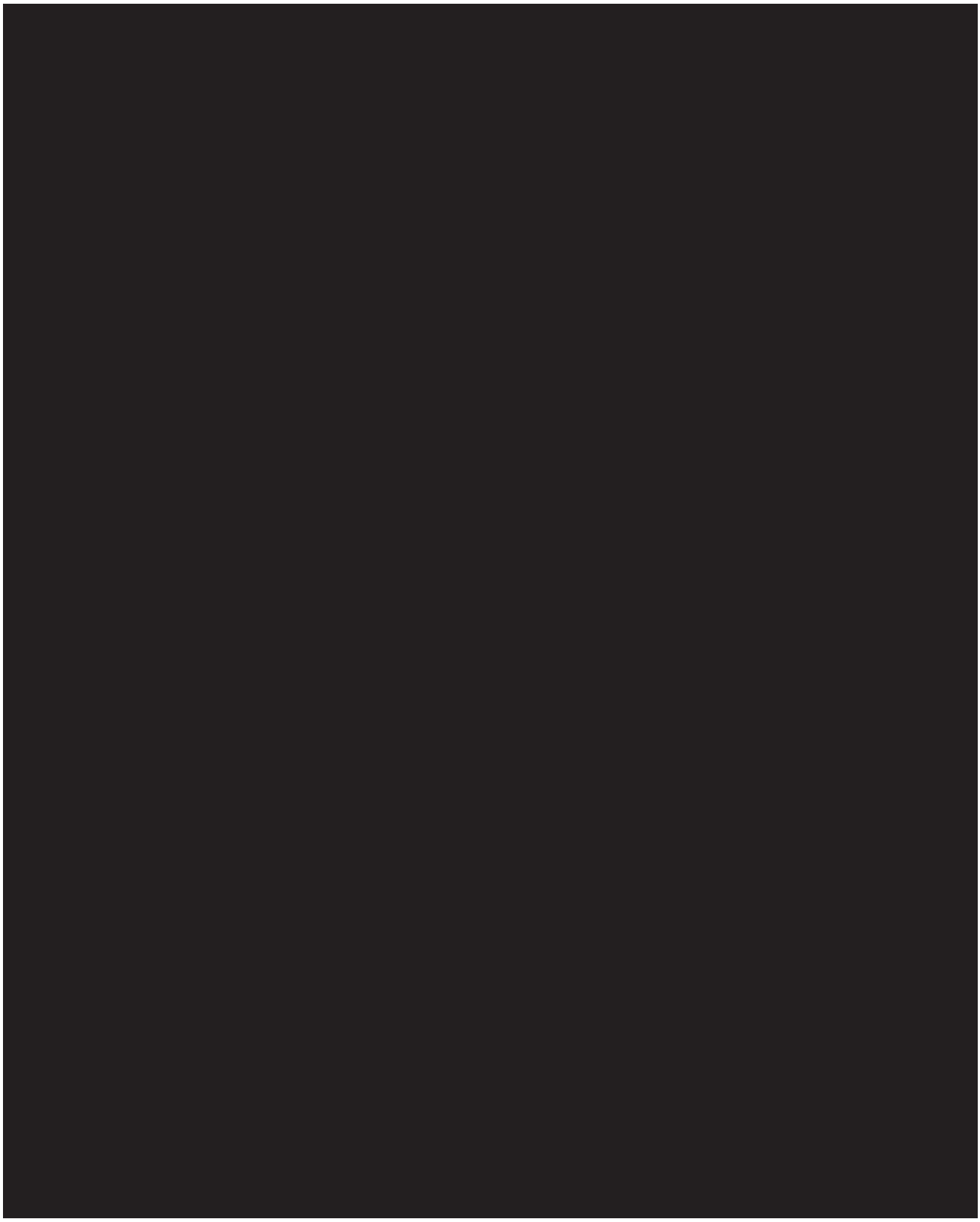
[redacted]

[redacted]

8.1.2.3.2 [redacted]

[redacted]

[redacted]



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8.1.2.3.3 [redacted]

8.1.2.3.3.1 [redacted]

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8.1.2.3.3.2 [redacted]

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[redacted]

8.1.2.3.3.3 [redacted]

[redacted]

8.1.2.3.3.4 [redacted]

[redacted]

8.1.2.3.3.5 [redacted]

[redacted]

8.2 OTHER INVESTIGATIONAL MEDICINAL PRODUCT(S)

Commercially available formulation of abiraterone acetate and enzalutamide will be used.

8.2.1 Administration

For abiraterone acetate and enzalutamide, refer to the package insert or summary of product characteristics for details on description, administration, and precautions for use.

8.2.2 [redacted]

8.2.2.1 [redacted]

In clinical studies, abiraterone acetate was generally tolerated without dose interruptions or

[redacted]

8.2.3 Management of Toxicity related to Abiraterone Acetate

For additional information refer to the ZYTIGA® (abiraterone acetate) package insert for details on description, preparation, administration, and precautions for use.

8.2.3.1 Management of Hypokalemia

At the initial observation of Grade 1 or 2 hypokalemia (serum potassium <3.5 mM or below lower limit of normal range, but ≥3.0 mM), oral potassium supplement will be initiated. The dose of potassium supplement must be carefully titrated to maintain serum potassium from 3.5 to 5.0 mM, inclusive. Any subject with low potassium during the study or a history of hypokalemia from a preexisting or concurrent medical condition will undergo at least weekly laboratory electrolyte evaluation until recovery to the range ≥3.0 mM. The investigator should consider maintaining potassium ≥4.0 mM in these subjects Table 6.

If any subject experiences Grade 3 symptomatic hypokalemia (serum potassium levels <3.0 to 2.5 mM, NCI-CTCAE version 4.0) or life-threatening hypokalemia with potassium levels <2.5 mM (NCI-CTCAE version 4.0, hypokalemia Grade 4), abiraterone acetate treatment will be withheld and the subject will be hospitalized for IV potassium replacement and cardiac monitoring. Re-initiation of abiraterone acetate treatment after normalization of potassium levels must be discussed with and approved by the Sponsor's medical monitor Table 6.

Table 6 - Management of Hypokalemia

Serum K+	Grade of Hypokalemia	Action	Further Action or Maintenance
Low potassium or history of hypokalemia		Weekly (or more frequent) laboratory electrolyte evaluations	Titrate dose to maintain a serum potassium ≥3.5 mM ≤5.0 mM (maintenance of subjects at ≥4.0 mM is recommended)
<3.5 mM to 3.0mM	Grade 1 or 2	Initiate oral or IV potassium supplementation Consider monitoring magnesium and replacement if needed	Titrate dose to maintain a serum potassium ≥3.5 mM to ≤5.0 mM (maintenance of subjects at ≥4.0 mM is recommended)
<3.0 mM to 2.5 mM	Grade 3	Withhold abiraterone acetate (and initiate oral or IV potassium and cardiac monitoring Consider monitoring magnesium and replacement if needed	Call the Sponsor's medical monitor prior to re-initiating study drug
<2.5 mM	Grade 4	Withhold abiraterone acetate and initiate oral or IV potassium and cardiac monitoring Consider monitoring magnesium and replacement if needed	Call the Sponsor's medical monitor prior to re-initiating study drug

IV=intravenous; mM=millimolar.

8.2.3.2 Management of Hypertension

- If Grade 1 or 2 AEs occur, management per investigator. No abiraterone acetate dose reduction.

- If Grade 3 or 4 AEs occur, withhold abiraterone acetate. Adjust or add medications to mitigate the toxicity or consider the specific mineralocorticoid receptor blocker, eplerenone (the dose not to exceed 200 mg/D). When hypertension resolves to ≤Grade 1, resume study drug at full dose.
- If toxicity recurs, withhold abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolved to ≤Grade 1, resume abiraterone acetate with the first dose level reduction (3 tablets, 750 mg of study drug).
- If toxicity recurs, withhold abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolved to ≤Grade 1, resume abiraterone acetate with the second dose level reduction (2 tablets, 500 mg of abiraterone acetate).
- If toxicity recurs despite optimal medical management and the dose reduction, discontinue abiraterone acetate.

8.2.3.3 Management of Fluid Retention/ Edema

- If lower limbs edema occurs, supportive management per investigator. No abiraterone acetate dose reduction.
- If Grade 3 pulmonary edema requiring supplemental oxygen occurs, withhold abiraterone acetate. Adjust or add medications to mitigate the toxicity and consider the specific mineralocorticoid receptor blocker, eplerenone (the dose not to exceed 200 mg/D). When toxicity resolves to ≤ Grade 1, resume abiraterone acetate at full dose.
- If toxicity recurs, withhold abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolved to ≤Grade 1, resume abiraterone acetate with the first dose level reduction (3 tablets, 750 mg of abiraterone acetate).
- If toxicity recurs, withhold abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolved to ≤Grade 1, resume abiraterone acetate with the second dose level reduction (2 tablets, 500 mg of abiraterone acetate).
- If toxicity recurs despite optimal medical management and the dose reduction, discontinue abiraterone acetate.

8.2.3.4 Management of Abnormal Liver Function Tests

For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]), treatment should be withheld immediately. Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (two tablets) once daily. For patients being re-treated, serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued. If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, treatment should be discontinued and patients should not be re-treated.

8.2.3.5 Management of Non-Mineralocorticoid Based Side Effects

- If Grade 1 to 2 toxicities occur, give supportive care per institutional guidelines. No abiraterone acetate dose reduction.
- If Grade 3 or higher toxicities occur, including headache (interferes with activities of daily living), nausea (total parenteral nutrition/IV fluids), vomiting (6 or more episodes in 24 hours, total parenteral nutrition/IV fluids), diarrhea (IV fluids, hospitalization, hemodynamic collapse), or any other toxicity judged related to abiraterone acetate is observed where the subjects safety is jeopardized, hold abiraterone acetate.
- When toxicity resolves to ≤Grade 1, resume abiraterone acetate at full dose.
- If toxicity recurs, withhold abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolved to ≤Grade 1, resume abiraterone acetate with the first dose level reduction (3 tablets, 750 mg of abiraterone acetate).
- If toxicity recurs, withhold abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolved to ≤Grade 1, resume abiraterone acetate with the second dose level reduction (2 tablets, 500 mg of abiraterone acetate).
- If toxicity recurs despite aggressive medical management and 2 dose level reductions, discontinue abiraterone acetate.

8.2.3.6 Drug interactions

Co-administration of a strong CYP3A4 inducer, decreases exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during abiraterone acetate treatment Appendix G.

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index Appendix G.

8.2.4 [redacted]

[redacted]

8.2.4.1 [redacted]

[redacted]

[redacted]

8.2.4.2 [redacted]

[redacted]

8.3 NON INVESTIGATIONAL MEDICINAL PRODUCT

Prednisone or prednisolone as associated product during treatment with cabazitaxel and abiraterone:

Commercially available products will be used (oral route). The choice of the product is left to the investigator's decision. The package insert or summary of product characteristics for details on description, administration, and precautions for use will be used.

8.4 BLINDING PROCEDURES

8.4.1 Methods of blinding

No blinded central review will be done, however all the images (MRI, CT scan and bone scan) will be archived centrally by the vendor in case of discrepancies, unexpected findings or regulatory may request a central review.

8.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

8.5.1 Patient number and treatment number

Patients who meet all inclusion criteria and none of the exclusion criteria are deemed eligible for randomization.

Randomization and treatment allocation(s) will be performed centrally by an interactive voice/Web response system (IVRS/IWRS). A randomized patient is a patient with a patient number and a treatment allocated by the IVRS/IWRS.

8.5.2 Allocation of treatment(s)

Treatment will be allocated by the IVRS/IWRS to either arm in a 1:1 ratio.

Randomization will be stratified by:

- Extra nodal visceral metastases (yes, no),
- Level of PSA decline within 12 months of initiation of AR targeted therapy (no decline, decline 1% to < 50%, decline ≥50%).
- Time from AR targeted agent initiation to progression ([0; 6 months],]6; 12 months]

8.6 PACKAGING AND LABELING

This is an open label study. The Investigational Medicinal Product (cabazitaxel) will be packaged in:

- Sterile, single-use vials

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

For infusion conditions, see Section 8.1.1.3 (PVC-free material).

8.7 STORAGE CONDITIONS AND SHELF LIFE

Cabazitaxel (concentrate for solution for infusion) as packaged should be stored between 15°C and 30°C. Do not refrigerate.

The solvent was also shown to be stable under these conditions.

All vials must be kept in their box until use.

Abiraterone acetate and Enzalutamide: refer to the package insert (PI) or the summary of product characteristics (SmPC).

8.8 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the Investigational Medicinal Product (IMP) will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allows the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.8.1 Treatment accountability and compliance

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational medicinal product. The study drug must be kept in a locked area with restricted access. The study drug must be stored and handled in accordance with the manufacturer's instructions. The investigator or pharmacist will also keep accurate records of the quantities of the study drugs dispensed and used by each patient. The study monitor will periodically check the supplies of study drugs held by the investigator or pharmacist to verify accountability of all study drugs used. At the conclusion of the study, all unused study drugs and all medication containers will preferably be destroyed at the investigational site (at a locally authorized facility) according to local regulation unless other arrangements have been approved by the Sponsor. Destruction of unused vials will occur only after drug accountability has been performed and written permission

for destruction has been obtained. Used medication vials may be destroyed during the conduct of the study as required by the institution.

The investigator or sub-investigator will supervise administration of the investigational drug. Any delegation of this responsibility must follow Section 13.1.

The person responsible for drug dispensing is required to maintain adequate records of all study drugs. These records (eg, drug inventory form) include the date the study medication is received from the Sponsor, dispensed for patient, and destroyed or returned to the Sponsor as detailed in (Section 8.8.2). The fixed label portions of all the cabazitaxel vials administered to patients must be completed (patient number, date of infusion). The batch number (PR number) on the vial must be recorded on the CRF/drug accountability form.

The person responsible for drug administration to the patient will record precisely the dose, date, and time the drug is administered to the patient.

8.8.2 Return and/or destruction of treatments

Partially used cabazitaxel will be destroyed on site according to standard practices of the site. Unused cabazitaxel will be destroyed on site after final batch accountability has been validated by the sponsor monitoring team representative and only after having received written authorization from the sponsor.

In the event of a potential defect in the quality of Investigational Medicinal Product, it may be necessary for the Sponsor to initiate a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Investigational Medicinal Product and eliminate potential hazards.

8.9 CONCOMITANT MEDICATION

All treatments being taken by the patient within 4 weeks prior to the start of study treatment, or at any time during the study and up to 30 days after the end of study treatment in addition to the Investigational Medicinal Product are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the Investigational Medicinal Product, they may be given at the discretion of the investigator and recorded in the eCRF.

The following concomitant treatments <u>are not permitted</u> during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy including immunotherapy, targeted therapy or biological therapies.

  Palliative radiotherapy given for pain control is a pain progression criterion (see Section 9.2.5.2). Therefore, palliative radiotherapy is not allowed, except if initiated within the 12 first weeks after initiation of the study treatment (pain alone within the first 12 weeks should not be considered as PD).

- Concurrent treatment with strong inhibitors of cytochrome P450 3A4 (Appendix G(, such as ketoconazole, itraconazole, clarythromycin. For patients who were receiving treatment with such agents, a two-week washout period is required prior to randomization.
- Concurrent treatment with potent strong or moderate inducers of cytochrome P450 3A4, such as the antiepileptic drugs carbamazepine, phenytoin, phenobarbital, and St John Wort (millepertuis) (Appendix G). For patients who were receiving treatment with such agents, a two-week washout period is required prior to randomization.
- Concurrent treatment with CYP2D6 substrates and that have a narrow therapeutic window. For patients who were receiving treatment with such agents, a two-week washout period is required prior to randomization (Appendix G).
- Concurrent treatment with strong or moderate inducers or strong inhibitors of CYP2C8. For patients who were receiving treatment with such agents, a two-week washout period is required prior to randomization (Appendix G).
- Concurrent treatment with CYP3A4, CYP2C9 and CYP2C19 substrates with a narrow therapeutic index. For patients who were receiving treatment with such agents, a two-week washout period is required prior to randomization (Appendix G).

The following concomitant treatments <u>are permitted</u> during this study:

- LH-RH agonists or antagonist that are ongoing prior to study entry. In addition, patients who are treated with LH-RH agonists or antagonist (ie, without orchiectomy) should continue this therapy during the study treatment period
- The use of bisphosphonates and denosumab are allowed, however the dose must be stable for 4 weeks prior to enrollment and during the study treatment period (though bisphosphonate or denosumab treatment may be discontinued during the study treatment period). Vitamin D and calcium are allowed to treat osteoporosis.
- Ancillary treatment must be given as medically indicated; they must be specified in the CRF.
- Primary prophylactic with G-CSF should be considered in patients with high-risk clinical features (age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status or other serious comorbidities) according to ASCO guidelines (33) and is left to the investigator's judgment.
- Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrheal treatments (eg, loperamide) are recommended (see Section 8.1.2.3.3.3).
- Supportive treatment as medically indicated for the patient's well-being (including hyperalimentation and blood transfusion) may be prescribed at the investigator's discretion. Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded on the CRF.
- Use of erythropoietin for chemotherapy-related anemia.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

Radiographic Progression-Free Survival (rPFS) defined as the time from randomization to the occurrence of one of the following:

- Radiological tumor progression using RECIST 1.1 (Appendix B).
- Progression of bone lesions using 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 taken ≥6 weeks later showing ≥2 additional new lesions compared to week 9 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).

  Lymph nodes that progress but <20 mm in short axis should not be considered as PD.
- Death due to any cause

9.2 SECONDARY ENDPOINTS

The secondary efficacy endpoints will include:

9.2.1 PSA endpoints

PSA-derived efficacy endpoints in this study will include PSA response, duration of PSA response and Time to PSA progression. 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. Two PSA determinations are needed to define PSA progression.

9.2.1.1 PSA response

PSA response defined as a decline of serum PSA from baseline of ≥50% confirmed at least 3 weeks later. It will be calculated among patients with a baseline PSA ≥10 ng/mL. Increases (of any magnitude) in PSA during the first 12 weeks should be ignored in determining PSA response.

9.2.1.2 Time to PSA progression (TTPP)

Time to PSA progression is defined as the time interval between the date of randomization and the date of first documented PSA progression.

PSA progression is defined as (2) (Appendix A):

- Decline from baseline: an increase of ≥25% (at least 2ng/mL) over the nadir value, confirmed by a second PSA value at least 3 weeks apart.
- No decline from baseline: an increase of ≥25% (at least 2ng/mL) over the baseline value after 12 weeks of treatment, confirmed by a second PSA value at least 3 weeks apart.

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 was associated with another sign of disease progression.

9.2.2 Progression free survival

Progression free survival (PFS) will be evaluated from the date of randomization to the date of the first documentation of any of the following events:

- Radiological tumor progression using RECIST 1.1.
- Progression of bone lesions using 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 taken ≥6 weeks later showing ≥2 additional new lesions compared to week 9 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).

  Lymph nodes that progress but < 20 mm in short axis should not be considered as PD.
- PSA progression,
- Pain progression,
- Or death due to any cause.

9.2.3 Overall Survival

The Overall Survival (OS) is defined as the time interval from the date of randomization to the date of death due to any cause.

9.2.4 Tumor endpoints

9.2.4.1 Tumor response

Tumor response will be analyzed in patients with measurable disease (RECIST 1.1).

Tumor response is defined as either a partial response (PR) or complete response (CR) according to the RECIST 1.1 criteria (see Appendix B).

9.2.4.2 Duration of tumor response

Duration of tumor response is defined as the time between the first evaluation at which the response criteria (PR-CR as per RECIST 1.1) are met and the first documentation of tumor progression.

9.2.5 Pain endpoints

Diary will be utilized to collect analgesic consumption and pain scores in all patients (Appendix E). The Brief Pain Inventory-Short Form (BPI-SF) will be utilized to assess pain). Pain scores (WHO Analgesic Ladder and BPI-SF) will be assessed in all patients at baseline, before each cycle, at the end of treatment and then every 12 weeks until disease progression, start of another anticancer therapy or study cut off, whichever comes first.

9.2.5.1 Pain response

Pain response is defined as:

- A decrease by <30% from baseline in the average of BPI-SF pain intensity score observed at 2 consecutive evaluations ≥3 weeks apart without increase in analgesic usage score (defined as a ≥1 point increase on the WHO analgesic scale).

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

Increases in pain during the first 12 weeks should be ignored in determining pain response.

9.2.5.2 Time to pain progression

Time to pain progression is defined as the time interval between the date of randomization and the date of either first documented pain progression.

Pain progression is defined as:

- An increase by ≥30% from baseline in the average of 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 of 30% or greater.

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.

9.2.6 Symptomatic skeletal events

9.2.6.1 SSE rate

SSE assessment will be performed by clinical evaluation. Occurrence of SSE is defined as:

- The occurrence of a new symptomatic pathological fracture, or
- The use of external beam radiation to relieve bone pain,or
- The occurence of spinal cord compression, or
- Tumor-related orthopeadic surgical intervention

SSE is not a criterion of progression.

9.2.6.2 Time to occurrence of SSE

Time to SSE is defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SSE, whichever is earlier. For each patient, SSE will be assessed at baseline, every 3 weeks during study treatment, and every 12 weeks during follow-up until occurrence of first SSE or study cut off, whichever comes first.

9.2.7 Biomarkers

Analysis of messenger RNAs including androgen-receptor splice variant 7 messenger RNA (AR-V7) at baseline and post-treatment in Circulating Tumor Cells (CTCs).

Detection of AR-V7 in CTCs from patients with CRPC may be associated with resistance to enzalutamide and abiraterone (22).

9.3 SAFETY ENDPOINT

9.3.1 Adverse events

Treatment-emergent adverse events: Type according to MedDRA (Medical Dictionary for Regulatory Activities), frequency, severity according to NCI CTCAE V4.0, seriousness, and relationship to study treatment will be assessed.

Refer to Section 10.4 to Section 10.6 for details.

9.3.2 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry and urinalysis). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

Laboratory abnormalities will be assessed according to the NCI CTCAE v.4.0.

9.3.3 Vital signs

Vital signs include: blood pressure, heart rate.

9.3.4 Electrocardiogram variables

ECG data will be assessed by the Investigator based on the automatic device reading.

ECG parameters include: normal or abnormal.

9.4 [redacted]

Additional Exploratory Collaborative End-Points include:

- Analysis of Circulating Tumor Cells (CTCs) phenotypes as well as expression and localization of proteins including androgen receptors (AR) isoforms in CTCs at baseline.
- Analysis of tumoral genetic and genomic variations in circulating free nucleic acids derived from plasma at baseline, on treatment and post-treatment. Subtractive mutation analysis will be performed with germline DNA data to identify tumoral specific variations.

Special procedure for collection, storage and shipping of samples will be described in the laboratory manual.

9.5 FUTURE USE OF SAMPLES

Not all of the blood samples obtained during this study may be used for the tests that are part of the clinical trial. Following the conclusion of the study, the samples may be used for additional research. This research will help to understand disease subtypes, drug response, and toxicity, and possibly to identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done in accordance with the guidelines defined by the FDA document “Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable” (issued 25 April 2006) and European Medicines Agency’s (EMA’s) “Reflection Paper on Pharmacogenetic Samples, Testing, and Data Handling” (EMA 2007). If a subject requests destruction of their blood samples, and the samples have not yet been de-identified, the sponsor (or central laboratory) will destroy the samples as described in this FDA guidance. The sponsor (or central laboratory) will notify the investigator in writing that the samples have been destroyed.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

All patients entering the study must be evaluated according to the schedule outlined in the study Flow Chart (see Section 1.2) and described below. The results of the evaluation will be recorded on the appropriate eCRF pages until the patients are not followed any longer (End of Study)

10.1.1 Screening

Each potential patient will be examined before the start of the study to determine his eligibility for participation. These tests are to be performed within 4 weeks prior to study randomization, with the exception of physical examination, biological tests, PSA measurement and ECG that must be performed no more than 8 days before randomization. If the time between biological baseline work-up and first administration of study treatment is more than 8 days, biological tests should be done again to check that eligibility criteria are still met. The written informed consent will have to be signed by the patient before any protocol specific procedures.

The following examinations will be performed:

- **Inclusion/Exclusion criteria** within 8 days prior randomization.
- **Demographic characteristics** within 4 weeks prior randomization.
- **Physical examination** within 8 days prior randomization including major body systems exam, height and weight, ECOG performance status (PS), and vital signs (blood pressure, heart rate).
- **Pain assessment and analgesic for cancer pain**: diary information should be collected within 3 days before first treatment administration using the BPI-SF (Appendix E) and WHO Analgesic Ladder (Appendix F).
- **Medical, surgical and oncological history** including significant prior and concurrent illnesses, primary diagnosis and prior antitumor therapy. Renal medical history which should include co-morbidities at risk of renal impairment (eg, diabetes) and medication at risk of renal function impairment (such as bisphosphonates, non-steroids anti-inflammatory drugs, aminoglycosides antibiotics, etc) should be documented within 4 weeks prior randomization
- **Concomitant medications** will be recorded from 4 weeks prior to randomization.
- **Symptomatic Skeletal Events** within 8 days before randomization: The use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture, or occurrence of spinal cord compression, or tumor-related orthopeadic surgical intervention.
- **12-lead ECG** within 8 days prior randomization

- **Hematology** within 8 days prior D1 cycle 1 (time between hematological work-up and day 1 cycle 1 should not exceed 8 days; if time exceed 8 days, hematological work-up should be repeated): WBC with differential count, hemoglobin, platelet count. To be repeated before cycle 1 if the time between baseline biological work-up and first administration of study treatment is more than 8 days, to check that eligibility criteria are still met.
- **Blood Chemistry and Coagulation tests** within 8 days prior D1 cycle 1 (time between biochemistry work-up and day 1 cycle 1 should not exceed 8 days; if time exceed 8 days, biochemistry work-up should be repeated): sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose, lactate deshydrogenase (LDH), and INR . To be repeated before cycle 1 if the time between baseline biological work-up and first administration of study treatment is more than 8 days, to check that eligibility criteria are still met. In addition and only at baseline: serum Chromogranin A (CgA).
- **Blood sample for CTCs assay:** 3 samples will be taken within 8 days prior randomization and 2 of them at least 24h apart before first cycle administration.
- **Blood sample for cfDNA/cfRNA/germline assay**: 3 samples will be taken within 8 days prior randomization and 2 of them at least 24h apart before first cycle administration.
- **PSA** (last PSA if progression is defined by rising PSA) within 8 days prior randomization: in case of rising PSA alone 2 sequential increases above the previous lowest reference value obtained at least 1-week apart are required. A PSA value at study entry of at least 2 ng/mL is required.
- **Serum testosterone measurement** within 4 weeks prior to randomization
- **Tumor assessment** within 4 weeks prior to randomization (6 weeks for bone scan): whole body (abdominal/pelvic/chest) CT-Scan or MRI, bone scan and all other exams as clinically indicated (eg, brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions (measurable and non-measurable). CT-Scan/MRI will be preferred to X-Ray for the purposes of efficacy assessment. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (ie, CT-scan or MRI, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). When available, spiral CT acquisition should be done. Slice thickness should be adapted to the anatomical area and presumed size of the lesions. Slice thickness of 5 to 8 mm should be favored rather than 10 mm, especially during spiral acquisition.

If limitations appear in volume acquisition, it is encouraged to choose a 1.5 pitch and thin slices, rather than a 1 pitch with thick slices. A centimeter scale should appear on films.

- **Other investigations** if clinically indicated.

10.1.2 Randomization

Randomization will take place once the consented patient has completed all the necessary screening procedures and is deemed eligible for study entry by the investigator or designee. All eligible patients must be randomized by contacting the IVRS/IWRS (see Section 8.5).

The results of the screening examinations will be recorded in each randomized patient's CRF. Source documentation to support the screening results must be maintained in the patient's medical record. Treatment should begin within 7 days after randomization.

10.1.3 During study treatment

- **Physical examination** before each cycle including major body systems exam, weight, ECOG performance status (PS), and vital signs (blood pressure, heart rate).
- **Adverse events** assessment: at each cycle
- **Pain assessment and analgesic for cancer pain**: diary information should be collected using the BPI-SF (Appendix E) and WHO Analgesic Ladder at D1 prior each cycle (Appendix F).
- **Symptomatic Skeletal events**: Assessment will be done at each cycle. The use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture, or occurrence of spinal cord compression, or tumor-related orthopeadic surgical intervention.
- **Concomitant medications** will be recorded at every cycle.
- **Hematology** will be done before each study treatment administration (-3 days window is allowed) and in case of fever or infection: WBC with differential count, hemoglobin, platelet count.

  In addition, hematology will be performed every week (D8 and D15) during the 3 first cycles (+/- 1 day window is allowed) and then within further cycles in case of fever or infection.
- **Blood Chemistry** will be done before each study treatment administration (-3 days window is allowed): sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose, LDH.

  In addition, blood chemistry (sodium, potassium, calcium, BUN, magnesium, creatinine, SGOT (AST), SGPT (ALT), total bilirubin) will be performed every week (D8 and D15) during the 3 first cycles (+/-1 day window is allowed).
- **Patient's diary** to be used by all patients to record the consumption of abiraterone acetate or enzalutamide (in Arm B) and/or prednisone or prednisolone.
- **Blood sample for cfDNA/cfRNA assay**: 1 sample will be taken at C4D1.
- **PSA**: before each next cycle.

- **Tumor assessment** every 9 weeks after first study treatment administration for the first 6 months (27 weeks) and then every 12 weeks: whole body (abdominal/pelvic/chest) CT-Scan or MRI, bone scan and all other exams as clinically indicated (eg, brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions should be assessed. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (ie, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).
- **Other investigations** if clinically indicated

10.1.4 End of treatment

All patients must continue to be observed for at least 30 days after the final dose of study treatment. The following procedures should be performed within the 22-30 days following the final dose of study treatment:

- **Physical exam**:

  ECOG PS, weight, examination of major body systems, including vital signs (blood pressure, heart rate).
- **12-lead ECG** only if clinically indicated or cardiac event during the treatment period.
- **Adverse events** assessments.
- **Pain assessment and analgesic** for cancer pain(Appendix E)(Appendix F).
- **Symptomatic Skeletal events**: The use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture, or occurrence of spinal cord compression, or tumor-related orthopeadic surgical intervention.
- **Hematology:** WBC with differential count, hemoglobin, platelet count.
- **Blood Chemistry**: sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose, LDH.
- **Blood sample for CTCs assay**: 1 sample will be taken at relapse or EOT
- **Blood sample for cfDNA/cfRNA assay**: 1 sample will be taken at relapse or EOT
- **Concomitant medications** assessments
- **PSA**
- **Tumor assessment**, if end of treatment visit occurs at the time of a planned tumor assessment:

  whole body (abdominal/pelvic/chest) CT-Scan or MRI, bone scan and all other exams as clinically indicated (eg, brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions (measurable and non-measurable).
- **Other investigations** if clinically indicated

10.1.5 Follow-up period

All patients will be followed every 12 weeks (after end of treatment visit) until death, cut-off date, or withdrawal of patients'consent whichever comes first:

- **Survival status**
- ECOG PS, weight until disease progression, start of another anticancer therapy or cut-off date, whichever comes first.
- **All serious adverse events** and/or related to study treatment adverse events ongoing at the end of the study, or new related to study treatment adverse event which occur during the follow-up period will be recorded until recovery, or stabilization of patient's condition.
- **Concomitant medications** if correspond to treatment of related adverse events.
- **Pain and analgesic** for cancer pain: until disease progression, start of another anticancer therapy or cut-off date, whichever comes first. The diary information should be collected at each scheduled visit.
- **Symptomatic Skeletal events**: The use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture, or occurrence of spinal cord compression, or tumor-related orthopeadic surgical intervention, until the occurrence of first SSE or study cut-off date, whichever comes first.
- **PSA**: until the end of the first further anticancer therapy if any or the study cut-off date, whichever comes first.
- **Tumor assessment** until radiological PD, start of another anticancer therapy or study cut-off if patient discontinued study treatment without radiological progressive disease:

  whole body (abdominal/pelvic/chest) CT-Scan or MRI, bone scan and all other exams as clinically indicated (eg, brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions should be assessed. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (ie, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).
- **Further anticancer therapy** if any, which is at the discretion of the investigator. In case of patient discontinues study treatment due to reason other than progressive disease, further anticancer therapy will not be initiated before progression is documented. In case it occurs within the 4 first cycles, initiation or not of further anticancer therapy before radiographic progression is documented, is left to the investigator decision. Data related to the first further anticancer therapy response will be collected.

10.1.6 Post study cut-off date

Patients still on study treatment at the cut-off date can continue study treatment until at least 1 treatment permanent discontinuation criterion as defined in Section 10.3.2 is met. The following information will be collected during the study treatment administration:

- IMP administration
- All serious adverse events regardless of relationship to study treatment and adverse events considered related to study treatment.
- End of treatment reason.
- No follow-up information will be collected after these patients discontinue study treatment except all serious adverse events still ongoing at the end of study treatment and all adverse events considered as related to study treatment still ongoing or occurring after the end of study treatment, which will be followed until resolution/stabilization.

10.2 DEFINITION OF SOURCE DATA

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcripts certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments) involved in the clinical study. Source documentation must be maintained to support information provided within a CRF.

The results of certain examinations or evaluations recorded in the CRF may be considered to be source data (such as patient's BPI-SF, WHO Analgesic Ladder)

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

Patients will be followed up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IP.

All permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages when considered as confirmed.

10.3.1 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.2 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the eCRF.

- The patients may withdraw from treatment if they decide to do so, at any time and irrespective of the reason or at the request of their legally authorized representative. "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research.
- If, in the investigator's opinion, continuation of the treatment would be detrimental to the patient's well-being, such as:
  - Radiographic disease progression as defined in Section 9.1,
  - Unacceptable adverse event(s) not manageable by symptomatic therapy, dose delay or dose modification (see Section 8.1),
  - Intercurrent illness that prevents further administration of study treatment,
  - Non-compliance to the study protocol or logistic consideration.
- Patient is lost to follow-up.

In all cases, the reason for and date of withdrawal must be recorded in the eCRF and in the patient's medical records. The patient must be followed up to establish whether the reason was an adverse event, and, if so, this must be reported in accordance with the procedures in Section 10.4.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation after 24 hours for making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.3 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed.

10.3.4 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site for the EOT visit, unless the patient withdraws the consent for follow-up, the Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

SAE is any untoward medical occurrence that at any dose:

- Results in death, or

- Is life-threatening, or;

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event:
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse
  - ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions
  - Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies)
  - Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require

further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

- Pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP;
  - Pregnancy occurring in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).
  - Follow-up of the pregnancy is mandatory until the outcome has been determined. Additional follow-up information may be requested about the baby until at least one year after the birth of the baby.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as increase of at least 30% of the highest dose of cabazitaxel (ie, 30% of 25 mg/m²) to be administered.

Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the eCRF. Obligations of the Sponsor

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected (20).

Any other AE not listed as an expected event in the Investigator’s Brochure or in this protocol will be considered unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.5 SAFETY INSTRUCTIONS

10.5.1 Physical examination

Physical examination will include, but not limited to the examination of major body systems:

- Vital signs (blood pressure, heart rate),
- Height (screening only), body weight,
- ECOG performance status (Appendix C).

If abnormal findings emerge or worsen or become serious from the baseline assessment, then the adverse event page of the CRF should be completed for these findings. If a finding meets the criteria for a serious adverse event, then the appropriate procedures for reporting such events should be followed as described in Section 10.4.3. Height will be recorded at baseline only. Body weight and ECOG PS will be recorded at baseline, prior to the start of each treatment cycle (every 3 weeks) and every follow up visit (every 12 weeks) until death or cut-off date whichever comes first.

Every attempt should be made to have the same study personnel to perform the assessment throughout the study for any given patient for consistency of grading.

10.5.2 Laboratory variables

Hematology panel and blood chemistry profile will be performed by a local laboratory. Baseline results must be available for eligibility determination. At the start of each new treatment cycle, results must be available prior to treating the patient with the study drug. In addition, hematological test will be performed every week (D8 and D15) during the 3 first cycles and then within further cycles only in case of fever or infection.

10.6 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

The material of Section 11 of the Clinical Trial Protocol is the basis for the Statistical Analysis Plan (SAP) for the study. This plan may be revised during the study to accommodate Clinical Trial Protocol amendments and to make changes to adapt to unexpected issues in study execution and data that affect planned analyses.

11.1 [redacted]

Based on bibliographic references (6)(7)(8)(9)(10), a Hazard Ratio of 0.67 is targeted as the smallest effect of clinical interest. The following table presents how such a HR translates for a variety of envisaged median rPFS in the abiraterone acetate or Enzalutamide group (11)(12).

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 155 patients with event are needed to achieve 80% power to demonstrate rPFS superiority of Cabazitaxel over abiraterone acetate or Enzalutamide by one-sided log rank test at 0.05 type I error rate. Further assuming the accrual is at a constant rate of 4 patients per month for 5 months and then 11 patients per month, a total of 206 patients in 2 arms (103 patients per arm) is anticipated to be needed to reach the targeted number of patients with event.

Calculations were made using East 6.2 software.

11.2 DISPOSITION OF PATIENTS

The total number of patients for each of the following categories will be provided into a summary table:

- Intent to Treat (ITT) patients
- Safety population patients
- Evaluable patients

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

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.

11.3 ANALYSIS POPULATIONS

Screened patients are defined as patients who meet the inclusion criteria.

Allocation of randomized treatment to eligible patients (patients who meet all inclusion/exclusion criteria) will be centrally performed using an IVRS/IWRS. A patient is considered as randomized as soon as there is confirmation of successful allocation of a randomization number through the IVRS/IWRS.

Patients allocated outside the IVRS/IWRS will not be taken into account in any of the analyses.

11.3.1 Efficacy populations

11.3.1.1 Intent–to-treat population

The primary efficacy population is the Intent-To-Treat (ITT) population which includes all randomized patients. The patients will be analyzed in the treatment group to which they will be allocated by the IVRS/IWRS (ie, “as randomized” regardless of treatment actually received).

11.3.1.2 Evaluable populations

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

- Tumor response will be evaluated in patients with measurable disease at baseline, with at least one post baseline assessment.
- PSA response will be evaluated in patients with PSA level >10 ng/dL at baseline, with at least one post baseline assessment.
- 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”.

11.3.2 Safety population

This population includes all patients who receive at least one dose (either full or partial dose) of the study drug. 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, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, as soon as a patient will receive any study drug injection of Cabazitaxel, he/she is considered as a Cabazitaxel treated patient.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure

Extent of exposure will be assessed on the Safety population as follows:

Number of patients treated, number of cycles administered, duration of dosing (weeks), cumulative dose (mg/m²), dose intensity (mg/m²/3 weeks) and relative dose intensity (%) will be summarized.

Dose delays and dose reductions will also be analyzed.

Further details of the statistical evaluation of the extent of exposure will be provided in the SAP.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

Primary analysis will consist of rPFS comparison between abiraterone acetate or enzalutamide group and Cabazitaxel group through a one-sided 5% log-rank test adjusted for the stratification factors (extra nodal visceral metastases, level of PSA decline and time from AR targeted agent initiation to progression) as specified at the time of randomization. This analysis will be performed on the ITT population. If radiological progression or death is not observed during the study, data on rPFS will be censored at the date patient is known to be alive or at the cut-off date, whichever comes first.

The primary Efficacy endpoint will also be analyzed (secondary analyses) as follows:

The estimates of the hazard ratio and corresponding 90 and 95% confidence interval will be provided using a Cox proportional hazard model stratified by the same stratification factors as those described above.

Hazard ratios will also be provided on the subpopulations defined by the stratification factors.

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

Finally, the 2 arms will also be compared (sensitivity analysis) using a one-sided 5% un-stratified log-rank test.

11.4.2.2 Analyses of secondary efficacy endpoints

Time To event endpoints will be compared between the 2 treatment arms using the same methodology as the primary efficacy endpoint primary analysis.

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

Hazard ratios and 95% confidence intervals will be provided using a Cox proportional hazard model.

Continuous data will be summarized using number of available data, mean, standard deviation, median, minimum, Q1, Q3 and maximum for each dose level. The 2 arms will be compared using either t-test or non-parametric Mann-Whitney U test (depending on the Normality of the data, the SAP will detail which method will be used).

Categorical data will be summarized using number and percentage of patients in each dose level (patients with missing data will not be included in the percentage calculation). The 2 arms will be compared using chi-square test. Tumor, PSA, and pain response will be analyzed on their respective evaluable population.

11.4.2.3 Multiplicity considerations

Not applicable.

11.4.3 Analyses of safety data

The summary of Safety results will be presented by treatment group (abiraterone acetate and Enzalutamide will also be presented separately). Analysis of adverse events and laboratory data will be descriptive and conducted on the Safety population. Summary of safety data will also be performed by patient and by cycle. For each of the Safety parameters, a baseline value will be defined as the last value or measurement taken up to the first dose in the study. Similar analysis will be presented for serious adverse events and adverse events that cause dose reduction, dose relay and treatment discontinuation.

Adverse events will be considered as treatment-emergent if they first occur or worsen after the first day of dosing and up to 30 days after the last administration of study drug.

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), High level group term (HLGT), High level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

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 1 to the numerator for each cycle in which an episode occurred (ie, 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).

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received,
- Death in non-randomized patients or randomized and not treated patients,
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) and related TEAEs leading to death by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.
- 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.

Hematological toxicities will be assessed from laboratory parameters. Worst NCI CTCAE grades of leukopenia, neutropenia, thrombocytopenia, and anemia will be calculated according to the NCI common terminology criteria.

Qualitative and quantitative results will be summarized for hematological toxicities. Qualitative data (worst NCI CTCAE grade) will be summarized by cycle and by patient.

Biochemistry will be analyzed using the worst NCI CTCAE grade, whenever applicable (laboratory normal ranges, otherwise) calculated from laboratory values.

11.4.4 Analyses of Pharmacogenetic variables

NA

11.5 INTERIM ANALYSIS

NA

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

Prior to a patient's participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as

possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized

personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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