AMENDED CLINICAL TRIAL PROTOCOL 5

COMPOUND: XRP6258

A Randomized, Open Label Multi-Center Study of XRP6258 At 25 mg/m^2 in Combination With Prednisone Every 3 Weeks Compared To Mitoxantrone in Combination With Prednisone For The Treatment of Hormone Refractory Metastatic Prostate Cancer Previously Treated With A Taxotere®-Containing Regimen

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CLINICAL TRIAL SUMMARY

COMPOUND: XRP6258	**STUDY No.: EFC6193**
TITLE	A Randomized, Open Label Multi-Center Study of XRP6258 At 25 mg/m^2 in Combination With Prednisone Every 3 Weeks Compared To Mitoxantrone in Combination With Prednisone For The Treatment of Hormone Refractory Metastatic Prostate Cancer Previously Treated With A Taxotere®-Containing Regimen* *Docetaxel will be permitted.
INVESTIGATOR/TRIAL LOCATION	Worldwide (except Japan)
STUDY OBJECTIVES	**Primary:** • To determine whether XRP6258 in combination with prednisone improves overall survival (OS) when compared to mitoxantrone in combination with prednisone **Secondary:** • To compare efficacy between the two treatment arms: – PSA Response – PSA Progression – Progression Free Survival (PFS) defined as the first occurrence of any of the following events: tumor progression per Response Evaluation Criteria In Solid Tumors (RECIST), PSA progression, pain progression or death due to any cause. – Overall Response Rate (ORR) – Pain Response – Pain Progression • To assess the overall safety of XRP6258 in combination with prednisone • To assess the pharmacokinetics of XRP6258 and its metabolite, RPR123142, in this patient population and effect of prednisone on the pharmacokinetics of XRP6258
STUDY DESIGN	Phase III, randomized, open-label, multi-center, multi-national
STUDY POPULATION	Hormone Refractory Metastatic Prostate Cancer (HRPC) Patients Previously Treated With A Taxotere®-Containing Regimen

Main selection criteria:	**Inclusion Criteria:** The Patient must have: 1. Diagnosis of histologically or cytologically proven prostate adenocarcinoma, that is refractory to hormone therapy and previously treated with a Taxotere® (or docetaxel)-containing regimen. Patient must have documented progression of disease during or within 6 months after prior hormone therapy and disease progression during or after Taxotere® (or docetaxel)-containing therapy. 2. Patient must have either measurable or non-measurable disease. • Patient with measurable disease must have documented progression of disease by RECIST criteria demonstrating at least one visceral or soft tissue metastatic lesion (including new lesion). This lesion must measure at least 10 mm in the longest diameter (or two times the slice thickness) on spiral CT scan or MRI (chest, abdomen, pelvis) or 20 mm on conventional CT or Chest X-ray for biopsy proven, clearly defined lung lesion surrounded by aerated lung. (Previously irradiated lesions, primary prostate lesion, and bone lesions will be considered non-measurable disease) • Patient with non-measurable disease must have documented rising PSA levels or appearance of new lesion. [Rising PSA is defined 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]

Main selection criteria:	**Inclusion Criteria (con't.):** 3. Received prior castration by orchiectomy and/or Luteinizing Hormone-Releasing Hormone (LH-RH) agonist with or without antiandrogen, antiandrogen withdrawal, monotherapy with estramustine, or other hormonal agents. (A prior treatment by antiandrogen is not mandatory. However, if the patient has been treated with antiandrogens, **and** PSA is above 5 ng/mL at the last administration of antiandrogens, presence or absence of antiandrogen withdrawal syndrome* should be confirmed prior to the study entry). (LH-RH agonist treatment should continue during the study treatment period. Chlormadinone acetate or flutamide must have been stopped at least 4 weeks prior to, while bicalutamide must have been stopped at least 6 weeks prior to, the last PSA evaluation.) (* *The antiandrogen withdrawal syndrome is a decrease in PSA seen upon stopping an antiandrogen such as chlormadinone acetate, flutamide, or bicalutamide; this occurs because the antiandrogen has induced a mutation in the androgen receptor which is allowing the antiandrogen to stimulate prostate cancer growth rather than inhibit it)* 4. Life expectancy > 2 months 5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 – 2 (ie, patient must be ambulatory, capable of all self-care, and up and about more than 50% of waking hours) 6. Age ≥18 years **Exclusion Criteria:** 1. Previous treatment with mitoxantrone 2. Previous treatment with <225 mg/m^2 cumulative dose of Taxotere® (or docetaxel) 3. Prior radiotherapy to ≥40% of bone marrow. Prior treatment with one dose of a bone-seeking radio-isotope (samarium-153, strontium-89, or P-32) is allowed, but 8 weeks must have elapsed after samarium-153 or P-32 and 12 weeks must have elapsed after strontium-89 prior to first study drug administration. 4. Prior surgery, radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to enrollment in the study 5. Active grade ≥2 peripheral neuropathy. 6. Active grade ≥2 stomatitis. 7. Active secondary cancer including prior malignancy from which the patient has been disease-free for ≤5 years (However, adequately treated superficial basal cell skin cancer before 4 weeks prior to entry can be eligible to the study) 8. Known brain or leptomeningeal involvement 9. History of Severe hypersensitivity reaction (≥grade 3) to polysorbate 80 containing drugs 10. History of severe hypersensitivity reaction (≥grade 3) or intolerance to prednisone 11. Other concurrent serious illness or medical conditions

Main selection criteria:	**Exclusion Criteria (con't.):** 12. Inadequate organ function as evidenced by the following peripheral blood counts, and serum chemistries at enrollment: • Neutrophils ≤1.5 x 10^9/L • Hemoglobin ≤10 g/dL • Platelets ≤100 x 10^9/L • Total bilirubin ≥ Upper limit of normal (ULN) • AST (SGOT) ≥1.5 x ULN • ALT (SGPT) ≥1.5 x ULN • Creatinine ≥1.5 x ULN 13. Uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension. History of congestive heart failure, or myocardial infarction within last 6 months is also not allowed. 14. Left ventricular ejection fraction (LVEF) ≤50% by multi-gated radionuclide angiography (MUGA) scan or echocardiogram 15. Uncontrolled diabetes mellitus 16. Active uncontrolled gastroesophalgeal reflux disease (GERD) 17. Active infection requiring systemic antibiotic or anti-fungal medication 18. Participation in another clinical trial with any investigational drug within 30 days prior to study enrollment. 19. Concurrent or planned treatment with strong inhibitors of cytochrome P450 3A4/5. (A one week washout period is necessary for patients who are already on these treatments) 20. For patient enrolled in the United Kingdom, the following exclusion criterion must be applicable: Patient with reproductive potential not implementing accepted and effective method of contraception, described in Appendix I.
Total expected number of patients:	Approximately 360 patients per arm (at least 511 deaths total)
Expected number of sites:	Approximately 150 centers
INVESTIGATIONAL PRODUCT(S)	XRP6258 25 mg/m² intravenously (Day 1) every 3 weeks, plus prednisone 10 mg orally given daily Versus Mitoxantrone 12 mg/m² intravenously (Day 1) every 3 weeks, plus prednisone 10 mg orally given daily In those countries where prednisone is not commercially available, prednisolone, 10 mg orally given daily, may be used.

Formulation(s):	**XRP6258 (RPR116258)** XRP6258 is supplied as a sterile, non-pyrogenic, non-aqueous yellowish to brownish yellow, 80 mg/2 mL concentrate for solution for infusion. It is packaged in 15 mL single dose clear type I glass vial stoppered with a rubber closure. The stopper is crimped to the vial with a green flip-off aluminum cap. The solution contains the following excipient: Polysorbate 80. **Solvent:** The solvent for XRP6258 is supplied as a 13 % m/m ethanol solution in water for injection. This solvent is supplied in a 15 mL single dose clear type I glass vial stoppered with a rubber closure and capped with a transparent flip-off aluminum cap. The preparation of the XRP6258 (RPR116258) infusion solution for administration requires preparation of a premix solution at 80 mg/8 mL (nominal concentration). This must be done with a 13 % m/m ethanol solution in water for injection supplied with the XRP6258 concentrate for solution for infusion. Each XRP6258 vial and each solvent vial are overfilled to ensure that 80 mg dose can be extracted after the preparation of the premix. Each vial of XRP6258 must be diluted with the ENTIRE content of the solvent vial.
Route(s) of administration:	XRP6258 and mitoxantrone will be administered by IV route. Prednisone will be administered by oral route.
Dose regimen:	Patients will be randomly assigned (1:1) to receive either mitoxantrone or XRP6258 every 3 weeks: **Arm A: Mitoxantrone 12 mg/m² intravenously (Day 1) every 3 weeks, plus prednisone 10 mg orally given daily** **Arm B: XRP6258 25 mg/m² intravenously (Day 1) every 3 weeks, plus prednisone 10 mg orally given daily** On Day 1 of each cycle, patients will receive either XRP6258 at a dose of 25 mg/m², administered by IV route in 1 hour along with 10 mg of prednisone orally given daily or mitoxantrone 12 mg/m² within 15 –30 minutes, administered by IV route along with 10 mg of prednisone orally given daily. Cycle length for both XRP6258 and mitoxantrone is 3 weeks. New cycles of therapy may not begin until ANC ≥1500/mm³, platelet count ≥75 000/mm³, and non-hematological toxicities (except alopecia) have recovered to baseline. A maximum of 2 weeks delay is allowed between 2 treatment cycles. Patients should come off study treatment, if treatment delay is more than 2 weeks. Patients will be monitored closely for toxicity. In addition to optimizing supportive care, chemotherapy doses may be adjusted after the first cycle of therapy and/or recovery to grade ≤1. Each patient will be treated until disease progression, death, unacceptable toxicity or for a maximum of up to ten cycles. **Arm B Only**: Required IV premedication will include: Antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg or other antihistamines); steroid (dexamethasone 8 mg or equivalent steroid).

	H2 antagonist (Ranitidine or other H2 antagonist with the exception of cimetidine). These premedications will be administered by IV infusion, at least 30 minutes prior to each dose of XRP6258. Antiemetic prophylaxis with ondansetron, granisetron, or dolasetron can be administered whenever it is necessary. Premedication for Arm A should be at the discretion of the physician. As in Arm B, pre-medication with a H2 antagonist (Ranitidine or other H2 antagonist with the exception of cimetidine) is recommended. Antiemetic prophylaxis with ondansetron, granisetron, or dolasetron can be administered whenever it is necessary.
PRIMARY ENDPOINT (S) AND MAIN SECONDARY ENDPOINT (S)	**Primary End-point:** • OS will be assessed from the date of randomization to the date of death (whatever the cause). **Main Secondary End-points:** • **PSA Response (Applies to patients with baseline PSA ≥20 ng/mL):** Response requires a PSA decline of ≥50% confirmed by a second PSA value at least three weeks later. The duration of PSA response will be measured from the first to the last assessment at which the above criteria are satisfied. • **PSA Progression (Applies to all patients):** **In PSA non-responders**, progression will be defined as a ≥25% increase over the nadir (provided that the increase in the absolute value PSA level is at least 5 ng/ml), confirmed by a second value at least 1 week later. **In PSA responders and in patients not evaluable for PSA response at baseline**, progression will be defined as a ≥50% increase over the nadir (provided that the increase in the absolute value PSA level is at least 5 ng/ml), confirmed by a second value at least 1 week later. • **Progression Free Survival:** PFS will be evaluated from the date of randomization to the date of tumor progression, PSA progression, pain progression, or death due to any cause, whichever occurs first.

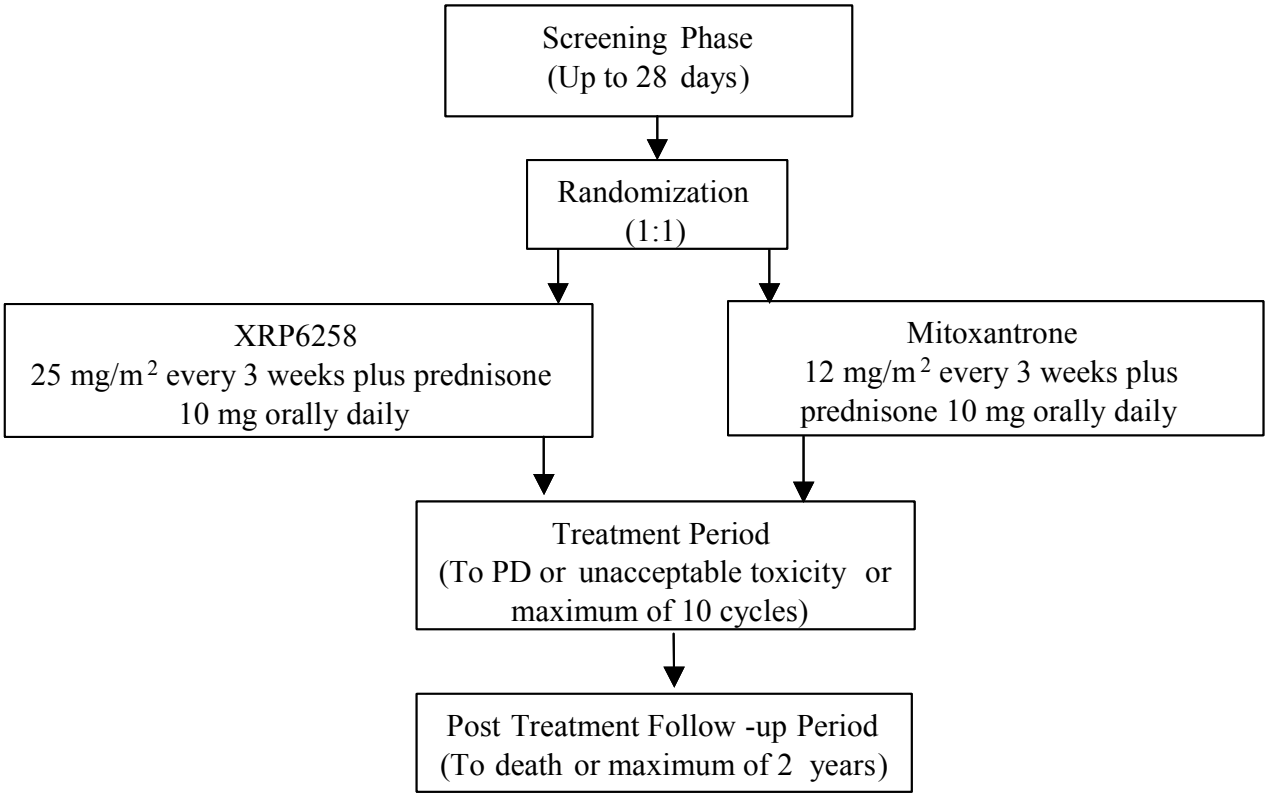
PRIMARY ENDPOINT (S) AND MAIN SECONDARY ENDPOINT (S)	**Main Secondary End-points (con't.):** • **Overall Response Rate (in patients with measurable disease):** ***Objective responses (CR and PR)*** for measurable disease as assessed by investigators according to RECIST criteria. Confirmation of objective responses will be performed by repeat tumor imaging (CT scans, MRI, bone scans) at least 4 weeks after the first documentation of response • **Pain Response** (***applies only to patients with median PPI ≥2 on McGill-Melzack scale and/or mean Analgesic Score (AS) ≥10 points at baseline):*** Pain Response will be defined as a 2-point or greater reduction from baseline median PPI with no concomitant increase in analgesic score, OR a reduction of at least 50% in analgesic use from baseline mean AS (only in patients with baseline mean AS ≥10) with no concomitant increase in pain. Either criterion must be maintained for two consecutive evaluations at least 3 weeks apart. • **Pain Progression *(applies to all patients)*:** Pain Progression will be defined as an increase of ≥1 point in the median PPI from its nadir noted on two consecutive three-week-apart visits OR ≥25% increase in the mean analgesic score compared with the baseline score and noted on two consecutive three-week-apart visits OR requirement for local palliative radiotherapy. Patients should only be discontinued from study treatment for cancer-related pain progression (ie, pain progression supported by clinical and/or radiological evidence of disease progression).

ASSESSMENT SCHEDULE	**Safety Data:** Vital signs, physical examinations (PEs), ECOG PS, ECG, LVEF, and laboratory safety tests [including complete blood counts (CBCs) and serum chemistries] will be obtained prior to drug administration and at designated intervals throughout the study. Adverse events (AEs) will be collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (NCI CTCAE v.3.0) during the study. **Efficacy Data:** Anti-tumor activity will be assessed by computerized tomography (CT) or magnetic resonance imaging (MRI) of the whole body (chest, abdomen, and pelvis) and by bone scan, at baseline. These assessments, other than bone scan, will be repeated at the end of each even-numbered treatment cycle (Cycles 2, 4, 6, 8 and 10), whenever disease progression is suspected, and at the end of treatment/withdrawal visit, using the same method for each assessment. Bone scans will only be performed at these visits if clinically indicated. PSA and pain assessments will be performed in all patients at baseline and then periodically at scheduled intervals, whenever disease progression is suspected, and at the end of treatment/withdrawal visit. During the first 6 months of the follow-up period, patients who went off study treatment prior to documented disease progression will be evaluated by CT/MRI for tumor progression every 6 weeks from End of Study Treatment until disease progression or start of other anticancer therapy. For rest of the follow-up period, patients will be evaluated every 3 months. Bone scan will be performed during the follow-up period when clinically indicated. In addition, during the first 6 months of the follow-up period, patients will be evaluated every 6 weeks for PSA and/or pain progression until documented progression or start of other anticancer therapy. For the rest of the follow-up period, patients will be evaluated every 3 months.
	Pharmacokinetic data: In Arm B, blood samples will be collected according to a sparse sampling strategy in as many patients as possible during Cycle 1 and in 25 of these patients at Cycle 2.
STATISTICAL CONSIDERATIONS	**Statistical hypotheses and sample size calculation:** Assuming the median overall survival time in the control group is 8 months, then total of at least 511 deaths in two arms will be needed to detect a 25% reduction in hazard rate in XRP6258 group relative to the control with a power of 90% at a 2-sided 5% alpha level. To achieve the targeted number of deaths, approximately 720 (360 per arm) patients need to be randomized for the study. **Randomization:** All eligible patients will be randomly assigned to one of the two groups (either mitoxantrone or XRP6258 every 3 weeks) using an interactive voice response system (IVRS). Randomization will be stratified for measurability of disease per RECIST criteria (measurable vs. non-measurable disease) and ECOG PS (0-1 vs. 2).

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

	• All-Treated (AT) population: This population includes all patients who took 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. **Analysis of the primary endpoint:** Primary analysis will consist of Overall Survival (OS) comparison between the two treatments through a log-rank test procedure stratified by stratification factors (measurability of the disease and ECOG PS) as specified at the time of randomization. This analysis will be performed on the ITT population. If death is not observed during the study, data on OS 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 95% confidence interval will be provided using a Cox proportional hazard model stratified by the same stratification factors as those used for the log-rank test described above. The survival curves will be estimated using Kaplan-Meier estimates. **Interim Analysis (IA):** An interim (futility) analysis of PFS (either tumor progression, PSA progression, or pain progression, as defined above, or death from any cause) will be performed after 225 PFS events have occurred, ie, 33% information fraction at an estimated cut-off of 12 months after 1st patient has been randomized. Approximately 360 patients will have been accrued when futility analysis is performed. This interim analysis (IA) will be used to estimate the probability that the null hypothesis of no treatment differences will be rejected upon completion of the trial. Early termination for futility will be considered if the conditional power of observing a significant effect at the end of the study, assuming the current trend continues, is less than 10%. The futility analysis on PFS is not considered an interim analysis on the primary endpoint of overall survival and the final p-value for the analysis of overall survival will not be adjusted. The second interim analysis will be performed at the time of the 307 deaths (the 60% of the 511 deaths in the final analysis of the protocol) to assess the primary efficacy endpoint of overall survival based on the O'Brien-Fleming type I error spending function. The statistical significance level at the interim analysis will be 0.0076 for the 2-sided stratified log rank test. In case the stopping criteria are not met at the time of this second interim analysis the study will continue and the final overall survival analysis will be performed with the 2-sided stratified log rank test at the 0.0476 significance level.
DURATION OF STUDY PERIOD (per patient)	Each patient will be treated until disease progression, death, unacceptable toxicity or for a maximum of up to ten cycles (30 weeks), and then will have long-term follow-up until death or for a maximum follow-up of up to 2 years (104 weeks).

1 FLOW CHARTS



1.1 STUDY FLOWCHART

Evaluation	Screening (-28 days)	Prior to each infusion (Day 1) (a)	Cycle 1 through Cycle 10	End of Study Treatment**	Post-treatment Follow-up***
Informed Consent Form	X*				
Contraceptive Counseling	X				
Previous Medical/Surgical History (b)	X*				
Physical Examination including vital signs/Height/Weight/BSA/ECOG PS (c)	X*	X		X	
Randomization (g)	X				
XRP6258 + Prednisone or Mitoxantrone + Prednisone Administration (h)			X		
Concomitant Medication (k)	X*	X		X	X
Hematology (d)	X*	X		X	
Biochemistry (e)	X*	X		X	
Testosterone	X			X	
ECG (f)	X			X	
LVEF (n)	X*	X		X	
Pharmacokinetic Sampling			X (o)		
PSA (l)	X*	X		X	X (m)
Bone Scan (l)	X	X		X	X (m)
CT Scan or MRI of Whole Body (l)	X	X		X	X (m)
Pain Assessment (i)(l)	X	X		X	X (m)
Analgesic Diary (i)(l)	X	X		X	X (m)
AE/SAE Recording (if any) (j)	X	X		X	X

* Assessment must be performed prior to registration (rather than prior to initial dose) for eligibility determination.

** End of study treatment assessment to be performed within 30 days (+ 3 days) after the last study drug infusion.

*** In patients that have progressed or started another anticancer therapy, performed every 3 months for a maximum of 2 years. In patients that have not progressed or started another anticancer therapy, performed every 6 weeks for first 6 months and then every 3 months for rest of the period (a maximum total of 2 years).

a **Day 1:** Cycle 1 Day 1 (Day 1 of the study) refers to the day the patient receives the initial dose of study medication. The Cycle 1 Day 1 Assessments noted in the Study Schedule are not required if acceptable screening for the assessment is performed within 5 days prior to the start of treatment with study drug. However, all of these assessments must be performed for subsequent cycles (eg, Cycle 2 Day 1, Cycle 3 Day 1, etc.). Day 1 of each subsequent cycle is defined by the date that study drug administration is started within that cycle. Patients must be seen by the responsible physician on Day 1 of each cycle

b **Medical & Oncologic History:** including: diagnosis; prior surgery, radiotherapy, systemic therapy, hormonal therapy, concurrent illness; history of allergy.

c **Physical Examination:** Examination of major body systems including vital signs (temperature, blood pressure, heart rate), height (Screening only), body weight, and ECOG PS. Results will be recorded on appropriate CRFs (eg, medical/tumor history, adverse events).

d **Hematology:** CBC, Diff., Platelets will be assessed on Day 1, Day 8, and Day 15 of every treatment cycle and repeated when clinically indicated. There is a –3-day window allowed at Day 1 and a ±1 day window allowed at Day 8 and Day 15.

e **Biochemistry:** Total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase, creatinine, BUN, glucose, sodium, potassium, chloride and bicarbonate will be assessed on Day 1 of every treatment cycle and repeated when clinically indicated. There is a –3-day window allowed at Day 1 of every treatment cycle.

f **ECG:** To be performed at baseline and end of study. Additional tests should be performed if clinically indicated.

g **Randomization:** Patient treatment arm will be assigned by an IVRS after investigator confirmation of eligibility

h **BSA, Study Drug Administration, Dispensing, and Accountability**: At the start of each treatment cycle, the patient's BSA will be determined using the current weight and screening height. Study drug will be administered in the clinic.

i **Pain Assessment and analgesic diary**: Pain will be assessed using the McGill-Melzack Present Pain Intensity (PPI) scale and Analgesic Score (AS) derived from analgesic consumption in morphine equivalents.

j **Adverse Event Assessment**: The period of observation for collection of adverse events extends from the time of the first dose of the study drug until 30 days after the final dose of study drugs. Serious adverse events should be followed as described in the protocol. All AEs/SAEs that were considered related to study medication and are ongoing at the end of treatment must be followed to resolution and recorded in the CRF, as applicable. New onset study drug related SAEs in FUP should be reported as described in the protocol and recorded in the CRF.

k **Assessment of Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 30 days prior to the initial dose of study drugs until 30 days after the final dose of study drugs. In FUP, only further anti-cancer therapies will be recorded on the CRF.

l **Tumor Assessment:**

- **CT or MRI** of the whole body (chest, abdomen, and pelvis) to be performed in all patients at baseline (screening). Repeat at the end of every other cycle (2, 4, 6, and 8), whenever disease progression is suspected, and at the end of treatment/withdrawal visit, using the same method for each assessment.
- **Bone Scan** will be performed in all patients at baseline and should be repeated when clinically indicated.
- **PSA** will be performed at baseline and every cycle. PSA response will be evaluated at the end of every other cycle (2, 4, 6, and 8), whenever disease progression is suspected, and at the end of treatment/withdrawal visit.
- **Pain** will be assessed at baseline and every cycle. Pain response will be evaluated only in those patients with median PPI ≥2 on McGill-Melzack scale and/or mean Analgesic Score ≥10 points at baseline. Pain response will be evaluated at the end of every cycle, whenever disease progression is suspected, and at the end of treatment/withdrawal visit.

m **Post-Study Therapy and Survival Status:** During the first 6 months of the follow-up period, patients who went off study treatment prior to documented disease progression will be evaluated by CT/MRI for tumor progression every 6 weeks from End of Study Treatment until disease progression or start of other anticancer therapy. For rest of the follow-up period, patients will be evaluated every 3 months. Bone scan will be performed during the follow-up period when clinically indicated. In addition, during the first 6 months of the follow-up period, patients will be evaluated every 6 weeks for PSA and/or pain progression until documented progression or start of other anticancer therapy. For the rest of the follow-up period, patients will be evaluated every 3 months.

n **LVEF:** To be assessed via MUGA or echocardiogram in all patients at baseline. For the mitoxantrone treatment arm only, to be repeated prior to every other treatment cycle, and at the end of treatment/withdrawal visit using the same method of assessment at all time points. Additional tests should be performed if clinically indicated. For the XRP6258 treatment arm, LVEF should be repeated if clinically indicated.

o **Pharmacokinetic sampling:** In the XRP6258 treatment arm, blood samples will be collected using sparse sampling strategy in as many patients as possible in Cycle 1 and in 25 of these patients in Cycle 2.

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3 LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute Neutrophil Count
AS	Analgesic Score
AT	All-Treated
AUC	Area Under The Concentration Curve
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CL	Clearance
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DLT	Dose Limiting Toxicity
DRF	Discrepancy Resolution Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	Ejection Fraction
EOS	End of Study
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GERD	Gastroesophageal Reflux Disease
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HRPC	Hormone Refractory Prostate Cancer
HSR	Hypersensitivity Reaction
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IP	Investigational Product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent to Treat
IV	Intravenous
IVRS	Interactive Voice Response System
LD	Longest Diameter
LHRH	Luteinizing Hormone-Releasing Hormone
LVEF	Left Ventricular Ejection Fraction
MBC	Metastatic Breast Cancer
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multi-gated radionuclide angiography

NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-Inflammatory Drug
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Physical Examination
PFS	Progression Free Survival
PI	Package Insert
PK	Pharmacokinetics
PPI	Personal Pain Index
PR	Partial Response
PS	Performance Status
PSA	Prostate-Specific Antigen
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	Rest of World
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SGPT/ALT	Serum Glutamate Pyruvate Transaminase/Alanine Aminotransferase
SGOT/AST	Serum Glutamate Oxaloacetate Transaminase/Aspartate Aminotransferase
TEAE	Treatment-Emergent Adverse Event
TTP	Time to Progression
ULN	Upper Limit of Normal Range
US	United States

4 INTRODUCTION AND RATIONALE

4.1 BACKGROUND

Prostate cancer is a major worldwide health problem and is the most frequently diagnosed male malignancy. It is the most common cancer in humans with 232,000 new cases diagnosed in the US each year and a similar incidence in the rest of the Western Hemisphere. (1). The initial treatment for metastatic adenocarcinoma of the prostate consists of androgen ablation, either surgically with bilateral orchiectomy, or medically with Luteinizing Hormone-Releasing Hormone (LHRH) receptor agonists (2). Responses are observed in up to 85 % of patients (3). However, this androgen ablation is not curative and the disease will eventually recur in virtually all patients. At this stage, further hormonal manipulations such as treatment with antiandrogens, and subsequent antiandrogen withdrawal (4) can be associated with responses of short duration but without improvement in survival duration (5). Treatment options for patients with hormone-refractory disease remain limited and include palliation of symptoms (especially pain) and/or systemic cytotoxic chemotherapy (3).

The use of cytotoxic chemotherapy has not been routine practice whereas the role for chemotherapy in symptom palliation and Prostate Specific Antigen (PSA) response is established. Single agent chemotherapy has been associated with relevant palliative effects but no single agent has been associated with an objective response rate greater than 30% (6). Combinations of cytotoxic agents have been tested with evidence of frequent enhanced activity in terms of palliation and PSA decline (3, 5, 6) but the safety profile of these combinations remains problematic, especially in elderly men with concurrent medical problems and limited bone marrow reserve. No survival advantage can be ascribed to any of the treatments tested in these studies. More effective systemic therapies are needed to have an impact on the morbidity and mortality caused by this disease (7).

Until recently the therapeutic options for such patients were limited to cyclophosphamide, anthracyclines (doxorubicin and mitoxantrone), and estramustine (combination alkylating agent and hormone); the efficacy of these regimens was relatively modest. Taxotere® in combination with prednisone was approved in 2004 for the treatment of androgen independent metastatic prostate cancer patients and demonstrated a 2.4 month survival benefit compared to mitoxantrone plus prednisone, prolonging survival from 16.5 months to 18.9 months. Standard of care in second line prostate is evolving following the adoption of Taxotere® as standard first line therapy for Hormone Refractory Prostate Cancer (HRPC). Palliative effects have been observed in HRPC patients following the administration of either corticosteroid alone (8) or, mitoxantrone with either prednisone or hydrocortisone (9, 10, 11, 12). Supportive care, with various non-approved agents with limited activity is currently used in this setting, palliation being the main goal of therapy. Based on results from two phase III trials, the combination of mitoxantrone with corticosteroid is recognized as the reference treatment in metastatic HRPC (6, 11, 12).

There is a strong need for new therapies based on novel methods of inhibiting cancer growth. There is uniform agreement that responses in advanced prostate cancer are difficult to assess due to the heterogeneity of the disease and the lack of consensus on response criteria complicates the evaluation of new treatments (13). Many patients with metastatic prostate cancer do not have measurable disease but have symptoms dominated by osseous metastases. PSA as a measure of disease outcome in metastatic HRPC has emerged as an acceptable surrogate endpoint to evaluate new agents in this clinical setting (13, 14, 15). There is also some evidence of correlation between PSA response and survival based upon retrospective data but a cause and effect relationship remains to be confirmed through prospective investigations. Very recently, eligibility and response guidelines for phase II trials in HRPC have been established by the PSA Working Group in an attempt to promote common standards for reporting PSA decline and to develop a common approach to outcome analysis (16).

In an attempt to provide an accurate picture of the potential therapeutic benefit of new treatments, it has been recommended that different types of response to therapy should be reported separately: these include changes in PSA, measurable disease, bone-only disease, quality of life, pain control. This method seems preferable to pigeonholing heterogeneous responses into categories of complete or partial (13). These progresses in the standardization of outcome analysis and reporting should contribute to the refinement of the assessment of the risk/benefit ratio of new cytotoxic agents in HRPC (5, 13, 16).

The broad spectrum of XRP6258 efficacy in pre-clinical models, and subsequent clinical activity observed in early clinical trials along with data in patients with breast cancer progressing after taxane therapy suggest that it may also be effective in other tumors where other taxanes have been shown to be active. It is also suggested that XRP6258 would be useful especially in cancers that have progressed after taxane therapy, and probably in settings where taxane resistance is present.

4.2 XRP6258

XRP6258 is a new taxoid, which promotes tubulin assembly *in vitro* and stabilizes microtubules against cold-induced depolymerization as efficiently as docetaxel. *In vitro*, XRP6258 demonstrates equipotent cytotoxic activity of docetaxel.

4.2.1 XRP6258 Preclinical activity

In vivo, XRP6258 has a broad spectrum of antitumor efficacy including efficacy on measurable diseases in tumor models of murine and human origin. 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.

Compared to other taxoids on the market, the striking feature of XRP6258 is its minimal recognition with the multidrug resistance P-glycoprotein. Using CaCo-2 cell lines, which express a basal level of P-glycoprotein, XRP6258 was found 4.9 times more active 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 XRP6258 and for

docetaxel, respectively. This weak recognition of XRP6258 by the P-glycoprotein *in vitro* is also supported by the antitumor efficacy observed *in vivo* against B16 melanoma which expresses low levels of *mdr1* mRNA and is resistant to docetaxel. In addition, XRP6258 was found active *in vivo* against intracranial glioblastomas confirming blood brain barrier penetration.

XRP6258 is formulated in polysorbate 80 and premedication is required to prevent allergic-like reactions which were noted in phase I studies. These adverse events are predictable and clinically manageable, and are similar to those experienced with docetaxel. The incidence of nail changes, fluid retention and hypersensitivity reactions (HSR) seems to be less frequent than that observed for docetaxel, and the premedication required to prevent allergic reactions is less than that recommended for docetaxel (1 day of antihistamines vs. 3 days of corticosteroids).

4.2.2 Clinical Activity of XRP6258: Available Results

As of April 2006, 4 clinical studies have been completed. Three single-agent dose and schedule finding studies in solid tumors (V101-103) were conducted to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of XRP6258 in patients with advanced solid tumors. These studies of XRP6258 in solid tumors have demonstrated a promising safety profile and early clinical activity especially in patients with breast cancer, sarcoma, and prostate cancer (2 responses). A total of 77 patients were treated with approximately 241 cycles of the treatment.

Doses of 10-30 mg/m^2 were administered as a one-hour infusion every three weeks in studies V-101 and 103. The MTD in study V-101 was 30 mg/m^2, while it was 25 mg/m^2 in study V-103. The DLTs were grade 4 neutropenia>5 days and febrile neutropenia in V-101 while grade 3 diarrhea at 15 mg/m^2 and febrile neutropenia and grade 4 neutropenia > 5 days at 25 mg/m^2 were DLTs in study V-103. 1.5-12 mg/m^2 doses were administered as a one-hour infusion weekly for 4 weeks followed by one-week rest in study V-102. The MTD in study 102 was 12 mg/m^2 while the DLT was grade 3 diarrhea.

Major treatment emergent adverse events reported regardless of relationship in these phase 1 studies were:

Fatigue	62-88%
Diarrhea	52-76%
Pain Due to Tumor	43-77%
Nausea	32-72%
Sensory Neuropathy	24-60%
Vomiting	24-44%
Infection/Febrile Neutropenia	19-39%
Fever	19-33%
Cough	13-29%
Dyspnea	13-36%
Bone Pain	7-28%

Serious adverse events (SAEs) occurred with similar frequency in study V-101 and V-102 (42.9 and 45.2%, respectively), while they occurred in 24% of patients in study V-103. The most common SAE was febrile neutropenia and most of the SAEs occurred in 1or 2 patients. In study V-101, two patients withdrew from the study due to neutropenic infection and peripheral ischemia, and 17 deaths were reported, all due to disease progression. In study V-102, eight patients withdrew due to adverse events (2 asthenia, 1 sensory neuropathy, 1 diarrhea, 1 peripheral edema, 1 dysuria/hematuria, 1 bile duct obstruction, and 1 elevated transaminases), and 15 deaths were reported, all due to disease progression, except one death due to pneumonia. In study V-103, no patient withdrew from the study due to adverse events, and 22 deaths were reported, all due to disease progression.

Because of differing MTD reached in studies, the dose of 20 mg/m² administered every 3 weeks as a one-hour intravenous (IV) infusion (with a possible intra-patient escalation to 25 mg/m^2 at Cycle 2, in absence of toxicity >grade 2 during the first 3 weeks) was initially selected for further development.

Subsequently a Phase II study (Study 2001) was performed in metastatic breast cancer (MBC) patients who were resistant to prior taxane therapy given either as adjuvant therapy (Stratum 1) or as first-line or second-line therapy (Stratum 2). Safety and anti-tumoral activity were assessed at the dose of 20 mg/m² every 3 weeks at the first cycle, with possible intra-patient escalation to 25 mg/m^2 at Cycle 2 was allowed in the absence of any toxicity grade>2 at Cycle 1. A total of 71 patients were treated with a total of 345 cycles of treatment in Arm A. Two (2) CR and 8 PR were observed in as treated patients with an overall response rate (ORR) of 14.1%. The response rates were 14.6% and 9.5% in stratum 1 and stratum 2, respectively. The median time to progression (TTP) was 2.7 months and the median overall survival (OS) was 12.3 months. With the exception of Grade 3 or 4 neutropenia (73% in the overall population), the other adverse events were considerably lower compared to docetaxel.

Major treatment emergent adverse events reported regardless of relationship in this phase II study were:

Fatigue	51%
Nausea	44%
Diarrhea	40%
Myalgia	25%
Anorexia	25%
Weight loss	25%
Vomiting	24%
Infection/Febrile Neutropenia	18%
Headache	18%
Sensory Neuropathy	17%
Constipation	16%
Bone Pain	16%

In this study, 29.6% of patients reported serious adverse events; most common SAEs were hypersensitivity reaction (4.2%), and infection without neutropenia (4.2%). Four patients withdrew from the study due to non-fatal adverse events (2 elevated transaminases, 1 hepatitis, 1 hypersensitivity reaction), while 52 deaths were reported during the study, 50 of them were due to disease progression, 1 patient died due to unknown cause, while the other died due to shock with respiratory failure.

4.2.3 Clinical PK of XRP6258: Preliminary Available Results

Human pharmacokinetics of XRP6258 have been investigated during the Phase I studies.

Following 1h IV infusion, every 3 weeks, no major deviation to the dose proportionality has been observed from 10 to 30 mg/m². The terminal half-life was about 70 hours (62h in study V-101 and 77h in V-103 study). The total plasma clearance (CL) was high, with value of 27 L/h/m² in V-103 study and of 45 L/h/m² in V-101 study. The volume of distribution was large and quite similar in both studies (2034 and 2484 L/m², in studies V-103 and V-101, respectively).

After weekly administration (study V-102) some accumulation in the deep distribution compartment, consistent with the long elimination half-life, appears to occur with a 40% increase in AUC (0-t) after the fourth administration of Cycle 1, but with no increase in C_{max}. However, no difference in exposure has been observed between the first administrations of Cycle 1 and Cycle 2 or in the 3-weekly schedule.

Metabolism investigations with unlabelled drug after a one-hour infusion (IV) were carried out in 8 patients at 20 mg/m² on Cycle 2 (Day 21) in study V-103. The main circulating metabolite was RPR123142, with a mean metabolic ratio compared to parent drug of 0.196.

The *ex vivo* human plasma protein binding of XRP6258 was moderate to high (91.6%), in agreement with the *in vitro* data. The main cytochrome P450 isoenzymes involved in human XRP6258 biotransformation are CYP3A4 and CYP3A5, with further CYP2C8. Based on in vitro data, inhibition of CYP3A4 in vivo cannot be excluded.

4.3 RATIONALE

Based on a very good pre-clinical activity, a favorable safety profile in addition to the early activity observed in prostate cancer (2 responses out of seven prostate cancer patients treated were observed in phase I studies) and taxane resistant MBC patients, clinical development of XRP6258 is focused on late stage metastatic disease where the primary objective of treatment with cytotoxic agents is to provide palliation treatment as the ability of these patients to tolerate chemotherapy is limited due to adverse events.

The two phase III randomized studies conducted using mitoxantrone with prednisone suggest that there is palliative benefit from the addition of mitoxantrone to corticosteroids in the extent and duration of pain control in these hormone-refractory patients. However, there is no evidence of prolongation of survival. The combination mitoxantrone-corticosteroids are now considered as

the reference combination to treat HRPC patients. Mitoxantrone combined with prednisone has been approved in the United States (US) for the treatment of pain related to HRPC.

4.3.1 Rationale for Dose Selection

Because of differing MTD reached in phase I studies, the dose of 20 mg/m² administered every 3 weeks as a one-hour intravenous infusion was selected initially for further clinical development, with a possible intra-patient escalation to 25 mg/m^2 at Cycle 2, in absence of toxicity >grade 2 during the first 3 weeks. One partial response was observed in study V-103 at the 25 mg/m^2 dose. In a Phase II MBC (study ARD6191), safety and anti-tumoral activity were assessed at the dose of 20 mg/m² every 3 weeks at the first cycle, with possible intra-patient escalation to 25 mg/m^2 at Cycle 2 allowed in the absence of any toxicity grade >2 at Cycle 1. A total of 21 patients were treated at the 25 mg/m^2 dose after the 1st cycle with a favorable safety profile. The 25 mg/m² dose may provide more optimum dose intensity and potentially increase clinical benefit. Dose reduction will be permitted in the protocol in case a patient experiences grade 2 or worse toxicity.

4.3.2 Rationale for Pharmacokinetics

In vitro experiments with human microsomes have shown that XRP6258 is metabolized by both cytochrome P450 isoenzymes 2C8 and 3A4/5 [17]. Prednisone was found to be a significant inducer of CYP3A4/5 in vitro [18]. Plasma samples will be collected at Cycle 1 *i*n as many patients as possible at Cycle 1 in order to assess the PK profile in this population, assuming no effect of the day of administration of prednisone on PK of XRP6258. In addition, 25 patients who have already been sampled for PK at Cycle 1 will be sampled for PK evaluation at Cycle 2 in order to assess the effect of repeated administrations of prednisone on the PK of XRP6258.

It should be noted that the total plasma clearance of docetaxel (CYP3A4 substrate and lower plasma clearance than XRP6258 one) was not modified by repeated administration of prednisone in the same combination with prednisone (10 mg daily administration of prednisone) for the treatment of HRPC [19].

5 STUDY OBJECTIVES

5.1 PRIMARY

To determine whether XRP6258 in combination with prednisone improves overall survival when compared to mitoxantrone in combination with prednisone.

5.2 SECONDARY

- To compare efficacy between the two treatment arms:
  - PSA Response
  - PSA Progression
  - Progression Free Survival (PFS) defined as the first occurrence of any of the following events: tumor progression (RECIST: Response Evaluation Criteria in Solid Tumors), PSA progression, pain progression or death due to any cause.
  - Overall Response Rate (ORR)
  - Pain Response
  - Pain Progression
- To assess the overall safety of XRP6258 in combination with prednisone
- To assess the pharmacokinetics of XRP6258 and its metabolite, RPR123142, in this patient population and effect of prednisone on the pharmacokinetics of XRP6258

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a phase III, randomized, open-label, multi-center, multinational study.

The randomization will be performed by an Interactive Voice Response System (IVRS). Randomization between the two treatment arms will be stratified using the following factors:

- Measurability of disease per RECIST criteria (measurable vs. non-measurable disease), and
- ECOG performance status (0-1 vs. 2).

A dynamic allocation method will be used to avoid extreme imbalance of treatment assignment within a center.

6.2 DURATION OF STUDY PARTICIPATION

Each patient will be treated until disease progression, death, unacceptable toxicity or for a maximum of up to ten cycles (30 weeks). Each patient will have long-term follow-up until death or for a maximum of up to 2 years (104 weeks). Maximum study duration including long-term follow-up for each patient will be about 134 weeks.

6.3 STUDY COMMITTEES

An executive steering committee will be formed of 2-3 clinical experts in the prostate cancer field and representatives of the trial sponsor. The committee will provide scientific input and advice regarding the scientific content of the protocol and the study conduct. The committee will meet periodically at a scheduled interval. Roles and responsibilities will be described in the charter for the committee.

An Independent Data Monitoring Committee (IDMC) will be set up with the objective to review trial enrollment, compliance to protocol, safety of the administered treatments, and quality of the data. The IDMC will consist of two external independent physicians and a statistician not associated with the conduct of the study. This committee will convene periodically at a scheduled interval to review safety and other issues related to the appropriate conduct of the trial as well as efficacy at the occasion of the interim futility analysis. IDMC procedures will be detailed in the IDMC charter and approved by the IDMC members.

7 SELECTION OF PATIENTS

This study will enroll hormone resistant metastatic prostate cancer patients who were previously treated with a Taxotere® (or docetaxel)-containing regimen.

7.1 NUMBER OF PATIENTS PLANNED

The study will enroll approximately 720 patients (360 in each arm) at approximately 150 study centers in United States, Canada, European Union, and in other selected countries in the Rest of the World (ROW).

7.2 INCLUSION CRITERIA

Inclusion Criteria:

The Patient must have:

1 Diagnosis of histologically or cytologically proven prostate adenocarcinoma, that is refractory to hormone therapy and previously treated with a Taxotere® (or docetaxel)-containing regimen. Patient must have documented progression of disease during or within 6 months after prior hormone therapy and disease progression during or after Taxotere® (or docetaxel)-containing therapies.

2 Patient must have either measurable or non-measurable disease.

- Patient with measurable disease must have documented progression of disease by RECIST criteria demonstrating at least one visceral or soft tissue metastatic lesion (including new lesion). This lesion must measure at least 10 mm in the longest diameter (or two times the slice thickness) on spiral CT scan or MRI (chest, abdomen, pelvis) or 20 mm on conventional CT or Chest X-ray for biopsy proven, clearly defined lung lesion surrounded by aerated lung. (Previously irradiated lesions, primary prostate lesion, and bone lesions will be considered non-measurable disease)
- Patient with non-measurable disease must have documented rising PSA levels or appearance of new lesion. [Rising PSA is defined 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 (2^{nd} 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]

3 Received prior castration by orchiectomy and/or Luteinizing Hormone-Releasing Hormone (LH-RH) agonist with or without antiandrogen, antiandrogen withdrawal, monotherapy with estramustine, or other hormonal agents. (A prior treatment by antiandrogen is not mandatory.

However, if the patient has been treated with antiandrogens, **and** PSA is above 5 ng/mL at the last administration of antiandrogens, presence or absence of antiandrogen withdrawal syndrome* should be confirmed prior to the study entry). (LH-RH agonist treatment should continue during the study treatment period. Chlormadinone acetate or flutamide must have been stopped at least 4 weeks prior to, while bicalutamide must have been stopped at least 6 weeks prior to, the last PSA evaluation.) (* *The antiandrogen withdrawal syndrome is a decrease in PSA seen upon stopping an antiandrogen such as chlormadinone acetate, flutamide, or bicalutamide; this occurs because the antiandrogen has induced a mutation in the androgen receptor which is allowing the antiandrogen to stimulate prostate cancer growth rather than inhibit it)*

4 Life expectancy >2 months

5 Eastern Cooperative Oncology Group (ECOG) performance status 0 – 2 (ie, patient must be ambulatory, capable of all self-care, and up and about more than 50% of waking hours)

6 Age ≥18 years

7.3 EXCLUSION CRITERIA

1 Previous treatment with mitoxantrone

2 Previous treatment with <225 mg/m^2 cumulative dose of Taxotere® (or docetaxel)

3 Prior radiotherapy to ≥40% of bone marrow. Prior treatment with one dose of a bone-seeking radio-isotope (samarium-153, strontium-89, or P-32) is allowed, but 8 weeks must have elapsed after samarium-153 or P-32 and 12 weeks must have elapsed after strontium-89 prior to first study drug administration.

4 Prior surgery, radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to enrollment in the study

5 Active Grade ≥2 peripheral neuropathy.

6 Active Grade ≥2 stomatitis.

7 Active secondary cancer including prior malignancy from which the patient has been disease-free for ≤5 years (However, adequately treated superficial basal cell skin cancer before 4 weeks prior to entry can be eligible to the study)

8 Known brain or leptomeningeal involvement

9 History of severe hypersensitivity reaction (≥grade 3) to polysorbate 80 containing drugs

10 History of severe hypersensitivity reaction (≥grade 3) or intolerance to prednisone

11 Other concurrent serious illness or medical conditions

12 Inadequate organ function as evidenced by the following peripheral blood counts, and serum chemistries at enrollment:

- Neutrophils ≤1.5 x 109/L
- Hemoglobin ≤10 g/dL
- Platelets ≤100 x 109/L
- Total bilirubin ≥Upper limit of normal (ULN)
- AST (SGOT) ≥1.5 x ULN
- ALT (SGPT) ≥1.5 x ULN
- Creatinine ≥1.5 x ULN

13 Uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension. History of congestive heart failure, or myocardial infarction within last 6 months is also not allowed.

14 Left ventricular ejection fraction (LVEF) ≤50% by multi-gated radionuclide angiography (MUGA) scan or echocardiogram

15 Uncontrolled diabetes mellitus

16 Active uncontrolled Gastroesophageal Reflux Disease (GERD)

17 Active infection requiring systemic antibiotic or anti-fungal medication

18 Participation in another clinical trial with any investigational drug within 30 days prior to study enrollment.

19 Concurrent or planned treatment with strong inhibitors of cytochrome P450 3A4/5. A one-week washout period is necessary for patients who are already on these treatments.

20 For patient enrolled in the United Kingdom, the following exclusion criterion must be applicable: Patient with reproductive potential not implementing accepted and effective method of contraception, described in Appendix I.

8 TREATMENTS

8.1 INVESTIGATIONAL PRODUCT (IP)

XRP6258 is supplied as a sterile, non-pyrogenic, non-aqueous yellowish to brownish yellow, 80 mg/2 mL concentrate for solution for infusion. The solution contains the following excipient: Polysorbate 80. The fill volume has been established to include an 18 % overfill, ie, 2 mL (nominal volume) + 0.36 mL. This overfill was determined to ensure that an 80 mg dose can be extracted after the preparation of the premix.

The solvent for XRP6258 is supplied as a 13 % m/m ethanol solution in water for injection. The fill volume has been established to include a 22 % overfill, ie, 6 mL (nominal volume) + 1.33 mL.

MITOXANTRONE

Commercially available mitoxantrone will be supplied by the site/hospital pharmacy. As a standard treatment, it should be submitted to the patients medical insurance for reimbursement. In cases where third party insurance will not cover the cost, Sponsor will reimburse.

PREDNISONE

Commercially available prednisone will be supplied by the site/hospital pharmacy. In those countries where prednisone is not commercially available, prednisolone may be used.

As a standard treatment, it should be submitted to the patients medical insurance for reimbursement. In cases where third party insurance will not cover the cost, Sponsor will reimburse.

8.2 PACKAGING AND LABELING

XRP6258 is packaged in 15 mL single dose clear type I glass vial stoppered with a rubber closure. The stopper is crimped to the vial with a green flip-off aluminum cap. The solvent is supplied in a 15 mL single dose clear type I glass vial stoppered with a rubber closure and capped with a transparent flip-off aluminum cap. Each XRP6258 vial and each solvent vial are overfilled to ensure that an 80 mg dose can be extracted after the preparation of the premix. Each XRP6258 vial should be diluted with the **entire** content of the solvent vial.

The XRP6258 and solvent vials will be supplied in boxes each containing 3 vials XRP6258 and 3 vials solvent.

Batch number and number of vials dispensed to each patient must be recorded in the Case Report Form (CRF)/drug accountability form.

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

8.3 STORAGE CONDITIONS

Storage: XRP6258 (concentrate for solution for infusion) as packaged should be stored between 2°C and 30°C.

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

All vials must be kept in their box until use.

8.3.1 Mitoxantrone

Mitoxantrone available at the site/hospital pharmacy will be used. For storage, handling, and administration conditions, refer to package insert (PI).

8.3.2 Prednisone

Prednisone available at the site/hospital pharmacy will be used. In those countries where prednisone is not commercially available, prednisolone may be used. For storage, handling, and administration conditions, refer to package insert.

8.4 PREPARATION OF INVESTIGATIONAL PRODUCT

The preparation of the XRP6258 (RPR116258) infusion solution for administration requires the preparation of a premix solution at 80 mg/8 mL (nominal concentration). This must be done with a 13 % m/m ethanol solution in water for injection (the "solvent") supplied with the XRP6258 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.

a) Preparation of the premix solution under aseptic conditions

Set aside the required number of solvent vials (one solvent vial for each vial of XRP6258). For each XRP6258 vial:

If the drug product vial is stored under refrigerated conditions, it should stand one hour at room temperature before preparation of the premix and the refrigerated solution may be hazy.

- Using a syringe fitted with a needle, withdraw the **ENTIRE** CONTENTS of the solvent vial and inject it into the corresponding vial of XRP6258.
- The addition of the ENTIRE CONTENTS of one solvent vial ensures a minimal extractable volume of the premix solution of 8 mL, containing 10 mg/mL of XRP6258.
- Remove the syringe and needle and shake the mixture manually for at least 15 seconds.

- Allow the premix solution to stand for 5 minutes at room temperature and then check that the solution is homogeneous and clear. It is normal for foam to persist after this time period.

The premix solution contains 10 mg/mL of XRP6258.

b) 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 XRP6258 that corresponds to the required dose (mg) for administration of XRP6258
- 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 0.012 mg/mL and 0.252 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 using a rocking motion.

Therefore:

If the quantity of XRP6258 to administer is between 1.5 mg and 31.5 mg, use a 125 mL infusion container,

If the quantity of XRP6258 to administer is between 31.6 mg and 63 mg, use a 250 mL infusion container,

If more than 63 mg of XRP6258 is required, use a larger volume of infusion vehicle (ie, 500 mL).

c) Infusion conditions

The recommended infusion duration is one hour. The infusion solution should be used within 8 hours (including the one hour infusion time) and administered at room temperature under normal lighting conditions.

Infusion bags and infusion administration set made of PVC-free material should be used.

Glass bottles could also be used.

In line 0.22 µm filter made of PVC-free material should be used.

d) Storage period of premix and infusion solution

The premix solution of XRP6258 should be used immediately after preparation.

The infusion solution is stable for 8 hours from preparation to end of infusion.

e) Recommendation for safe handling

XRP6258 is an anti-neoplastic agent and, like other potentially toxic compounds, caution should be exercised in handling and preparing XRP6258 solutions. The use of gloves is recommended.

If XRP6258 concentrate, premix solution, or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If XRP6258 concentrate, premix solution, or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

MITOXANTRONE

The mitoxantrone should be administered according to its labeling. Please refer to package insert.

PREDNISONE

The prednisone should be administered according to its labeling. Please refer to package insert.

8.5 DOSING REGIMEN

There will be centralized randomization (1:1) and patients will be stratified for measurability of disease per RECIST criteria (measurable vs. non-measurable disease) and ECOG PS (0-1 vs. 2) for the following treatment assignment:

Arm A: Mitoxantrone 12 mg/m² intravenously (Day 1) every 3 weeks, plus prednisone 10 mg orally given daily

Arm B: XRP6258 25 mg/m² intravenously (Day 1) every 3 weeks, plus prednisone 10 mg orally given daily

On Day 1 of each cycle, patients will receive either XRP6258 at a dose of 25 mg/m^2, administered by IV route in 1 hour, or mitoxantrone 12 mg/m^2, administered by IV route in about 15-30 minutes. In addition, patients in both treatment groups will receive prednisone 10 mg orally daily.

Cycle length for both XRP6258 and mitoxantrone is 3 weeks. New cycles of therapy may not begin until Absolute Neutrophil Count (ANC) ≥1500/mm^3, platelet count ≥75 000/mm^3, and non-hematological toxicities (except alopecia) have recovered to baseline. A maximum of 2 weeks delay is allowed between 2 treatment cycles. Patients should come off study treatment, if treatment delay is more than 2 weeks. Patients will be monitored closely for toxicity. In addition to optimizing supportive care, chemotherapy doses may be adjusted after the first cycle of therapy and/or recovery to grade ≤1. Each patient will be treated until disease progression, death, unacceptable toxicity or for a maximum of up to ten cycles.

Arm B Only: Required IV 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 or other H2 antagonist with the exception of cimetidine). These premedications will be administered by IV infusion, at least 30 minutes prior to each dose

of XRP6258. Antiemetic prophylaxis with ondansetron, granisetron, or dolasetron can be administered whenever it is necessary.

Premedication for Arm A should be at the discretion of the physician. As in Arm B, pre-medication with a H2 antagonist (Ranitidine or other H2 antagonist with the exception of cimetidine) is recommended. Antiemetic prophylaxis with ondansetron, granisetron, or dolasetron can be administered whenever it is necessary.

8.5.1 Dose Modifications

General Rules

Every effort will be made to administer the full dose regimen to maximize dose-intensity.

If possible, toxicities should be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms including antiemetics for nausea and vomiting, antidiarrheals for diarrhea, and antipyretics, and/or antihistamines for drug fever.

Dose reduction

Dose can be reduced to 20 mg/m^2 for XRP6258 and 10 mg/m^2 for mitoxantrone when necessary as described below. The dose, which has been reduced for toxicity, must not be re-escalated. Only one dose reduction will be allowed per patient. If a second dose reduction is required per the modifications below, the patient should go off study.

Chemotherapy Delay

A treatment delay ≥4 days should be justified (ie, to be reported in the CRF). Treatment may be delayed no more than 2 weeks to allow recovery from acute toxicity. In case of treatment delay greater than 2 weeks, patient should go off study.

8.5.1.1 Myelosuppression

Table 1 - Chemotherapy dose modifications for hematologic toxicity

Hematologic Toxicity	Grade 3	Grade 4
Neutropenia If duration ≥7 days, or if complicated by T ≥38.5°C, or T ≥38.1°C x 3 during a 24-hour period, or infection.	Delay** next infusion until ANC ≥1.5 x 10^9/L: 1st episode: Administer prophylactic G-CSF treatment in subsequent cycles. 2nd episode: Reduce XRP6258 to 20 mg/m^2 or mitoxantrone to 10 mg/m^2. 3rd episode: Withdraw from study treatment.	
Thrombocytopenia	Delay** infusion until platelets ≥75 x 10^9/L. No dose reduction is required.	Delay** infusion until platelets ≥75 x 10^9/L and reduce XRP6258 to 20 mg/m^2 or mitoxantrone to 10 mg/m^2. Withdraw from study treatment in case of recurrence.

**Maximum of 2 weeks delay, otherwise the patient will be withdrawn from study treatment
T temperature
Prophylactic use of Granulocyte Colony-Stimulating Factor (G-CSF) is permitted, except for Cycle 1 of the treatment, at the discretion of investigator.

8.5.1.2 Allergy (Anaphylactic and Hypersensitivity reactions)

Mitoxantrone in combination with prednisone (Arm A): No anaphylactic and hypersensitivity reactions are expected. However, if a patient experiences such reactions, the same recommendations as for the XRP6258 arm apply (see table below).

XRP6258 in combination with prednisone (Arm B): Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of start of the first or of the second infusion of XRP6258. Therefore, during the 1st and the 2nd infusions, careful evaluation of general sense of well being and of blood pressure and heart rate will be performed for at least the first 10 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation along with the medications (ie, antihistamine, corticosteroids, aminophylline, and epinephrine) must be immediately available. If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (eg, epinephrine in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.) will be instituted. In addition, it is recommended to take the measures listed below:

Mild: localized cutaneous reaction, such as: pruritus, flushing, rash.	• Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside • Complete study drug infusion at the initial planned rate.
Moderate: Generalized pruritus, more severe flushing or rash, mild dyspnea, hypotension with systolic B.P. >80 mmHg	• Stop study drug infusion • Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg • Once all signs and/or symptoms of hypersensitivity reaction disappear, study drug may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible. • Re-administer premedication regimen as described in Section 8.5 when study drug is reinfused more than 3 hours after the interruption • Administer study drug over 2 hours for all subsequent infusions.
Severe: bronchospasm, generalized urticaria, hypotension with systolic B.P. ≤80 mmHg, angioedema.	• Stop study drug infusion • Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg • Add epinephrine** or bronchodilators and/or IV plasma expanders if indicated. • Once all signs and/or symptoms of hypersensitivity reaction disappear, study drug may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible. • Re-administer premedication regimen as described in Section 8.5 when study drug is reinfused more than 3 hours after the interruption • Administer study drug over 2 hours for all subsequent infusions. • If a severe reaction recurs, patient will go off protocol therapy
Anaphylaxis (Grade 4 reaction)	NO FURTHER PROTOCOL TREATMENT

8.5.1.3 Nausea/Vomiting

A prophylactic anti-emetic treatment should be given to the patients in Arm B in all cycles. The use of metoclopramide is recommended. More aggressive anti-emetic prophylaxis (ie, ondansetron, etc.) should be given to the patient who has experienced grade ≥3 nausea/vomiting in a preceding cycle. If despite the appropriate medication, grade ≥3 nausea/vomiting still occur, reduce the dose of study drug. If despite dose reduction, nausea/vomiting still occur at grade ≥3, the patient will go off study.

8.5.1.4 Diarrhea

No prophylactic treatment for diarrhea is recommended in Cycle 1. However, following the first episode of diarrhea, the patient should receive symptomatic treatment with loperamide 4 mg orally and then 2 mg orally following each new episode until recovery of diarrhea (no more than 16 mg daily). If despite the use of loperamide, grade ≥3 diarrhea still occurs, reduce the dose of study drug. If despite dose reduction, diarrhea still occurs at grade ≥3, the patient will go off study.

8.5.1.5 Stomatitis

If grade 3 or worse stomatitis occurs, study drug should be withheld until resolution to grade ≤1. Treatment may then be resumed, but the dose of study drug should be reduced for all subsequent doses. In case of grade 4 stomatitis, the patient will go off study.

8.5.1.6 Peripheral neuropathy

In case of symptoms or signs experienced by the patient, dose modification should be performed as follows:

- Grade ≤1: No change
- Grade 2: Retreat with reduced dose
- Grade 3: Patient will go off protocol therapy

8.5.1.7 Liver toxicity

In case of increase of SGOT and/or SGPT to >1.5 x ULN or bilirubin to >ULN, delay study drug treatment for up to 2 weeks until SGOT and/or SGPT returned to ≤1.5 x ULN and bilirubin to ≤ULN. Then retreat patient at reduced dose for rest of the treatment.

8.5.1.8 Other Toxic Effects

For any other toxicity grade 2, manage symptomatically, and retreat without dose reduction.

If it is grade 3 or worse, study drug administration should be held (except for alopecia) until resolution to grade 2, then re-instituted, if medically appropriate, with reduced dose.

8.5.1.9 Mitoxantrone-induced cardiac toxicity

The total cumulative dose of mitoxantrone must be restricted to ≤140 mg/m²; electrocardiogram (ECG) changes, arrhythmia, tachycardia, and/or chest pain should be managed based on the specific findings.

For monitoring the potential cardiotoxicity of mitoxantrone, all patients randomized to Arm A will be followed by MUGA scan or echocardiogram (using same method at all time points) to determine the LVEF values according to the following schedule:

- Baseline LVEF at rest before registration.
- LVEF will be repeated prior to every other treatment cycle, and/or the end of study (EOS) if the treatment is discontinued earlier.
- Once the treatment is discontinued/completed, LVEF will be repeated every month in patients whose LVEF decreased by ≥10% or to a level of <50% (EF units) during the study treatment period. This monitoring may be discontinued once the LVEF has recovered to baseline or the

investigator has deemed it to be chronic/stable and/or to be followed by the primary care physician.

If a patient presents with clinical symptoms suggesting congestive heart failure (ie, shortness of breath, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, etc.), LVEF should be repeated earlier to confirm this diagnosis and the patient must be removed from protocol treatment.

The patient should also go off study if there is an absolute decrease in LVEF ≥10% (EF units) associated with a decline to a level <50% (EF units) [20].

Alopecia and nail changes will not require dose modification.

8.6 COMPENSATION FOR LACK OF BLINDING

Primary endpoint of this open label study is overall survival. All assessments for tumor measurement and staging are objective measurements. In addition, a Steering Committee and Independent Data Monitoring Committee will be in place to closely monitor the data and study conduct. These measures will significantly reduce and/or eliminate any bias.

8.7 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Informed Consent

An interview will take place involving the patient and the Investigator to determine whether or not the patient is eligible to enter the study.

The patient must be aware of the neoplastic nature of his/her disease and must willingly consent after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required.

If it is determined that the patient is a candidate for the study, the patient (or his legally authorized representative) and the Investigator or a specific designee (previously approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)) will sign the informed consent form approved by the IRB/IEC of each center following guidelines related to the use of human patients in research.

Randomization Procedures

If the patient's characteristics comply with all clinical and laboratory criteria necessary for enrollment, the patient may be randomized into the study.

Once the investigator has verified all eligibility requirements, study site personnel will call the IVRS in order to randomize the patient. The IVRS will assign the patient to a treatment arm and if applicable, a PK sampling schedule. A confirmation will be sent to the investigator to verify

the patient's randomization, treatment arm assignment, and PK sampling schedule assignment. The investigator should keep this page with the patient's Case Report Form (CRF). All patients should begin protocol treatment within 96 hours of being randomized whenever possible.

8.8 RESPONSIBILITIES

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

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

Any quality issue noticed with the receipt or use of an Investigational Product (deficient IP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly reported to the Sponsor, who will initiate a complaint procedure.

Under no circumstances will the Investigator supply Investigational Product to a third party, allow the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

8.9 RETRIEVAL AND/OR DESTRUCTION OF TREATMENTS

Partially used XRP6258 will be destroyed on site according to standard practices of the site. Unused XRP6258 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 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 Product and eliminate potential hazards.

8.10 CONCOMITANT TREATMENT

Concomitant therapy with agents known to have anticancer activity is not permitted during the treatment phase of the study. Treatment with radiotherapy, *hormones or chemotherapeutic agents* is not permitted; except for the following, LH-RH agonists that are ongoing prior to study entry, steroids given for new adrenal failure and hormones administered for non-disease related conditions (eg, insulin for diabetes). The use of bisphosphonates will be allowed, however the dose must be stable for 12 weeks prior to enrollment and during the study treatment period (though bisphosphonate treatment may be discontinued during the study treatment period). In

addition, patients who are treated with LH-RH agonists (ie, without orchiectomy) should continue this therapy during the study treatment period.

Patients may not participate in any other investigational trials while participating in the treatment phase of this trial.

Patients should receive *full supportive care*, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. All blood products should be irradiated to prevent transfusion-associated graft versus host disease.

Myalgias and tumor pain may be treated with narcotics and/or non-narcotic agents, such as ibuprofen (400-800 mg three times daily) or another non-steroidal anti-inflammatory drug (NSAID), at the discretion of the treating physician.

If filgrastim (G-CSF) and sargramostim (GM-CSF) treatment are used therapeutically, they must be noted on concomitant CRF pages. Prophylactic use of G-CSF is permitted, except for Cycle 1 of the treatment, at the discretion of investigator.

Medications related to management of the symptoms of the disease or toxicity related to the protocol specified treatment is permitted and should be recorded in the concomitant medications page of the CRFs. Concomitant treatment should be used with caution.

8.11 TREATMENT ACCOUNTABILITY AND COMPLIANCE

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational 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 15.1.

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 8.9. The fixed label portions of all the 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 lot/batch numbers for mitoxantrone and prednisone administered to patients must be recorded on the CRF, as well as the total number of vials/units per cycle.

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

9 ASSESSMENT OF INVESTIGATIONAL PRODUCT

9.1 EFFICACY

9.1.1 Primary Criteria

9.1.1.1 Overall Survival

Overall survival will be measured in all randomized patients. Overall survival **will be assessed from the date of randomization to the date of death (whatever the cause). If death is not observed during the study, data on OS will be censored at the earlier of the last date patient is known to be alive and the cut-off date.**

9.1.2 Secondary criteria

9.1.2.1 Prostate-Specific Antigen

PSA will be assessed during the 28 days prior to first infusion (protocol-defined rising PSA), every three weeks during the treatment period (on Day 1 prior to each infusion), at the end of study treatment. In addition, during the first 6 months of the follow-up period, patients will be evaluated every 6 weeks for PSA progression until documented progression or start of other anticancer therapy. For the rest of the follow-up period patients will be evaluated every 3 months. To ensure comparability, PSA assessments for one patient must be performed in the same laboratory from baseline up to the end of the study.

PSA Response [16]: ***Applies to patients with baseline PSA ≥20 ng/mL***

Response requires a PSA decline of ≥50% confirmed by a second PSA value at least three weeks later. The duration of PSA response will be measured from the first to the last assessment at which the above criteria are satisfied.

PSA Progression [16]: ***Applies to all patients***

In PSA non-responders: progression will be defined as a ≥25% increase over the nadir (provided that the increase in the absolute value PSA level is at least 5 ng/ml), confirmed by a second value at least 1 week later.

In PSA responders and in patients not evaluable for PSA response at baseline: progression will be defined as a ≥50% increase over the nadir (provided that the increase in the absolute value PSA level is at least 5ng/ml), confirmed by a second value at least 1 week later.

9.1.2.2 Tumor Lesion Assessment

Anti-tumor activity will be assessed by computerized tomography (CT) or magnetic resonance imaging (MRI) of the whole body (chest, abdomen, and pelvis) and by bone scan, at baseline. These assessments, other than bone scan, will be repeated at the end of each even-numbered treatment cycle (Cycles 2, 4, 6, 8 and 10), whenever disease progression is suspected, and at the end of treatment/withdrawal visit, using the same method for each assessment. Bone scans will only be performed at these visits if clinically indicated. During the first 6 months of the follow-up period, patients who went off study treatment prior to documented disease progression will be evaluated by CT/MRI for tumor progression every 6 weeks from End of Study Treatment until disease progression or start of other anticancer therapy. For rest of the follow-up period, patient will be evaluated every 3 months. Bone scan will be performed during the follow-up period when clinically indicated. Confirmation of response (CR or PR) must be performed at least 4 weeks following the initial response and requires the assessment of all measurable and non-measurable disease.

Summary of Response Evaluation Criteria in Solid Tumors (RECIST)

Measurability of Tumor Lesions

At Screening, tumor lesions will be categorized by the investigator as measurable or non-measurable by RECIST as described below.

Measurable Disease – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed.

Measurable Lesions – lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm with conventional CT. With spiral CT, lesion must be ≥10 mm in at least one dimension.

Non-Measurable lesions – all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan) and other non-measurable lesions. These include: bone lesions; leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitis cutis/pulmonis; abdominal masses that are not confirmed and followed by imaging techniques; and cystic lesions.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

In the present study, lesions in previously irradiated fields cannot be used for the determination of response but can be used for the determination of progression.

Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinically detected lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography-including a ruler to estimate the size of the lesion-is recommended.

Lesions on chest X-ray are not acceptable as measurable target lesions. CT is required.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

Ultrasound (US) should not be used to measure tumor lesions that are not easily accessible. It may be used as a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Tumor markers will not be used in the assessment of response.

Tumor Response Evaluation

Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (those with longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of LD of target lesions taking as reference baseline sum LD.

Progression (PD): At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum LD since the treatment started.

Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease: Persistence of one or more non-target lesion(s).

Progression (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. The overall assessment of response will involve all parameters as depicted below.

Table 2 - Overall Assessment of Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete Response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Frequency of Tumor Re-evaluation

In the present study, tumor will be re-evaluated every 6 weeks during treatment, and at least 4 weeks after the first observation of a complete or partial response. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 6 weeks for first 6 months, and then every 3 months, until progression, unless they have started a new anti-cancer therapy.

Confirmatory Measurements

Confirmation

The main goal of confirmation of objective response is to minimize the risk of overestimation of the response rate. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed. In the present study, responses always need to be confirmed.

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate. In the present study, any interval of longer than 4 weeks is appropriate, but it is recommended to use a 6 week interval.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval defined in the protocol. In the present study, this interval is 35 days.

9.1.2.3 Progression-Free Survival

Progression-Free Survival will be evaluated in all randomized patients. PFS is defined as the time between randomization and the date of progression or date of death (due to any cause) where a progression is either a PSA progression, or a tumor progression, or a pain progression (pain progression must be supported by clinical evidence of disease progression).

9.1.2.4 Pain

Pain (PPI and AS) will be assessed prior to every treatment cycle and at the end of study treatment visit. In addition, during the first 6 months of the follow-up period, patients will be

evaluated every 6 weeks for pain progression until documented progression or start of other anticancer therapy. For the rest of the follow-up period, patients will be evaluated every 3 months until documented progression or start of other anticancer therapy.

Pain will be assessed using the Present Pain Intensity scale from the McGill-Melzack questionnaire [21]. The patient will be asked to complete the PPI every day for the one-week period prior to each evaluation. The questionnaire should be administered before any treatment infusion occurs. If treatment is delayed, the assessment schedule should be defined from the actual date of beginning of treatment. Median PPI is calculated from the PPI values over the one-week prior to treatment.

Pain will also be assessed using an Analgesic Score derived from analgesic consumption (in morphine equivalents). The patient will be asked to record all analgesic use for the one-week period prior to each evaluation. Mean Analgesic Score is calculated as the mean daily score of analgesics, averaged over the prior week, using the table described in Appendix G:

Pain response (***applies only to patients with median PPI ≥2 on McGill-Melzack scale and/or mean Analgesic score ≥10 points at baseline)*** will be defined as a 2-point or greater reduction from baseline median PPI with no concomitant increase in analgesic score,

OR

A reduction of at least 50% in analgesic use from baseline mean AS (only in patients with baseline mean AS ≥0) with no concomitant increase in pain.

Either criterion must be maintained for two consecutive evaluations at least 3 weeks apart. The duration of pain response will be measured from the first to the last assessment at which the above pain response criteria are satisfied.

Pain progression (***applies to all patients)*** will be defined as an increase of ≥1 point in the median PPI from its nadir noted on two consecutive three-week-apart visits

OR

≥25% increase in the mean analgesic score compared with the baseline score and noted on two consecutive three-week-apart visits

OR

requirement for local palliative radiotherapy.

Pain progression as defined above must be cancer-related (ie, supported by clinical and/or radiological evidence of disease progression). Patients should only be discontinued from study treatment for cancer-related pain progression.

Median PPI and mean AS will be calculated only if 5 of the 7 expected values are actually available in the Patient Pain Diary. Otherwise, the patient will be considered as not evaluable for pain efficacy criteria at the corresponding cycle:

- Pain response is not evaluable if >2 AS are missing and/or >2 PPI values are missing (over the same week)
- Pain progression is not evaluable if >2 AS are missing and/or >2 PPI values are missing (over the same week) unless a complete evaluation (ie, at least 5 values) of AS or PPI shows a pain progression.

9.2 SAFETY

Safety profile will be determined by the incidence of clinically significant adverse events (AEs) including serious adverse events (SAEs) and laboratory abnormalities. AEs will be collected from the time the first dose of the study drug until 30 days after the administration of the last cycle of study treatment. SAE will be collected from the time patient sign the informed consent form until 30 days after the last cycle of the study treatment. Toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (NCI CTCAE v. 3.0) and summarized using MedDRA terminology.

Vital signs, physical examination, ECOG performance status and ECG and LVEF and laboratory tests will be performed prior to drug administration and at specified regular intervals throughout the study.

9.3 PHARMACOKINETICS

9.3.1 Sampling time

The aim of the sampling strategy is to define the PK profile over the whole population by drawing a small number of samples in a sufficient number of patients [22], as opposed to standard PK protocols where a small number of patients are extensively sampled.

Blood sample collection will be performed according to a sparse sampling strategy in as many patients as possible in Arm B (XRP6258 arm) at Cycle 1 and in 25 patients in Cycle2.

The selection of sampling time was based on both known pharmacokinetic characteristics of XRP6258 and methodological consideration (need to vary sampling times) across patients for insuring the robustness of the analysis [23]

Four sampling schedules with each 6 samples of 4 mL each have been designed according to a full PK screening in Phase I as described in Table 3

Sampling schedules will be randomly assigned to patients via the IVRS in order to have balanced numbers of patients in each sampling schedule.

Table 3 - Blood sampling schedules for XRP6258

Sampling schedule	Sampling Time for XRP6258					
	Before the infusion	During infusion	Post end of infusion			
1	Before the infusion	30 min before the end of infusion	5 min	1h	6-10h	24h-168h
2	Before the infusion	10 min before the end of infusion	10 min	2h	8-12h	24h-168h
3	Before the infusion	30 min before the end of infusion	20 min	3h	10-20h	24h -168h
4	Before the infusion	10 min before the end of infusion	30 min	4h	10-22h	24h-168h

This procedure should be done with the maximum number of samples according to the assigned schedule and according to center feasibility

A total of 24 mL of whole blood will be collected for pharmacokinetic evaluation of XRP6258 and its metabolite (RPR123142) when patients are sampled at Cycle 1 and 48 mL, if blood collection occurs at Cycles 1 and 2.

9.3.2 PK handling procedure

Venous whole blood samples will be collected into heparinized coated tubes (lithium heparinate) for XRP6258.

Blood samples should not be taken at the infusion site.

After centrifugation, plasma samples will be stored frozen at approximately -20°C until analysis.

Central collection facilities will be used to collect the plasma samples from various sites and then will be shipped in batches to sanofi-aventis GMPK Department, Alfortville, France.

Specific instructions for specimen collection, processing, and shipping are described in Appendix C.

9.3.3 Bioanalytical method

The plasma concentrations of XRP6258 and its metabolite, RPR123142, will be determined by a liquid chromatography mass spectrometry technique (LC/MS-MS) in Bioanalytical Department, GMPK, sanofi-aventis, Alfortville, France. The limit of quantitation for both compounds is 1ng/mL using 200 µL of plasma.

10 PATIENT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

Serious Adverse Events will be collected from the time patient signs an informed consent form until 30 days after the administration of the last cycle of study treatment. Adverse events will be collected from the time of the first dose of the investigational product. Toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (NCI CTCAE v. 3.0) and summarized using MedDRA terminology. Safety evaluations will include vitals signs, physical examination, ECOG performance status, ECG, LVEF, and laboratory tests. These evaluations will be performed prior to drug administration, at specified regular intervals, and as required throughout the study.

10.2 ADVERSE EVENTS MONITORING

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

10.3 DEFINITIONS OF ADVERSE EVENT (AE) AND SERIOUS ADVERSE EVENT (SAE)

An **Adverse Event** 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.

A priori, efficacy endpoints will not be considered as AEs except if, because of the course or severity or any other features of such events, the Investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition.

A **Serious Adverse Event** 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;
- Results in 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 intervention to prevent one of the other outcomes listed in the definition above.

These should also usually be considered serious.

Note: Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or asymptomatic ALT increase ≥10 ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

Adverse Events

For this study, Serious Adverse Events, regardless of relationship to study medication, will be collected from the time a patient signs an informed consent form until 30 days after the administration of the last cycle of study treatment. SAEs occurring more than 30 days after the last dose of study medication that are considered to be related to study medication will also be collected. Adverse events, regardless of relationship to study medication, will be collected from the time of the first dose of study medication until 30 days after the administration of the last cycle of study treatment. At the end of study treatment, all AEs and SAEs considered related to study medication must be followed to resolution and recorded on the CRF, as applicable.

Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to Investigational Product, corrective treatment/therapy given, outcome, and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by the Investigational Product.

Laboratory, vital signs, or ECG abnormalities are to be recorded as Adverse Events only if they are associated with the following clinical consequences: fulfilling a seriousness criterion, leading to treatment discontinuation, and/or leading to a dose modification.

Serious Adverse Events

In the case of a Serious Adverse Event the Investigator must immediately:

- SEND (within 1 working day, preferably by fax) the signed and dated corresponding page(s) in the Case Report Form to the representative of the Monitoring Team whose name, address, and fax number appear on the Clinical Trial Protocol;
- ATTACH the photocopy of all examinations carried out and the dates on which these examinations were performed. 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 source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges;

- Follow-up of any Serious Adverse Event that is fatal or life threatening should be provided within one additional calendar week.

Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he should follow up the outcome of any Adverse Events (clinical signs, laboratory values or other, etc.) until the return to normal or consolidation of the patient's condition;
- In the case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the Clinical Trial and that additional investigations may be requested by the Monitoring Team;
- In the case of any Serious Adverse Event brought to the attention of the Investigator at any time after cessation of Investigational Product and considered by him/her to be caused by the Investigational Product with a reasonable possibility, this should be reported to the Monitoring Team.

10.5 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 IP, to the Investigators, to the Authorities, and to the IECs / IRBs as appropriate. Any other SAE not listed as an expected event in the Investigator's Brochure will be considered as unexpected. The Sponsor will report all safety observations made during the conduct of the trial in the CSR.

11 HANDLING OF PATIENT TEMPORARY OR DEFINITIVE TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

11.1 DEFINITIVE TREATMENT DISCONTINUATION WITH INVESTIGATIONAL PRODUCT(S)

11.1.1 List of criteria for definitive treatment discontinuation

The patients may withdraw from treatment with Investigational Product if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision.

11.1.2 Handling of patients after definitive treatment discontinuation

Patients will be followed 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 a followed AE, whichever comes last.

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

11.2 PROCEDURE FOR WITHDRAWAL OF PATIENTS FROM STUDY FOLLOW-UP SCHEDULE

The patients may withdraw from the study at any time, for any reason, prior to study completion. The Investigator may decide to withdraw the patient for safety or other reason at any time during the study prior to study completion.

- All study withdrawals should be recorded by the Investigator in the appropriate pages when considered as confirmed;
- If possible, the patients are assessed using the procedure normally planned for the end-of-study visit if appropriate (or according to other procedures to be specified here such as follow-up phase);

The Investigator should make every effort to recontact the patient, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including at least his/her vital status.

Patients who did not complete the study and for whom no endpoint data are available will be considered as lost to follow-up. The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

List of withdrawal criteria

Withdrawal from study drug

Patients will be withdrawn from the study drug for the following medical and/or administrative reasons. Post-study treatment follow-up will continue, as described in Section 6.2.

- Completion of the study treatment (ie, 10 cycles of treatment)
- Disease progression (or death due to progressive disease): the date and evidence for disease progression will be documented in the medical record. Note that patients should only be removed from treatment for pain progression if pain is cancer-related and supported by clinical evidence and/or radiological of disease progression.
- Adverse event (including death), treatment-limiting toxicity, intercurrent medical problem, that contra-indicate continuation of anticancer chemotherapy
- Voluntary withdrawal
- Patient lost to follow-up
- Other reason (eg, protocol violation, investigator's decision)

Withdrawal from trial

Patients will be withdrawn from the trial for the following medical and/or administrative reasons:

- Completed follow-up period (2 years)
- Death
- Poor compliance to protocol
- Voluntary withdrawal
- Patient lost to follow-up
- Other reason

When a patient withdraws from the trial, the reason of withdrawal will be documented in the medical chart and recorded on the CRF. An attempt to obtain all end of study evaluations is expected. All data collected for the entire course of the study must be recorded on CRFs and provided to the Sponsor.

Reasons for withdrawal

The patients may withdraw from the trial or from treatment at any time if they decide to do so, regardless of the reason. Patients may also be removed from the trial or from treatment at the discretion of the investigator.

Withdrawal follow-up procedure

- All withdrawal information should be documented in the medical chart and recorded on the appropriate page of the CRF.
- The CRF is to be completed up to the last visit performed for the patients considered lost to follow up. The investigator should make several attempts to re-contact the patient, and document these phone contacts/visits in the medical chart. Every attempt should be made to obtain the patient's health status and the reason for withdrawal from the trial.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

12.1.1 Screening/Baseline

The Screening period is from Day-28 to randomization/initial dose of study drug, as indicated below or in the flow chart.

12.1.1.1 Day –28 to Randomization/initial dose of study drug

- Informed Consent
- Contraceptive Counseling
- Medical, Oncologic, and Surgical History, including demography
- Physical Examination, height, weight, vital signs (heart rate, blood pressure, temperature)
- Body surface area calculation
- ECOG performance status
- Assessment of prior treatment medication use, administered within the 30 days prior to the study registration
- CBC, Diff, Platelets
- Total Bilirubin, AST/ALT, Alkaline Phosphatase, Creatinine, BUN, Glucose, Serum Electrolytes (sodium, potassium, chloride, and bicarbonate)
- Testosterone levels
- ECG
- Left Ventricular Ejection Fraction (By MUGA or Echocardiogram)
- Prostate Specific Antigen (PSA)
- Bone Scan
- Radiological tumor measurement
- Pain Assessment by McGill-Melzack Present Pain Intensity (PPI) scale
- Analgesic diary
- Adverse Event recording (SAE only)
- Randomization

After review of the screening assessments and confirmation of eligibility criteria, patients are randomized into the study via IVRS. All patients should begin protocol treatment within 96 hours of being randomized if possible.

12.1.2 Study Days

The period called Study Days begins when the patient receives the first dose of study drug (Cycle 1, Day 1). Each cycle consists of 21 days (±3 days). Cycle length may be extended if additional time is required for resolution of study drug-related toxicities or other adverse events. If the assessment is scheduled for a day in which the patient is also scheduled to receive study drug, the assessment must be performed prior to the study drug administration unless otherwise indicated in the Flow Chart and not precluding additional assessments where necessary, eg, monitoring and recording any adverse events during and after study treatment.

12.1.2.1 Prior to each infusion (Day 1 of each cycle) unless otherwise indicated

- Physical Examination, weight, vital signs (heart rate, blood pressure, temperature)
- Body surface area calculation
- ECOG performance status
- Assessment of Concomitant Treatments
- CBC, Diff, Platelets (repeat on Day 8 and Day 15 of every treatment cycle, and when clinically indicated)
- Total Bilirubin, AST/ALT, Alkaline Phosphatase, Creatinine, BUN, Glucose, Serum Electrolytes (sodium, potassium, chloride, and bicarbonate) (repeat when clinically indicated)
- Left Ventricular Ejection Fraction (By MUGA or Echocardiogram, using the same method at all times) (every other cycle for mitoxantrone arm only)
- Prostate Specific Antigen (PSA)
- Bone Scan (when clinically indicated)
- Radiological tumor measurement (every other cycle)
- Pain Assessment by McGill-Melzack Present Pain Intensity (PPI) scale
- Analgesic diary
- Adverse Event recording
- PK blood draw (Refer to Section 9.3.1 for blood draw timing)

12.1.3 End of treatment / withdrawal

At the end of the study treatment, the following procedures should be performed within 30 (+3 days) days following the final dose of study drug.

- Physical Examination, weight, vital signs (heart rate, blood pressure, temperature)
- ECOG performance status
- Assessment of concomitant treatment medication use
- CBC, Diff, Platelets
- Total Bilirubin, AST/ALT, Alkaline Phosphatase, Creatinine, BUN, Glucose, Serum Electrolytes (sodium, potassium, chloride, and bicarbonate)
- Testosterone
- ECG
- Left Ventricular Ejection Fraction by (By MUGA or Echocardiogram, using the same method as previously used) (for mitoxantrone arm only)
- Prostate Specific Antigen (PSA)
- Bone Scan (when clinically indicated)
- Radiological tumor measurement
- Pain Assessment by McGill-Melzack Present Pain Intensity (PPI) scale
- Analgesic diary
- Adverse Event recording

During this period, the outcome of adverse events with a date of onset during the study period should be re-evaluated, and any new adverse events should be recorded. Serious adverse events should be followed as described in Section 10.4.

12.1.4 Post-treatment follow-up (survival or long term follow-up)

After withdrawal from study treatment, further treatment, if any, is at the discretion of the investigator. Please note that in the absence of progressive disease or of symptoms requiring anti-cancer treatment, follow-up without such treatment should be considered.

Once a patient has progressed or started another anti-cancer therapy, follow-up visits should be performed every 3 months for a maximum of 2 years. However, patients who went off study treatment prior to documented disease progression and who have not started another anti-cancer therapy will be evaluated by CT/MRI for tumor progression every 6 weeks for the first 6 months of the follow-up period or until disease progression or start of other anticancer therapy. For rest of the follow-up period, patient will be evaluated every 3 months. Bone scan will be performed during the follow-up period when clinically indicated. In addition, patients who went off study treatment prior to documented disease progression and who have not started another anti-cancer therapy will be evaluated every 6 weeks for PSA and/or pain progression for the first 6 months of

the follow-up period or until documented progression or start of other anticancer therapy. For the rest of the follow-up period, patients will be evaluated every 3 months.

The following procedures must be performed in follow-up:

- Assessment of anti-cancer treatment
- PSA measurement (until disease progression or initiation of further anti-cancer therapy)
- Bone scan (when clinically indicated until disease progression or initiation of further anti-cancer therapy)
- Tumor measurement (until disease progression or initiation of further anti-cancer therapy)
- Pain Assessment by McGill-Melzack Present Pain Intensity scale (until disease progression or initiation of further anti-cancer therapy)
- Adverse Event recording (pertaining to study drug only)
- Survival status evaluation

12.2 DEFINITION OF SOURCE DATA

According to the guidelines on Good Clinical Practice (GCP), the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre-identified source data directly recorded in the Case Report Form. 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 source data which supports the data on the Case Report Forms (eg, patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

13 STATISTICAL CONSIDERATIONS

The material of section 13 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.

13.1 SAMPLE SIZE DETERMINATION

The primary endpoint for the study is overall survival (OS). The median survival for patients receiving mitoxantrone plus prednisone is estimated to be 8.0 months (11). A 25% improvement in median overall survival from 8.0 months to 10.67 months, corresponding to a hazard ratio of 0.75 in patients treated with XRP6258 plus prednisone, is considered to be clinically meaningful.

Assuming that survival times are exponentially distributed in both treatment arms, a total number of 511 deaths are required to provide 90% power to detect a 25% reduction in hazard rate using a two-sided log-rank test at a significance level of 0.05.

Based on an anticipated uniform accrual rate over a period of 24 months, a total of 720 patients (360 patients per treatment arm) would need to be enrolled in order to achieve the required number of deaths by the end of the minimum follow-up period.

13.2 ANALYSIS VARIABLES

13.2.1 Demographic and baseline characteristics

Standard demographic and baseline characteristics (including age, race, height and weight), medical history, cancer diagnosis and prior anti-cancer therapy will be collected at baseline. Baseline efficacy variables, eg, tumor assessment, pain, PSA, and other prognostic variables will be assessed as well, baseline value being defined as the last value or measurement taken up to the first dose in the study.

13.2.2 Efficacy variables

13.2.2.1 Primary efficacy variable

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

13.2.2.2 Secondary efficacy variables

Main secondary efficacy variables are defined as follows:

- **PSA Response (Applies only to patients with baseline PSA ≥20 ng/mL):** Response requires a PSA decline of ≥50% confirmed by a second PSA value at least three weeks later. The duration of PSA response will be measured from the first to the last assessment at which the above criteria are satisfied.

- **PSA Progression (Applies to all patients):**

  ***In PSA non-responders*,** progression will be defined as a ≥25% increase over the nadir (provided that the increase in the absolute value PSA level is at least 5 ng/ml), confirmed by a second value at least 1 week later.

  In PSA responders and in patients not evaluable for PSA response at baseline, progression will be defined as a ≥50% increase over the nadir (provided that the increase in the absolute value PSA level is at least 5 ng/ml), confirmed by a second value at least 1 week later.

  The detailed censoring rules will be provided in the Statistical Analysis Plan (SAP).

  Progression Free Survival: PFS will be evaluated from the date of randomization to the date of tumor progression, PSA progression, pain progression (pain progression supported by clinical evidence and/or radiological of disease progression), or death due to any cause, whichever occurs first. The detailed censoring rules will be provided in the Statistical Analysis Plan (SAP).

- **Overall Response Rate (in patients with measurable disease):**

  Objective responses (CR and PR) for measurable disease as assessed by investigators according to RECIST criteria. Confirmation of objective responses will be performed by repeat tumor imaging (CT scans, MRI, bone scans) at least 4 weeks after the first documentation of response

- Pain Response (*applies only to patients with median PPI ≥2 on McGill-Melzack scale and/or mean Analgesic Score ≥10 points at baseline):* Pain Response will be defined as a 2-point or greater reduction from baseline median PPI with no concomitant increase in analgesic score, OR a reduction of at least 50% in analgesic use from baseline mean AS (only in patients with baseline mean AS ≥10) with no concomitant increase in pain. Either criterion must be maintained for two consecutive evaluations at least 3 weeks apart.

- Pain Progression *(applies to all patients):* Pain Progression will be defined as an increase of ≥1 point in the median PPI from its nadir noted on two consecutive three-week-apart visits OR ≥25% increase in the mean analgesic score compared with the baseline score and noted on two consecutive three-week-apart visits OR requirement for local palliative radiotherapy. The detailed censoring rules will be provided in the Statistical Analysis Plan (SAP).

Note that pain progression as defined above must be cancer-related (ie, supported by clinical and/or radiological evidence of disease progression).

13.2.3 Safety variables

Analysis of safety will be performed by summarizing Adverse Events, vital signs (blood pressure, heart rate, and temperature), ECG (only baseline and end of treatment), ECOG performance status, LVEF, and laboratory data.

13.2.4 Pharmacokinetic variables

The population PK analysis will be carried out using nonlinear mixed effect modeling and will be focused on the estimation of total plasma clearance (CL) and exposure (AUC) for XRP6258 and on exposure (AUC) and metabolic ratio (AUC metabolites/AUC parent compound) for RPR123142.

13.3 ANALYSIS POPULATIONS

13.3.1 Efficacy populations

13.3.1.1 Intent-to-treat (ITT) population

The intent-to-treat (ITT) population will include all randomized patients (ie, patients assigned to a treatment group by the randomization, regardless of whether patients received any study drug or received a different study drug from which they were randomized. Analysis of the primary efficacy endpoint will be performed using the ITT population. Secondary and exploratory efficacy endpoints will also be analyzed in the ITT population, and in evaluable patients whenever applicable (see Section 13.4).

13.3.1.2 Clinical Trial Protocol deviations

During a blinded review of the database, compliance with the protocol will be examined with regard to inclusion/exclusion criteria, prohibited therapies, and timing and availability of planned assessments. Protocol deviations will be identified by the clinical trial team before database lock and will be classified as minor or major deviations.

The detailed definition of all major deviations will be provided in the SAP. All major protocol deviations will be summarized to assess the quality of the study conduct.

13.3.2 Safety population

The safety population will include all patients who received at least part of one dose of study drug. Treatment compliance/administration and all clinical safety data will be summarized using this safety population.

13.3.3 Other analysis population

Not applicable

13.3.4 Disposition of patients

The number and percentage of patients in each of the above-defined populations will be provided.

In addition, reasons for treatment discontinuation as well as reasons for withdrawal from the study will be displayed for randomized patients by treatment group.

13.4 STATISTICAL METHODS

Categorical data will be summarized in contingency tables presenting frequencies and appropriate percentages for each treatment group. Continuous data will be summarized using frequency, mean, standard deviation, median (if appropriate), minimum and maximum by treatment group. Descriptive analyses will be summarized by treatment group and overall only for the description of baseline characteristics.

The chi-square test will be used to compare proportions (replaced by Fisher's exact test if the expected frequency in any one of the cells of the contingency table is <5).

The Kaplan-Meier method will be used to analyze time-to-event data and to estimate the median time. Kaplan-Meier curves will be presented as well. The 95% confidence interval for the median time will be calculated using the Brookmeyer and Crowley (1982) method.

Time-to-event distributions will be compared using the log rank test, stratified on the two stratification factors used in the randomization (namely measurability of disease and ECOG performance status).

Hazard ratios and their 95% confidence intervals will be estimated from Cox proportional hazards models stratified by the same stratification factors described above.

13.4.1 Demographic and baseline characteristics

13.4.1.1 Patients demographic characteristics, medical history and diagnoses

All patient demographic characteristics, medical history, and diagnoses will be tabulated based on the ITT population. Continuous variables (such as age, weight, and height) will be summarized as described above. Qualitative characteristics (such as race) will be summarized by counts and percentages (n;%).

13.4.1.2 Previous medications

Previous anti-cancer therapies (prior hormone therapy, prior surgery, prior radiotherapy, etc.) will be summarized by frequencies.

13.4.2 Extent of study treatment exposure and compliance

Extent of exposure will be assessed within the safety population.

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

Dose delays and dose reductions will be also analyzed.

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

13.4.3 Analysis of efficacy variables

13.4.3.1 Analysis of primary efficacy variable

OS will be compared between the two treatments by the log-rank test procedure at the 0.0076 significance level at the second interim analysis and 0.0476 significance level at the final analysis, stratified in the ITT population in the second interim analysis and the final analysis by stratification factors as specified at the time of randomization: measurability of disease per RECIST criteria (measurable vs. non-measurable disease) and ECOG PS (0-1 vs. 2) .

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

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

Additional exploratory analysis may be considered and will be detailed in the SAP. For example, the Cox proportional hazard model may be used to examine the effect of various prognostic factors on OS.

13.4.3.2 Analysis of secondary efficacy variables

All analyses for secondary efficacy variables will be carried out in the ITT population.

Progression Free Survival, PSA progression, and Pain progression will be compared between the two treatments 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.

Tumor, PSA, and pain response will be compared between groups using chi-square tests.

As a supportive analysis, PSA response will be also evaluated in the subset of patients with baseline PSA ≥20 ng/mL.

13.4.4 Analysis of safety data

Analysis of Adverse Events, vital signs, ECG, LVEF, and laboratory data will be descriptive and conducted on the exposed population as defined in Section 13.3.2, Safety population. Summary of safety data will also be performed by cycle (when applicable). 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.

13.4.4.1 Adverse Events

Serious Adverse Events will be collected from the time patient signs an informed consent form until 30 days after the administration of the last cycle of study treatment. Adverse events will be collected from the time of the first dose of the investigational product. Adverse events will be summarized with the number and percentage of patients with adverse events, classified by MedDRA preferred term and intensity as graded by the NCI CTCAE, v. 3.0.

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 end of treatment. Tables of treatment-emergent adverse events (TEAE) will be provided.

SAEs and Treatment–Emergent SAEs will be summarized using MedDRA classification to the preferred term. SAEs will be also presented by worst NCI grade by patient.

Adverse events will be analyzed regardless of their relationship to the study drug. However, summaries will be done for specific subsets of adverse events, such as events related to study drug.

13.4.4.2 Laboratory safety data

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.

13.4.5 Analyses of pharmacokinetic variables

13.4.5.1 Sample size determination for Pharmacokinetics

Effect of prednisone

Based on XRP6258 mean plasma clearance of 27.3 (±9.7) L/h/m² in 23 patients with various type of tumors from Phase I study V-103 (1 hour infusion every 3 weeks), a minimum total number of 21 patients is required to detect a 20% difference in mean clearance with 80% power using a one sample t-test at significance level 0.05 (each patient being its own reference).

13.4.5.2 Population PK model

Pharmacokinetic analysis of XRP6258 will be carried out using nonlinear mixed effect modeling (NONMEM software version V or more recent).

The analysis will involve an estimation of inter-patient PK variability, the population pharmacokinetic parameters estimates and the assessments of patho-physiologic covariate effects on CL and possibly on volume if warranted. Empirical Bayesian estimation of individual parameters and of individual exposure (AUC: Area Under the Curve) will also be performed.

PK estimates will then be investigated as prognostic factors for clinical outcome including safety and efficacy endpoints if possible.

13.4.5.3 Statistical on PK parameters

An *in vitro* study (SA 00-221) has been conducted to evaluate the potential of dexamethasone, hydrocortisone, methylprednisolone, prednisolone and prednisone to induce/inhibit cytochrome P450 isoenzymes in human primary human hepatocytes [24]. Prednisone was found to be a significant inducer of CYP3A4/5 and a slight inducer of CYP2A6. These results were similar to those found in the study by Pichard *et al*. [25]

Because XRP6258 is metabolized by CYP3A4/5, the effect of prednisone will be investigated by comparing the XRP6258 clearance at Cycle 1, on Day 1 (no effect of prednisone expected, since it corresponds to the first day of administration of prednisone) and at Cycle 2, on Day 1 (10 mg daily administration for 3 weeks) in Arm B.

Statistical analysis was performed using SAS software (SAS version 8.2 or more recent; SAS Institute INC, NC).

Comparison of XRP6258 CL and possibly of RPR123142 dose normalized AUC will be conducted using the PROC MIXED procedure after log transformation of the PK parameter. In the statistical model implemented, inter-individual variability will be considered as a random effect and treatment effect (Cycle 2 vs. Cycle 1) will be considered as fixed effects.

13.5 DATA HANDLING CONVENTIONS

In general there will be no imputation of missing data.

Some patients may be excluded from secondary or exploratory analyses as a result of missing data. Specifically, patients who are non evaluable for secondary/exploratory analysis will be excluded from the analyses on PSA response, tumor response, and pain response.

Specific rules will be applied to evaluate some efficacy variables, for example:

- PSA response will be assessed only among patients with a baseline PSA ≥20 ng/ml.
- Tumor response will be calculated among patients with measurable disease.
- Pain response is to be applied only to patients with baseline present pain intensity score (PPI) ≥2 on the McGill-Melzack scale and/or baseline mean analgesic score (AS) ≥10 points.

13.6 INTERIM ANALYSIS

An interim (futility) analysis of PFS (either tumor progression, PSA progression, or pain progression, as defined above, or death from any cause) will be performed after 225 PFS events have occurred, ie, 33% information fraction at an estimated cut-off of 12 months after 1st patient has been randomized. Approximately 360 patients will have been accrued when this futility analysis is performed.

This interim analysis (IA) will be used to estimate the probability that the null hypothesis of no treatment differences will be rejected upon completion of the trial. Early termination for futility will be considered if the conditional power of observing a significant effect at the end of the study, assuming the current trend continues, is less than 10%.

The futility analysis on PFS is not an interim analysis of the primary endpoint (OS). Therefore, no adjustment will be done on the final p-value for the OS analysis (once at least 511 deaths are observed).

The second interim analysis will be performed at the time of the 307 deaths (the 60% of the 511 deaths in the final analysis of the protocol) to assess the primary efficacy endpoint of overall survival based on the O'Brien-Fleming type I error spending function. The statistical significance level at the interim analysis will be 0.0076 for the 2-sided stratified log rank test. In case the stopping criteria are not met at the time of this second interim analysis the study will continue and the final overall survival analysis will be performed with the 2-sided stratified log rank test at the 0.0476 significance level.

14 ETHICAL AND REGULATORY STANDARDS

14.1 ETHICAL PRINCIPLES

This Clinical Trial will be conducted 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 International Conference for Harmonization (ICH) guidelines for Good Clinical Practice (GCP).

14.2 LAWS AND REGULATIONS

This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country(ies) in which the Clinical Trial is performed, as well as any applicable guidelines.

14.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the Patient of all pertinent aspects of the Clinical Trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

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.

If informed consent is obtained under special circumstances (emergency, from a guardian, minor, etc.), the method should be specified following the ICH requirements. The first part of the section should be adapted, keeping the point as appropriate.

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.

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

The Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the Sponsor a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (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 CV, etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Investigational Product will not be released at the study site and the Clinical Trial will not start until a copy of this written and dated approval/favorable opinion has been received by the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC) and patients should be notified of any modifications or Amendments to the Clinical Trial Protocol that may affect their safety. In addition, the IRB/IEC should 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 Ethics Committee (IRB/IEC).

If requested, a progress report is sent to the Ethics Committee (IRB/IEC) annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR (S)

The Investigator(s) undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

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 Case Report Form [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 particular circuits have to be defined (eg, e-CRF, Fax), 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 Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators 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.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the Case Report Forms. 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. During these monitoring visits, the following non-exhaustive list of points will be scrutinized with the Investigator: patient informed consent, patient recruitment and follow-up, Adverse Event, Serious Adverse Event documentation and reporting, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre-identified source data directly recorded in the Case Report Form. 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 source data which support the data on the Case Report Forms (eg, patient's medical file, appointment books, original laboratory records, etc.). Such personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

15.4 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. 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 information to be modified must not be overwritten. The corrected information will be transcribed by the authorized person next to the previous value, initialed and dated.

The computerized handling of the data by the Sponsor after receipt of the CRFs 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 appended to the CRFs held by the Investigator and the Sponsor.

15.5 USE OF COMPUTERIZED SYSTEMS

Identify at which steps a computerized system will be used to create, modify, maintain, archive, retrieve or transmit data (monitoring system, data entry, statistical analysis, etc.).

16 ADMINISTRATIVE RULES

16.1 CURRICULUM VITAE

An updated copy of the curriculum vitae (English or translated in English) limited to the experience, qualification and training for each Investigator and Sub-Investigator will be provided to the Sponsor prior to the beginning of the Clinical Trial.

16.2 RECORD RETENTION IN STUDY SITE(S)

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

It is recommended that the Investigator retain the study documents at least fifteen (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.

17 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, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential. 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 Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial.

The Investigator and the Sub-Investigators 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.

18 PROPERTY RIGHTS

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

The Investigator shall not 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 Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

19 DATA PROTECTION

The patient's personal data and Investigator's personal data which may be 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.

20 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy, which covers the liability of the Investigator. This insurance policy is in accordance with local laws and requirements.

An insurance certificate will be provided to the Investigator in countries requiring this document.

The insurance of the Sponsor does not relieve the Investigator and the collaborators of any obligation to maintain their own liability insurance policy as required by applicable law.

21 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 applicable regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this 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 future 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.

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

22.1 DECIDED BY THE SPONSOR IN THE FOLLOWING CASES:

- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all Investigational Product, means and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon;
- In the event the results of the Clinical Trial do not appear to be scientifically convincing to the Sponsor;
- If the aim of the Clinical Trial has become outdated or is no longer of interest;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice;
- If 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.

22.2 DECIDED BY THE INVESTIGATOR

The Investigator must notify (30 days prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed.

23 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a Clinical Study Report;

When the data from all investigational sites have been fully analyzed by the Sponsor, the latter will communicate the results of the Clinical Trial to the Investigator(s).

24 PUBLICATIONS AND COMMUNICATIONS

The Sponsor recognizes the Investigator's right to utilize data derived from the study for teaching purposes, communication at congresses and scientific publications. Nevertheless, in order to ensure the accuracy and scientific value of the information, while preserving the independence and accountability of the Investigator, and the confidentiality of the information, only cleaned, checked and validated data will be used. To that effect, it is essential that the parties exchange and discuss, prior to any publication or communication, any draft publication or communication made by the Investigator. Therefore, the Investigator undertakes, and will ensure that any Sub-Investigators undertake, not to make any publication, communication or release pertaining to the results of the study, without the prior written consent of the Sponsor.

The Investigator shall send to the Sponsor a copy of the manuscript for review and possible comments at least forty-five (45) days in advance of the date of submission to the journal and at least twenty (20) days in advance for abstracts. The publication shall be delayed until approval of publication is given in writing by the Sponsor, not to exceed ninety (90) days, it being understood that the Sponsor cannot refuse its consent without reasonable cause. The Investigator agrees to include the modifications requested by the Sponsor, provided they do not jeopardize the accuracy and/or the scientific value of the publication.

Should the Sponsor desire to protect by a property right any information contained in the publication, it has the right to postpone the publication, for a period not to exceed eighteen (18) months.

In multicenter studies, the Investigator agrees not to publish the results of the study pertaining to his/her center prior to the publication of the overall study results. If no publication has occurred within twelve (12) months of the termination of the study at all other sites, the Investigator shall have the right to publish independently the results of this study, patient to the review procedure set forth herein. If the study is conducted with the support of a Steering Committee, the latter may define specific rules for publication.

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.

25 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 Ethics Committee (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.

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27 APPENDICES

Appendix A ECOG Performance Status

GRADE	SCALE
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Ambulatory, capable of light or sedentary work. Restricted in physically strenuous activity.
2	Ambulatory, capable of all self-care, but not of work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Appendix B NCI Common Terminology Criteria

The NCI Common Terminology Criteria (Version 3.0) can be accessed through the following website:

http://ctep.cancer.gov/reporting/ctc.html

Appendix C Pharmacokinetic specifications (centrifugation / shipment)

1. SAMPLING SUPPLIES DESCRIPTION

Specimens	Collection tubes: Will be provided by Quest Diagnostics at the time of site initiation
	Storage tubes: Will be provided by Quest Diagnostics at the time of site initiation
Miscellaneous	Centrifuge: Site must have centrifuge available
	Specimen storage tube labels for plasma specimens - Quest
	Styrofoam shippers with boxes - Quest
	Shipping labels - Quest
	Ziploc storage bag to be used for samples shipment - Quest
	Bubble wrap (Source Packaging of NE, Inc. Part #BLP-1000) - Quest

2. Collection/Handling/Processing of Samples

Collection schedule (sparse PK profile for population PK)

Patients will be randomly assigned via the IVRS to one of the 4 schedules. Six samples (P00 to P05) per patient will be collected as follows:

Sampling Schedule	Tube numbers					
	P00	**P01**	**P02**	**P03**	**P04**	**P05**
	Before the infusion	*During infusion*	*Post end of infusion*			
Schedule 1	Before the infusion	30 min before the end of infusion	5 min	1h	6-10h	24h-168h
Schedule 2	Before the infusion	10 min before the end of infusion	10 min	2h	8-12h	24h-168h
Schedule 3	Before the infusion	30 min before the end of infusion	20 min	3h	10-20h	24h -168h
Schedule 4	Before the infusion	10 min before the end of infusion	30 min	4h	10-22h	24h -168h

Procedure

Since study treatment is administered intravenously, blood samples for pharmacokinetic analysis should not be collected where study treatment is infused (eg, from a central line used for study treatment administration).

For samples collected through a catheter, 1 mL of blood should be withdrawn and discarded to ensure that the solution used to maintain catheter potency not dilute the blood sample.

It is extremely important to collect all blood samples as close to the protocol-specified times as possible. The reasons for any missed or lost blood samples should be documented. Actual dates/times of blood collection should appear on the blood collection form in CRF at the study site. The times of drug administration (XRP6258) should also be precisely recorded.

At the protocol-specified intervals indicated in Section 9.3.1, one Lithium heparinate vacutainer tube will be used to collect 4 mL of whole blood from patient for plasma preparation for the determination of circulating XRP6258 for pharmacokinetic analysis.

It is important to carefully follow the steps outlined below:

- Collect 4 mL blood using a vacutainer tube containing lithium heparinate, and gently invert tube at least 8 times permitting specimen to mix with tubes anticoagulant
- The exact time of sample collection should be recorded on CRF.
- Within 30 min of collection, centrifuge at 2000 *g* for 15 min
- Immediately following the centrifugation, transfer the top layer of human plasma into a pre-labeled polypropylene tube, being careful not to transfer blood cells.
- Ensure that all sample tubes are clearly and appropriately labeled.
- Immediately cap tubes and freeze the plasma in an upright position at –20°C for storage.

No more than 1 hour is allowed between blood collection and plasma sample frozen to avoid degradation of XRP6258.

Storage

Sample should be grouped according to patient in bubble wrap and placed in plastic freezer bag. All specimens must be stored frozen at -20°C in a freezer that is not frost-free until shipped to the sponsor.

Labeling of specimens

Each sample must be labeled with the following minimum information:

Product code:	XRP6258
Protocol number:	EFC6193
Patient number:	XXXX XXX XXX (3 digit country number, 3 digit study site number + 3-digit patient number)
Sample number:	P00 to P05
Day and time interval of sample:	**Month –day – year** **Time of collection**

3. PACKAGING AND SHIPMENT OF SAMPLES

Packaging

- Samples must be packaged according to IATA Dangerous Goods Regulations, Packing Instructions 650.
- Absorbent material must be placed in the Ziploc storage bag containing samples packaged in bubble wrap (see above).
- All bagged samples are to be packed in dry ice in Styrofoam shippers with enough dry ice to ensure that the samples remain frozen for a 48-hour period for intra-continent shipments and for a 72-hour period cross-continent shipments. The following table indicates the recommended amount of dry ice that should be used.

Styrofoam Shipper	Shipper: World Courier Amount of Dry Ice	Shipper: Other Courier Amount of Dry Ice
Medium (15" X 13" X 12") (38 X 33 X 31 cm)	10 lb (4.6 kg)	20 lb (11.4 kg)
Large (15.4" X 22.5" X 15") (39 X 57 X 38 cm)	20 lb (11.4 kg)	40 lb (22.8 kg)

- Place dry ice along the bottom of the Styrofoam shipper.
- Place bagged samples on dry ice, add additional dry ice around the sides and top, and add lid.
- The Styrofoam shipper should be placed in the cardboard box in which the shipper arrived.
- The fully completed and signed “Sample Labels/Shipping Document” or “Sample Tracking Log and Shipping Form” corresponding to the samples shipped must be enclosed in a plastic resealable bag, then placed on top of the Styrofoam shipper between the lid and cardboard box.
- Seal cardboard box and place the “Dry Ice Label” and “UN3373” labels on the exterior of the cardboard box.
- The exterior of the box should be marked “RUSH – DIAGNOSTIC SPECIMENS PACKED IN COMPLIANCE WITH IATA PACKING INSTRUCTIONS – STORED AT -20°C”.

Shipment preparation

- The sender must notify the shipment receiver prior to shipment, with date of shipment and any tracking information.
- **Ship samples to Quest only Monday, Tuesday, or Wednesday for intra-continent shipments, only Monday or Tuesday for cross-continent shipments, and not on the eve of a public holiday.**

Acknowledgement of receipt

- Upon receipt of the samples, Quest will send an acknowledgment of receipt.

4. SHIPMENT CONTACT NAME AND ADDRESSES

Plasma samples for XRP6258 assay and will be shipped to [redacted] (see address below)

Samples from sites in US, L. America, Canada:

[redacted]

Samples from sites in Europe, S. Africa, & India:

[redacted]

Samples from sites in Asia:

[redacted]

Appendix D Mitoxantrone Package Insert

The mitoxantrone Package Insert can be accessed through the following website:

http://www.osip.com/OSI/images/docs/NovantronePI1-2005.pdf

Appendix E Personal Pain Intensity/Analgesic Score Scales

SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME: _____ **DATE:** _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING-EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING-CRUEL	0) _____	1) _____	2) _____	3) _____

P P I

0	NO PAIN	_____
1	MILD	_____
2	DISCOMFORTING	_____
3	DISTRESSING	_____
4	HORRIBLE	_____
5	EXCRUCIATING	_____

Non Narcotic Medications		Narcotic Medications			
1 POINT		4 POINTS			
Any route		Oral/Rectal		IV/IM/SC	
Generic Name	**Dose (mg)**	**Generic Name**	**Dose (mg)**	**Generic Name**	**Dose (mg)**
Aceclofenac	100	Anileridine	25		
Acemetacin	90	Buprenorphine	0.8	Buprenorphine	0.8
Acetaminophen / Paracetamol	325			Butorphanol	1
Aminophenazone	500	Codeine	60		
Aspirin	325	Dextropropoxyphene	50		
Celecoxib	100	Dihydrocodeine	30		
Diclofenac	25	Fentanyl*	100 µg	Fentanyl*	50 µg
Diflunisal	250	Hydrocodone	10	Hydrocodone	5
Dipyrone / Metamizole	500	Hydromorphone	2	Hydromorphone	1
Etodolac	200	Levorphanol	2	Levorphanol	2
Fenoprofen	200	Meperidine/Pethidine	100	Meperidine/Pethidine	50
Flurbiprofen	50	Methadone	10		
Ibuprofen	200	Morphine	10	Morphine	5
Indomethacin	25	Oxycodone	5	Oxycodone	2.5
Ketoprofen	25	Oxymorphone rectal	2.5		
Ketorolac	10			Papaveretum	15.4
Mefenamic Acid	250	Pentazocine	50	Pentazocine	30
Nabumetone	500	Piritramide	15		
Naproxen	250	Propoxyphene	50		
Nefopam	20	Tilidine	50		
Nimesulide	100	Tramadol	50	Tramadol	50
Piroxicam	10				
Propyphenazone	250				
Rofecoxib	12.5				
Tenoxicam	20	* Fentanyl patch (TTS) : 36 points / day for 25µg/hour patch			

Adapted from: Tannock et al., J. Clin. Oncol., 1996, 14 (6) : 1756-1764., Martindale 1996, 31st Ed., London Royal Pharmaceutical Societ

Appendix F RECIST Criteria

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

  Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

  Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

  Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement –

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid

nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

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

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

- All conclusions should be based on all eligible patients.

- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

- The 95% confidence intervals should be provided.

Appendix G Morphinic Equivalent

Preferred Term Decode	Route	Conversion Factor
Acetylsalicylic Acid	Oral	0.008
Acetylsalicylic Acid	Rectal	0.008
Indomethacin	Oral	0.07
Indomethacin	Rectal	0.07
Phenylbutazone	Oral	0.02
Phenylbutazone	Rectal	0.02
Codeine	Sublingual	0.08
Codeine	Intramuscular	0.08
Codeine	Intravenous	0.08
Codeine	Oral	0.05
Codeine	Rectal	0.05
Codeine	Subcutaneous	0.08
Pethidine	Sublingual	0.1
Pethidine	Intramuscular	0.1
Pethidine	Intravenous	0.1
Pethidine	Oral	0.033
Pethidine	Rectal	0.033
Pethidine	Subcutaneous	0.1
Dextropropoxyphene	Oral	0.066
Dextropropoxyphene	Rectal	0.066
Paracetamol	Oral	0.008
Paracetamol	Rectal	0.008
Salicylic Acid	Oral	0.008
Salicylic Acid	Rectal	0.008
Morphine	Sublingual	1
Morphine	Intramuscular	1
Morphine	Intravenous	1
Morphine	Oral	0.33
Morphine	Rectal	0.33
Morphine	Subcutaneous	1
Metamizole Sodium	Oral	0.005
Metamizole Sodium	Rectal	0.005
Mefenamic Acid	Oral	0.01
Mefenamic Acid	Rectal	0.01
Oxycodone	Sublingual	0.67
Oxycodone	Intramuscular	0.67
Oxycodone	Intravenous	0.67
Oxycodone	Oral	0.33
Oxycodone	Rectal	0.33
Oxycodone	Subcutaneous	0.67
Aminophenazone	Oral	0.005

Preferred Term Decode	Route	Conversion Factor
Aminophenazone	Rectal	0.005
Pentazocine	Sublingual	0.33
Pentazocine	Intramuscular	0.33
Pentazocine	Intravenous	0.33
Pentazocine	Oral	0.11
Pentazocine	Rectal	0.11
Pentazocine	Subcutaneous	0.33
Oxyphenbutazone	Oral	0.02
Oxyphenbutazone	Rectal	0.02
Hydrocodone	Oral	0.33
Hydrocodone	Rectal	0.33
Levorphanol	Sublingual	5
Levorphanol	Intramuscular	5
Levorphanol	Intravenous	5
Levorphanol	Oral	2.5
Levorphanol	Rectal	2.5
Levorphanol	Subcutaneous	5
Methadone	Sublingual	1
Methadone	Intramuscular	1
Methadone	Intravenous	1
Methadone	Oral	0.5
Methadone	Rectal	0.5
Methadone	Subcutaneous	1
Salsalate	Oral	0.007
Salsalate	Rectal	0.007
Hydromorphone	Sublingual	7
Hydromorphone	Intramuscular	7
Hydromorphone	Intravenous	7
Hydromorphone	Oral	1.33
Hydromorphone	Rectal	1.33
Hydromorphone	Subcutaneous	7
Ibuprofen	Oral	0.006
Ibuprofen	Rectal	0.006
Panadeine Co	Sublingual	0.08
Panadeine Co	Intramuscular	0.08
Panadeine Co	Intravenous	0.08
Panadeine Co	Oral	0.05
Panadeine Co	Rectal	0.05
Panadeine Co	Subcutaneous	0.08
Fentanyl	Sublingual	50
Fentanyl	Intramuscular	50
Fentanyl	Intravenous	50
Fentanyl	Oral	50
Fentanyl	Rectal	50
Fentanyl	Subcutaneous	50
Fentanyl	Topical	50

Preferred Term Decode	Route	Conversion Factor
Fentanyl	Transdermal	50
Oxymorphone	Sublingual	10
Oxymorphone	Intramuscular	10
Oxymorphone	Intravenous	10
Oxymorphone	Oral	2
Oxymorphone	Rectal	2
Oxymorphone	Subcutaneous	10
Naproxen	Oral	0.01
Naproxen	Rectal	0.01
Ketoprofen	Oral	0.05
Ketoprofen	Rectal	0.05
Diclofenac	Oral	0.1
Diclofenac	Rectal	0.1
Tolmetin	Oral	0.008
Tolmetin	Rectal	0.008
Mepergan	Oral	0.1
Mepergan	Rectal	0.1
Fenoprofen	Oral	0.01
Fenoprofen	Rectal	0.01
Sulindac	Oral	0.25
Sulindac	Rectal	0.25
Flurbiprofen	Oral	0.05
Flurbiprofen	Rectal	0.05
Buprenorphine	Sublingual	33
Buprenorphine	Intramuscular	33
Buprenorphine	Intravenous	33
Buprenorphine	Subcutaneous	33
Diflunisal	Oral	0.01
Diflunisal	Rectal	0.01
Butorphanol	Sublingual	5
Butorphanol	Intramuscular	5
Butorphanol	Intravenous	5
Butorphanol	Subcutaneous	5
Piroxicam	Oral	0.5
Piroxicam	Rectal	0.5
Meclofenamic Acid	Oral	0.05
Meclofenamic Acid	Rectal	0.05
Nalbuphine	Sublingual	1
Nalbuphine	Intramuscular	1
Nalbuphine	Intravenous	1
Nalbuphine	Subcutaneous	1
Tramadol	Oral	0.2
Tramadol	Rectal	0.2
Etodolac	Oral	0.01
Etodolac	Rectal	0.01
Alfentanil	Sublingual	3

Preferred Term Decode	Route	Conversion Factor
Alfentanil	Intramuscular	3
Alfentanil	Intravenous	3
Alfentanil	Subcutaneous	3
Nabumetone	Oral	0.01
Nabumetone	Rectal	0.01
Oxycocet	Oral	0.33
Oxycocet	Rectal	0.33
Oxaprozin	Oral	0.008
Oxaprozin	Rectal	0.008
Ketorolac	Sublingual	0.25
Ketorolac	Intramuscular	0.25
Ketorolac	Intravenous	0.25
Ketorolac	Oral	0.25
Ketorolac	Rectal	0.25
Ketorolac	Subcutaneous	0.25
Tylenol PM	Oral	0.008
Tylenol PM	Rectal	0.008
Choline Magnesium Trisalicylate	Oral	0.007
Choline Magnesium Trisalicylate	Rectal	0.007
Hydrocodone Compound	Oral	0.33
Hydrocodone Compound	Rectal	0.33
Celecoxib	Oral	0.025
Celecoxib	Rectal	0.025
Rofecoxib	Oral	0.4
Rofecoxib	Rectal	0.4

Appendix H List of Strong CYP450 3A4/5 inhibitors

STRONG INHIBITORS	Inhibitor Dose, interval	Maximum AUC fold increase	Substrate for the observed Maximum AUC fold increase
cyclosporine	5.2 mg/kg, qd	7.4	atorvastatin
chloramphenicol	600 mg, qid	7.5	tacrolimus
troleandomycin	500 mg, SD + 250, qid	8.6	alfentanil
telithromycin	800 mg, qd	9.4	simvastatin
clarithromycin	500 mg, bid	13.9	simvastatin
grapefruit juice	200ml, double strengh, tid	16.1	simvastatin
ketoconazole	200 mg, qd	25.3	nisoldipine
nefazodone	2.5 mg, bid	50.0	buspirone
itraconazole	200 mg, qd	36.4	lovastatin
ritonavir	600 mg, sd	111.7	saquinavir

Legend:
*: formulation vehicle,
R: fold increase,
sd: single dose
qd: repeated dose, once a day
bid: repeated dose, twice a day
tid: repeated dose, 3 times a day
qid: repeated dose, 4 times a day

Appendix I Effective method of contraception for United Kingdom

For patients enrolled in the UK, who are sexually active either during the study and/or for six months afterwards, must agree to use a condom during intercourse without fail, regardless of whether or not their partner is of childbearing potential.

In addition to the man using a condom, partners of childbearing potential must use an effective means of contraception as described below:

- A condom in combination with a secondary barrier (eg, intrauterine device or diaphragm)
- A barrier method in conjunction with contraceptive foam or jelly
- An intrauterine device in combination with a secondary barrier (eg, diaphragm)

For those patients who have partners who are post-menopausal for 6 months or more, or are surgically sterile for more than one month, their partners are not required to use the contraceptives. The patient must however still agree to use a condom. Partners who are postmenopausal for less than two years and are not surgically sterile must have a negative pregnancy test.

In case patient wants to have sexual intercourses with a pregnant or actively breast-feeding woman, he must also take precautions even if the risk of transmission of his treatment to this woman is low. Patient and his female partner should agree to use medically appropriate contraceptive measures as previously described.