A phase II clinical trial of radium-223 activity in patients with metastatic castration-resistant prostate cancer (mCRPC) with asymptomatic progression while on abiraterone acetate or enzalutamide besides AR-V7 mutational status

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SIGNATURE PAGE FOR THE STATISTICAL ANALYSIS PLAN

MedOPP098

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1. Synopsis

Type of application	Clinical Trial
Sponsor	Medica Scientia Innovation Research (MedSIR) Rambla Cataluña, 2-4, 2D, 08007-Barcelona, Spain Tel.: + 34 93 221 41 35; Fax: + 34 93 299 23 82
Clinical trial title	"A phase II clinical trial of radium-223 activity in patients with metastatic castration-resistant prostate cancer (mCRPC) with asymptomatic progression while on abiraterone acetate or enzalutamide besides AR-V7 mutational status"
Protocol number	MedOPP098
Study Coordinator and Principal Investigator	Dr. Joan Carles Galcerán Hospital Vall d´Hebrón
Expected sites	10 sites are expected to participate in Spain.
Central Ethics Committee/Institutional Review Board	Corporació Sanitaria Parc Taulí
Name and qualification of the persons in charge of Monitoring	Raquel Gordo Medica Scientia Innovation Research (MedSIR) Rambla Cataluña, 2-4, 2D, 08007-Barcelona, Spain Tel.: +34 93 221 41 35; Fax: +34 93 299 23 82
Investigational drug	Radio 223 (Xofigo®)
Trial phase	II
Objectives	<u>Primary objective</u> To assess the efficacy of radium-223 in asymptomatic patients with mCRPC who have progressed while on abiraterone acetate or enzalutamide treatment. <u>Secondary objectives</u> • Safety profile. • To determine the association between AR-V7 status (positive vs. negative) and progression-free survival (PFS). • To establish the relationship between circulating tumor cells (CTCs) number with radium-223 efficacy.
Design	Multicenter, single-arm, open-label, non-controlled phase IIa clinical trial.

Primary endpoint	The primary endpoint of this study is to assess the efficacy of radium-223 in terms of radiological rPFS.
Study population and total number of subjects	Patients ≥ 18 years of age diagnosed with mCRPC with bone metastases and asymptomatic progression after at least 24 weeks of treatment with abiraterone acetate or enzalutamide. A total of 52 patients will be enrolled into this trial. We expect to include 13 AR-V7-positive and 39 AR-V7-negative patients
Approximate duration of subject participation	Patients will be treated with radium-223 at four-week intervals for six intravenous injections. Patients who complete the study treatment during its active treatment phase will enter a follow-up period with radiological tumor assessment every three months (±7 days) from the last dose of study treatment until documented disease progression.
Calendar and estimated completion dates	Start Recruitment (FPI): Nov-2016 End of Recruitment (LPI): Oct-2018 Follow-up period for progression: Sep-2019 Follow-up extension for safety: Apr-2021 Final report: Mar-2018 Final safety report: Aug-2021

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3. Abbreviations

AE:	Adverse events.
AF:	Alkaline Phosphatase.
AR-V7:	Androgen Receptor Splice Variant-7.
CI:	Confidence Interval.
CTC:	Circulating Tumor Cells.
IC:	Informed Consent.
mCRPC:	metastatic Castration-Resistant Prostate Cancer.
MedDRA:	Medical Dictionary for Regulatory Activities.
OS:	Overall Survival.
PCWG:	Prostate Cancer Clinical Trials Working Group.
PFS:	Progression-Free Survival.
PT:	Preferred Term.
rPFS:	radiological Progression-Free Survival.
SAE:	Serious Adverse Events.
SOC:	System Organ Class.
SSE:	Symptomatic Skeletal Event.

4. Introduction

4.1 *General*

The present study (EXCAAPE) is a phase II clinical trial of radium-223 activity in patients with metastatic castration-resistant prostate cancer (mCRPC) with asymptomatic progression while on abiraterone acetate or enzalutamide besides AR-V7 mutational status.

The purpose of this statistical analysis plan (SAP) is to provide a protocol specific description of the statistical analysis that will be performed to produce an integrated clinical/statistical report.

This SAP is based upon the following study documents:

- Initial protocol version dated: 29th July 2016
- Protocol version dated: 20th December 2016
- electronic Case Report Form (eCRF), Version 4.0

4.2 *Type of study*

This a phase II clinical trial of radium-223 activity in patients with metastatic castration-resistant prostate cancer (mCRPC) with asymptomatic progression while on abiraterone acetate or enzalutamide besides AR-V7 mutational status.

4.3 *Study Protocol Amendments*

- Initial protocol version dated: 29th July 2016
- Protocol version dated: 20th December 2016

4.4 *Study Population*

Patients with mCRPC with asymptomatic progression while on abiraterone acetate or enzalutamide. The progression on enzalutamide or abiraterone acetate will be defined as patients who confirm radiographic progression and/or PSA progression with rapid PSA doubling time (less than three months).

4.5 *Study Design*

A total of 52 patients will be enrolled into this trial. We expect to include 13 AR-V7-positive and 39 AR-V7-negative patients.

The design of this study is divided into three well-defined phases:

- **Screening phase**

Subject eligibility is determined, including the documentation of baseline characteristics. This phase of the study will begin once the informed consent is signed by the patient.

- **Treatment phase:** Once the informed consent has been signed and the study screening criteria have been confirmed, the patient will be treated with radium- 223 at a dose of 55 kBq (after 2015 NIST implementation) per kilogram body weight, given at four-week intervals for six intravenous injections.

Patients will receive study treatment according to the protocol and will be prematurely discontinued in the following situations: disease progression, occurrence of unacceptable side effects, death, or withdrawal of consent, whichever occurs first.

- **Follow-up phase:**

Once the treatment phase is completed, patients will enter a follow-up period with radiological tumor assessment every three months (±7 working days) until disease progression and safety evaluation during 2 years from the last dose of study treatment. If patient discontinued treatment for any reason other than progression, tumor reevaluation will be included in the assessment. After disease progression, a safety follow-up visit will be performed within three following months and 2 years after last dose of study treatment (including survival status and post-study anticancer therapy evaluation). Safety evaluation after progression will include follow-up of symptomatic skeletal related events and overall survival.

4.6 *Study Schedule*

The schedule of visits for this study and procedures to be performed at each visit are shown in the appendix 1 of the protocol.

4.7 *Sample Size*

A total of 52 patients will be enrolled into this trial. We expect to include 13 AR-V7-positive and 39 AR-V7-negative patients.

Justification of sample size

The sample size is determined on the basis of the primary endpoint. The primary endpoint is defined as PFS according to the PCWG2 criteria. We will screen the AR-V7 mutation retrospectively, after the patient was included. We expect the number of AR-V7-positive patients will be 25% of total sample. Therefore, sample size has been estimated on AR-V7-positive cohort to ensure a minimum of 80% power in two cohort analysis. We hypothesized equally efficacy of radium-223 in AR-V7-negative and AR-V7-positive cohorts.

Previous studies in advanced refractory prostate cancer patients treated with docetaxel plus estramustine against mitoxantrone plus prednisone showed a median PFS of 6.3 and 3.2 months, respectively. According to these results, excluding a PFS ≤ 3 months while targeting an improvement of the PFS ≥ 6.3 months would be a conservative approach to evaluation of the radium-223 effect in both cohorts. The analysis will be performed with one arm one-sided Log-Rank test.

A maximum follow-up period of 34 months is planned. We assume an uniform accrual of 2.26 patients per month (both cohorts). A sample size of 52 patients will be needed to attain 80%

power at nominal level of one-sided alpha of 0.05. Therefore, we expect to include a total sample of 52 patients, 39 of them will be AR-V7-negative and 13 AR-V7-positive patients.

Safety follow-up extension of the study.

The maximum follow-up of the study for primary and secondary efficacy analysis will be 34 months. However, we will include a 2-years extension after the end of the treatment (April 2019) to evaluate bone lesions. Additionally, analysis of overall survival will be also extended.

5. Study objectives and variables

5.1 *Primary objective(s) and primary endpoint(s)*

Primary objective:

To assess the efficacy of radium-223 in asymptomatic patients with mCRPC who have progressed while on abiraterone acetate or enzalutamide treatment.

Primary endpoint:

To determine the efficacy of radium-223 in terms of radiological PFS (rPFS).

5.2 *Secondary objective(s) and secondary endpoints*

Secondary objectives:

- Safety profile.
- To determine the association between AR-V7 status (positive vs. negative) and rPFS.
- To establish the relationship between CTCs number with radium-223 efficacy.

Secondary endpoints:

Safety:

AEs will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) of the US National Cancer Institute (NCI) version 4.0. AEs and serious adverse events (SAEs) will be assessed to determine the safety and tolerability of the various combinations of drugs.

Efficacy:

- Radiographic progression-free survival (rPFS) depending on AR-V7 status.
- Overall survival (OS).
- Time to first symptomatic skeletal event (SSE).
- Time to PSA progression according to the ALSYMPCA study criteria.
- Determination percentage of PSA progression.
- Alkaline phosphatase level response (AF), normalization of alkaline phosphatase level, according to the ALSYMPCA study criteria.

Molecular aspects:

- Assessment of AR-V7 mutation evolution during the study treatment.
- Determination changes in CTCs number during the study treatment.

5.3 *Safety evaluation*

The safety evaluation has been included in secondary objective (see 5.2).

6. Analysis sets

Full analysis set

All patients that accomplish selection criteria and receive at least one dose of study medication.

Per protocol set (PP)

All patients that accomplished selection criteria, received the study drug according to protocol timelines and dosing, and had no major protocol deviations. Criteria for determining the PP group assignment would be established by the Steering Committee before the statistical analysis begins. Patients without AR-V7 status in the study will be excluded.

Modified full analysis set

All patients with determination of CTC that accomplish selection criteria and receive at least one drug dose.

Safety set

The safety set includes patients who receive at least one dose of study medication.

The primary analysis of efficacy will be performed in the full analysis and per protocol sets in all patients. Secondary and subgroup analysis of efficacy will be also performed in the full analysis and per protocol sets all patients and two study cohorts (AR-V7-negative and positive). Analysis of CTC will be performed in modified full analysis set in both cohorts and all study patients. Safety analyses will be performed in the safety set in both cohorts and all study patients.

6.1 *Protocol Deviations*

Protocol deviations will be recorded in the EXPERIOR database. A by-patient listing of protocol deviations and a by-patient listing of inclusion and exclusion criteria not met will be provided.

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatment.

To determine the per protocol set, all protocol deviations will be reviewed prior to database lock to determine which ones should be classified as major deviations. Patients with major protocol deviations will be excluded from the per protocol set.

Major protocol deviations may be discussed in the data review meeting. Criteria for determining full analysis set would be established by the Steering Committee (SC) before the statistical analysis begins.

Major protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined below.

A summary of the number and percentage of subjects with a major protocol deviation by type of deviation will be provided. Also, a by-subject listing of major and minor protocol deviations will be provided.

Description	**Category**	**Grade***	**Rationale**	**Comments**
Adult < 18 years	Inclusion/Exclusion criteria	Major	Safety	Automatic check
Informed consent form not signed	Inclusion/Exclusion criteria	Major	GCP breach	Automatic check. Patient data could not be used for efficacy assessment
Patient has not histologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features	Inclusion/Exclusion criteria	Major	Efficacy	Manual Review
Patient has not bone metastases due to the prostate cancer and presence of visceral metastases	Inclusion/Exclusion criteria	Major	Efficacy	Manual Review
Serum testosterone of > 1.7 nmol/L (or > 50 ng/dL) at screening	Inclusion/Exclusion criteria	Major	Efficacy Safety	Automatic check
<24 weeks of treatment with abiraterone acetate or enzalutamide within its approved label indication and discontinuation <4 weeks prior to start of study drug at day 1	Inclusion/Exclusion criteria	Major	Efficacy Safety	Manual Review

Castration-naïve patients treated >six cycles with docetaxel	Inclusion/Exclusion criteria	Major	Efficacy	Manual Review
Patient does not receive and will not continue to receive ongoing androgen deprivation with luteinizing releasing hormone (LHRH) analogue therapy throughout the course of the study or has not had a bilateral orchiectomy	Inclusion/Exclusion criteria	Major	Efficacy	Manual Review
Patient is not asymptomatic from prostate cancer (score on brief pain inventory short form (BPI-SF) Question #3 is not zero or one and use of opiate analgesics for prostate cancer-related pain currently or anytime within two weeks prior to screening)	Inclusion/Exclusion criteria	Major	Efficacy	Automatic check and Manual Review
ECOG >1 at screening	Inclusion/Exclusion criteria	Major	Safety	Automatic check
Patient receiving bisphosphonate or other approved bone-targeting therapy on non stable doses for at least four weeks prior to start of study drug at day 1	Inclusion/Exclusion criteria	On case by case	Efficacy	Manual Review
Life expectancy ≥ 12 months	Inclusion/Exclusion criteria	On case by case	Efficacy	Manual review on medical history

Participation in another interventional study while on study drug	Inclusion/Exclusion criteria	Major	Efficacy Safety	Manual review on medical history
Not use of two acceptable methods of birth control from screening until six months after final study drug administration	Inclusion/Exclusion criteria	Major	Efficacy Safety	Manual review on medical history
Parient has received any anti-neoplastic therapy following abiraterone acetate or enzalutamide discontinuation and prior to start of study drug at day 1	Inclusion/Exclusion criteria	Major	Efficacy	Manual Review
Patient has known or suspected brain metastases or active leptomeningeal disease	Inclusion/Exclusion criteria	Major	Efficacy Safety	Manual review
Subject has concurrent disease or any clinically significant abnormality at screening, which would interfere with the subject's participation or evaluation of study results.	Inclusion/Exclusion criteria	Case by case	Efficacy Safety	Manual review. If it is likely to interfere with study procedures or with response to study treatment**
Subject has a history of another invasive cancer within three years prior to Screening	Inclusion/Exclusion criteria	Case by case	Efficacy Safety	Manual review on medical history
Subject had major surgery within one month prior to	Inclusion/Exclusion criteria	Case by case	Safety	Manual review

screening				
Subject has received investigational therapy within 28 days or 5 half lives, whichever is longer, prior to start of study drug at day 1.	Inclusion/Exclusion criteria	Major	Efficacy Safety	Manual review
Absolute neutrophil count < 1,500/µL, at screening	Inclusion/Exclusion criteria	Case by case	Efficacy Safety	Automatic check
Platelet count < 100,000/µL, and hemoglobin < 6.25 mmol/L (or < 10 g/dL) at screening	Inclusion/Exclusion criteria	Major	Efficacy Safety	If clinically relevant** Automatic check
Subject has received growth factors or blood transfusions within seven days of the hematologic laboratory values obtained at screening	Inclusion/Exclusion criteria	Major	Efficacy Safety	Manual review
Subject has total bilirubin > 1.5 times the upper limit of normal (ULN) at screening, except for subjects with documented Gilbert's syndrome.	Inclusion/Exclusion criteria	Case by case	Efficacy Safety	Automatic check and Manual review
Subject has creatinine > 2.5 mg/dL at screening.	Inclusion/Exclusion criteria	Case by case	Efficacy Safety	Automatic check
Subject has albumin ≤ 30 g/L (or ≤ 3.0 g/dL) at screening.	Inclusion/Exclusion criteria	Case by case	Efficacy Safety	Automatic check
IMP not administered but screening completed	Inclusion	Major	Efficacy	Study discontinuation prior to treatment start

Hypersensitivity to IMP	Investigational Medicinal Product	Major	Efficacy Safety	Major if dose not administered completely
IMP overdose	Investigational Medicinal Product	Major	Efficacy Safety	
IMP underdose	Investigational Medicinal Product	Major	Efficacy Safety	
IMP administration dosing/Schedule/delays	Investigational Medicinal Product	On case by case	Efficacy Safety	If administered dose is systematically deviating from expected dose and delays not as described in protocol
IMP toxicity	Investigational Medicinal Product	On a case by case	Safety	If toxicity has not managed appropriately Listing with AE's grade 3/4 with action = none before the EOT date
Post-baseline tumor assessment not done	Study procedure	Major	Efficacy Safety	Major if no post baseline assessment done or if first post-baseline assessment is not at least after 8 weeks of treatment start.
Post-baseline tumor assessments out of the window	Study procedure	Minor	Efficacy	If done more than every 12 weeks +7 days. Major if only post-baseline assessment is not at least after 8 weeks of treatment start.
No baseline tumor assessment	Inclusion and Exclusion criteria/ Study procedure	Major	Efficacy	If not baseline values any post-baseline data indicating presence of new bone lesions/visceral lesions could be evaluated as evidence of PD Flag if baseline data (CT and and bone scans) are >28 days before day 1 cycle 1.

No post-baseline data indicating presence of ≥ 2 new bone lesions or progression as per RECIST 1.1	Study procedure	Major	Efficacy	No evidence of Radiological PD for patients not discontinued due to increased PSA, symptoms or clinical deterioration.
Visits out of window	Study procedure	Minor	Safety	If not performed every 28 days +7 days until EOT; if not performed every 3 months after EOT or if EOS not performed within 3 months after progression, lost to FUP.
Local laboratory tests out of window	Study procedure	Major	Safety	If tests scheduled for day 1 of all cycles (including screening) not performed within 72 hours prior to the dose
Screening assessments out of window	Study procedure	Case by case	Safety	If done >28 days before day 1 cycle 1. Not applicable to local lab tests.
Assessments not done during treatment period (lab value, HRQol..)	Study procedure	Case by case	Safety	Not applicable to Radiological Assessments. Flag if systematically not done.
Blood sample for translational study not obtained or obtained at incorrect timepoint	Study procedure	Case by case	Efficacy	Depending on which sample is not collected.
Blood sample for translational study obtained out of window at screening	Study procedure	Case by case	Efficacy	Sample not obtained within 72 hours prior to the first dose
Adequate follow-up	Study procedure	Major	Efficacy	If no post-treatment evaluation accord ing to protocol
Prohibited medication was taken	Concomitant medication	Major	Efficacy	If any therapies intended for the treatment of cancer prior to EoT (Cytotoxic chemotherapy, other systemic radioisotopes,

				radiotherapy, abiraterone acetate, enzalutamide or any antiandrogen)
Prohibited medication was taken	Concomitant medication	On a case by case	Efficacy Safety	If another investigational drug prior to EoT
Subject not withdrawn as per protocol	Administrative and Other	Major	GCP	If data is obtained after withdrawal

* Major protocol deviation excludes from the full analysis set

** Identification of clinically relevant conditions from the Medical History

7. Statistical strategy

Below are detailed the statistical aspects of the data analysis.

7.1 *Efficacy analysis*

All efficacy analyses will be based on the full analysis set. The primary analysis will be also assessed in per protocol set. Tumor response, bone lesion, SSE evaluation, biochemistry determinations, and predictive biomarkers are obtained at investigators' sites. There is not central and independent review of evaluations. Methodology for tumor assessment will be according to the RECIST version 1.1 and the PCWG2 criteria.

7.1.1 *Primary analysis*

The primary efficacy endpoint is the median PFS achieved with radium-223 treatment. The PFS will be evaluated at the first 34 months period of the study. The PFS will not be evaluated at the 2-years extension of the study for safety.

PFS is a composite endpoint defined as the time from the start of the radium-223 treatment to disease progression in bone or soft-tissue, symptoms, or death, according to the modified PCWG2 criteria.

Objective radiographic disease progression is defined as the presence of at least one of the following conditions:

- Bone lesion progression (appearance of ≥ two new bone lesions compared to baseline).
- Soft-tissue lesion progression according to the RECIST criteria version 1.1.
- Presence of symptomatic skeletal events (pathological fractures, spinal cord compression, radiation or surgery to bone), which should have been reported as adverse event/serious adverse events.

Patients with no progression will be censored at the date of their last evaluation (see Table 1 – Appendix I).

Methods for primary analysis

The study will be declared positive if the median PFS of radium-223 in total sample is

statistically significantly better compared with null hypothesis (PFS ≤ 3 months; p<0.05). The analysis will be based on the maximum-likelihood for exponential distribution test.

Additionally, the PFS will be analyzed with Kaplan Meier method in all patients and in both cohorts. We will provide the number and proportion of events and median survival time with corresponding 95% CI.

The primary analysis will be conducted on the full analysis set. The analysis in per protocol set will be considered as supportive.

7.2 *Secondary analysis*

All efficacy endpoints will be described in both study cohorts (AR-V7-negative and positive) and combining both cohorts.

All efficacy endpoints will be evaluated at the first 34 months period of the study. Additionally, OS will be evaluated at the 2-years safety extension after the end of the treatment. The other efficacy endpoints will not be evaluated at the 2-years safety extension.

All secondary analyses will be based on the full analysis and per protocol sets.

7.2.1 *Summary statistics*

Efficacy:

- OS is defined as the time from inclusion until death from any cause or the last date the patient was known to be alive. Patients who are lost to follow-up and the patients who are alive at the date of data cut-off are censored at the date the patient was last known alive (censoring rules are specified in
- – Appendix I). The OS will be assessed by cohorts.
- Time to first SSE is defined as the time from treatment initiation until SSE (pathological fractures, vertebral or non-vertebral, spinal cord compression, radiation or surgery to bone). For all other events, the start date of the event/medication/therapy was used as the time of the event. If an event has not occurred at the time of the analysis or the patient has been lost to follow-up, the time-to-event variables will be censored at the last disease assessment date.
- The time from the first study drug administration to when PSA progression was observed, defined as:
  - 1) In subjects with no PSA decline from baseline:
    a greater than or equal to 25% increase from baseline value and an increase in absolute value of greater than or equal to 2 ng/mL, at least 12 weeks from baseline;
  - 2) In subjects with initial PSA decline from baseline:

the time from start of treatment to first PSA increase that is greater than or equal to 25% increase and at least 2 ng/mL above the nadir value, which was confirmed by a second value obtained three or more weeks later.

- Determination percentage of PSA progression (defined as PSA elevation ≥ 25% and ≥ 2 ng/mL after 12 weeks).
- Alkaline phosphatase (AF) level response, normalization of alkaline phosphatase level (progression defined as AF elevation ≥ 25% after 12 weeks). The patients will be classified according on whether there is AF progression or not.
- Radiographic progression-free survival (rPFS) depending on AR-V7 status.

Molecular aspects:

- Assessment of AR-V7 mutation prior to the start of study treatment and at time to documented progression disease or treatment end.
- Determination changes in CTCs number prior to the start of study treatment and at time to documented progression disease or treatment end.
- The molecular analysis will be conducted on the modified full analysis set.

Methods for secondary efficacy analysis and molecular aspects.

The PFS, OS, time to first symptomatic SSE, rPFS and alkaline phosphatase level response (AF) will be described with Kaplan-Meier method. Number and proportion of events and median survival time, with corresponding 95% CI, will be calculated. We will describe the number and percentage of patients with AR-V7 mutation and CTCs at the start and at the end of the study. The evolution of these measures in the study will be analyzed with Mc Nemar's test. The 95% confidence interval for the difference of proportions will be based on the Wald with Bonett–Price Laplace adjustment. All tests were will be one-sided, and P values of 0.025 or less were considered to indicate statistical significance. If there are very few AR-V7 patients recruited, outcomes will be only described.

7.2.2 *Subgroup Analysis*

The AR-V7-negative and positive cohorts at baseline will be compared for all analysis. All subgroup analysis will be based on the full analysis and per protocol sets. If there are very few AR-V7 patients recruited, outcomes will be only described.

For time to event endpoints (PFS, OS, time to first symptomatic SSE, TTP-AF, and TTP-PSA), we will use the Kaplan-Meier method and Log-Rank test. For binary outcomes we will use Chi-squared or Fisher´s exact tests.

We also analyze PFS and OS with multivariable Cox proportional hazards models including AR-V7 status, CTCs levels and other relevant baseline covariates, including PSA level, number of prior hormonal treatments, the presence or absence of visceral metastases, the Eastern Cooperative Oncology Group (ECOG) score, and prior use of abiraterone acetate or enzalutamide. All tests were two-sided, and P values of 0.05 or less were considered to indicate statistical significance. We will examine the residuals to assess model assumptions and only first-order interactions will be evaluated. We will calculate relative risk (RR) and HR with corresponding 95% CI to compare dichotomous and time to event variables, respectively.

7.3 *Safety analysis*

All safety data will be evaluated at the first 34 months period of the study. Additionally, bone lesions will be evaluated at the 2-years safety extension after the end of the treatment. Analysis of safety-related data will consider:

- The degree of exposure (dose, duration and number of patients) will be assessed to determine the degree to which study safety can be assessed. These results will be summarized with descriptive statistics (n, NA, mean, standard deviation, median and range).
- Concomitant medications will be coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating 1st to 4th levels. The results will be showed by frequency tables (frequency counts and percentage).
- For AEs, and serious adverse events (SAEs) will be assessed to determine the safety. Severity, causality, relationship to study drug, body system, action taken, and outcome will be reported.

  Adverse events will be classified into standardized medical terminology from the verbatim description (investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be presented by preferred term (PT) and by system organ class (SOC). They will be analyzed using frequency tables.
- Deaths and study discontinuation for each study group will be described and assessed.

7.4 *Demographic and baseline characteristics*

Demographic and other baseline characteristics will be summarized and listed for the full analysis set. For continuous demographic/baseline variables, results will be summarized and presented as n, number of not available data (NA), mean, standard deviation, median, first and third quartiles and minimum and maximum values. For categorical variables, the number, frequency counts and percentage of subjects will be used.

Demographic and baseline characteristics are:

- Age (at the IC signature)
- Race
- Medical history
    - Diagnosis of adenocarcinoma, metastases and previous invasive cancer and other clinically significant events
    - Previous treatment for mCRPC coded according to ATC code, considering 1st to 4th levels.
    - Any other prior medications (in the 28 days prior to screening visit)
- Baseline signs/symptoms
- Physical examination and ECOG status
- Vital Signs
- Hematology and Coagulation
- PSA, testosterone determination and Biochemistry
- Brief pain inventory (short form)
- HRQoL questionnaire (FACT-P)
- AR-V7 mutational status and CTC count
- Radiological Tumor Assessment

7.4.1 *Summary for full analysis test and overall*

A baseline global table will be generated, showing the following demographic and baseline characteristics for the full analysis test and overall. This table will be used to present in a possible article.

- Age at informed consent signature, both as a continuous variable, and categorized (≥ 75 years vs. < 75 years).
- Prior use of Docetaxel for mCPRC
- Prior use of other anti-androgens for mCPRC
- Number of prior hormonal therapy lines for mCPRC before last abiraterone/enzalutamide treatment, categorized (0, 1, ≥2)

- Duration of abiraterone/enzalutamide treatment (weeks)
- Use of bisphosphonates/other bone targeted therapy
- ECOG performance status
- Extent of disease (bone lesions), categorized (<6 metastases, 6-20 metastases, >20 metastases)
- Lymph node involvement
- Hemoglobin at baseline
- Albumin at baseline
- Alkaline phosphatase at baseline
- LDH at baseline
- ALT at baseline
- PSA at baseline
- AR-V7 status at baseline
- Pain severity score at baseline
- Pain interference score at baseline
- Ongoing androgen deprivation with luteinizing releasing hormone (LHRH) analogue therapy
- Bilateral orchiectomy
- External beam radiation therapy within 12 weeks before study screening

A by-subject listing of all demographic and other baseline characteristics will be provided for all patients treated.

7.5 *Transformation of expected variables*

- The time to progression is defined as the difference between start of drug (C1D1) and the progression date or death (whichever occurs first) or the last radiological assessment documented.
- The time to death is defined as the difference between the time from inclusion and death.
- The time to first SSE is defined as the difference between start of drug and the first symptomatic skeletal symptom.

7.6 *Interim analysis protocol*

Before extension amendment, no interim analysis was planned, but an interim analysis was performed to provide results for a congress abstract.

After extension amendment, an interim efficacy analysis is planned to be performed when all patients have progressive disease.

8. Statistical Methods

8.1 *Data Quality Assurance*

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard EXPERIOR procedures. These checks will be done or coordinated within the Statistical Programming and Biostatistics department of EXPERIOR by the respective Primary Coordinator. All tables, figures and data listings provided by EXPERIOR will be also checked by MedSIR for consistency and integrity.

8.2 *General Methodology*

Definition of baseline: For each safety or efficacy parameter, the last valid assessment made before first study drug administration will be used as the baseline for all analyses of that safety or efficacy parameter unless otherwise specified.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (STD), median, minimum, maximum, first and third quartiles and NA (not available), unless otherwise stated. Where data are collected over time, both the observed data and change from baseline will be summarized at each time point.
The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median and first and third quartiles will be reported to one more decimal place than the raw data recorded in the database. The STD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Percentages will be presented to one decimal place. A percentage of 100% will be reported as 100%. Percentages will not be presented for zero counts. Unless otherwise

stated, percentages will be calculated using n as the denominator; for frequency tables not assessed by time point the number of patients considered for every analysis set will be used as denominator. If sample sizes are small, the data displays will show the percentages, but any textual report (e.g. clinical study report) will describe frequencies only.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. However, if a p-value is only presented to four decimal places it will not be rounded again but will be presented to four decimal places. P-values less than 0.0001 will be presented as “<0.0001”.

Confidence intervals will be presented to one more decimal place than the raw data. A two-sided significance level of 5% will be used for confidence intervals.

Statistical programming and analyses as well as all report outputs will be performed/produced using R software® version 3.3 or superior in a secure and validated environment. All report outputs will be provided to the Sponsor in a single Microsoft Word document.

8.3 *Subject Disposition*

Descriptive statistics will be provided for the following:

- Overall number of subjects in the screening population, number of screening failures, and the number of patients enrolled.
- Number and percentage of subjects in the full analysis set.
- Listing of subjects excluded along with reason for exclusion.
- Listing of protocol deviations.
- Study termination:
    - Number and percentage of subjects who completed the study.
    - Frequency of premature termination reasons.
    - Listing of all dropouts along with reason for termination, drug exposure and time of termination.

No statistical tests are planned for these data.

8.4 *Safety*

All safety tables will list or summarize subjects of full analysis set. Safety assessments will be subjected to clinical review and summarized by appropriate descriptive statistics.

8.4.1 *Degree of Exposure*

Degree of Exposure will be based on all patients that accomplished selection criteria and receive at least one drug dose (full analysis set)

- b: “Actual Cycle Duration” is the treatment duration for a cycle per CRF. It is the length of time (days) between actual and next cycle start date dose. At the last cycle is the difference between start and stop date dose.
- c: “Actual Total Dose per Cycle” is the total dose a patient actually took in a cycle (55 kBq/kg). No adjustment of dose level is permitted.
- d: “Intended Cycle Duration” is equal to 28 (+/- 7days), except for the last cycle that is the minimum of 28 (+/- 7 working days) and Actual Cycle Duration
- f: “Intended Cycle Dose Days” is equal to 1, except for the last cycle that is the minimum of 1 and Actual Cycle Duration.
- A: “Total number of cycles”. 6 cycles are expected for each patient.
- B: “Treatment Duration” = Sum over all cycles of (b).
- C: “Total Actual Dose” = Sum over all cycles of (c).
- D: “Total Intended Duration” = Sum over all cycles of (d).
- F: “Total Intended Dose Days” = Sum over all cycles of (f).
- K: “Ratio For Cycle Duration” = D/B

8.4.2 *Concomitant Medications*

The number and percent of unique patients taking concomitant medications will be summarized by ATC code. Elective surgeries/procedures performed during the study will be presented in a listing.

The following are conventions that will be used to classify individual medications as prior and/or concomitant:

- Medications with stop dates prior to enrollment will be considered prior.
- Medications with missing stop dates or stop dates the day of or after enrollment will be considered concomitant, regardless of start date. Additionally, if the start date is prior to enrollment or missing, the medication will also be considered prior.

Frequencies and by-subject listing of all prior and concomitant medications will be provided, containing variables listed on Prior/Concomitant Assessment eCRF, their corresponding categories (Prior or Concomitant), and WHO Anatomical Therapeutic Chemical (ATC) level 4.

8.4.3 *Adverse Events*

All AEs will be recorded on the eCRF “Adverse Events” page and will be coded using the current version of MedDRA® to give a system organ class (SOC) and preferred term (PT) for each event. All adverse event safety data will be updated to the version of MedDRA that is current at the time of the database lock and statistical analyses. Adverse events will be coded with grades defined according to CTCAE V4.0 criteria.

Treatment-emergent AEs (i.e. those events occurred after the first study medication administration and were not present at baseline or worsened in severity following the start of treatment) will be tabulated. The TEAE will be tabulated according to intensity and causality. If intensity of an AE or causality of an AE to the study medication is missing, a worst-case scenario will prevail (severe in intensity or probably related will be assumed). In the summary tables the number of subjects with events and the number of events will be presented.

The onset date of an AE will be compared to the date of first dose of study drug to determine whether or not the AE is treatment-emergent. Adverse events with an onset date on or after the date of first dose of study drug will be classified as treatment-emergent.

All deaths and SAEs, regardless of cause, from treatment up to three months after study discontinuation will be assessed. Non-fatal AEs occurring after treatment start regardless of cause, up to three months after study discontinuation or until start of new anti-cancer treatment, whichever is first will be assessed. SAEs and hospitalizations related solely and unequivocally to the progression of the established tumor disease will not be treated as SAEs as per protocol. Events that are continuations of baseline abnormalities are considered treatment emergent adverse events only if there is an increase in grade over baseline, or if there is an increase following a decrease during the study.

Treatment emergent adverse events with cause possibly related to treatment as judged by the investigator will be considered related to treatment. Events that are continuation of baseline abnormalities will not be considered treatment related unless there is an increase in grade, or if there is an increase following a decrease, and the increase is judged by the investigator to be due to treatment.

The following summaries will be provided:

- An overview of adverse events (number of subjects with at least one AEs, number of subjects with at least one TEAE, number of subjects with serious TEAE, number of subjects with non-serious TEAE, number of deaths, number of subjects with TEAE leading to discontinuation of study treatment, number of subjects dropped out due to AE).
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by treatment group, SOC, and PT.

- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event related to study drug by treatment group, SOC, and PT.

- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by treatment group, by maximum intensity, SOC and PT.

- A summary of the number and percentage of subjects reporting a serious treatment-emergent adverse event, by treatment group, SOC and PT.

- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event resulting in death during the study, by treatment group, SOC and PT.

- A summary of the number and percentage of subjects with adverse events leading to discontinuation of study drug, by treatment group, SOC and PT.
  For adverse events, we will report intensity, relationship to study drug, body system, action taken, and outcome.
  Serious adverse events, deaths and study discontinuations will be described and examined for full analysis set.

  Analysis of safety-related data will be considered at four levels:

- First, the extent of exposure (dose, duration, number of patients) will be examined to determine the degree to which safety can be assessed from the study.
- Second, we will describe and compare clinically relevant test, concomitant medications and adverse events reported in the full analysis set. For adverse events, we will report intensity, causality, relationship to study drug, body system, action taken, and outcome.
- Third, serious adverse events, deaths and study discontinuations will be described and examined in the full analysis set.
- Fourth, the occurrence and maximal grade of toxicity for the whole duration of treatment will be listed and tabulated by type. Adverse events reported as non-drug related by the responsible investigator will be reported as well.

8.4.4 *Clinical Laboratory Parameters*

All hematology, coagulation and biochemistry parameters (including PSA and testosterone) will be presented by descriptive statistics in a tabulated summary by time point of assessment for full analysis set together with the respective changes from baseline. In addition, a frequency table for clinically significant values will be presented by time point of assessment.

A by-subject listing for these parameters will be also provided. These listings will be presented for full analysis set and time point and will include: site, subject identifier, laboratory parameter, parameter values (in SI units), SI unit, normal range and a flag with respect to normal range (below, within and above normal range).

8.4.5 *Vital Signs*

Weight, systolic and diastolic blood pressure, heart rate and respiratory rate will be presented by descriptive statistics in a tabulated summary by time point of assessment for full analysis set together with the respective changes from baseline. In addition, frequency tables for the number of patients with increases or decreases from baseline in systolic/diastolic blood pressure of >20 mmHg and pulse rate of >15 bpm will be provided by time point of assessment and overall. A by-subject listing for all vital signs for full analysis set and time point will be provided.

8.4.6 *Physical Examination*

A frequency table for full analysis set, time point, and body system will be provided for assessment results of normal, abnormal and not done.

A by-subject listing for all body systems for full analysis set and time point will be provided. Only subjects with at least one abnormal finding will be included in this listing.

8.5 ***Handling of missing data***

For time-to-event endpoints, patients without a date of disease progression will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, patients will be censored at the date of first treatment + 1 day. Data for patients with an event (progression) who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.

For OS, patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of treatment + 1 day.

For objective response and clinical benefit, patients without any post-baseline assessment will be considered non-responders.

For patients with AR-V7 status not available at baseline, we will assume the AR-V7 status provided at end of treatment or progression, whichever occurs first. Patients with AR-V7 status not available in the study will be considered as AR-V7 negative.

8.6 ***Deviations from SAP***

Any deviations from the original statistical plan will be described and justified in the final clinical study report.

9. References

1. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL (http://www.R-project.org/).

Appendix I

Table 1. Censoring rules for PFS

Situation	Date of progression or censoring	Outcome
Progression documented between scheduled visits	Earliest of: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions); or • Bone lesion progression (appearance of ≥ two new bone lesions compared to baseline); or • Presence of symptomatic skeletal events (pathological fractures, spinal cord compression, radiation or surgery to bone)	Progressed
Death before first progression disease assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions	Censored
Death or progression after more than one missed visit	Date of last radiological assessment of measured lesions	Censored

Table 2. Censoring rules for OS

Situation	**End date**	**Status**
Death during study follow-up	Date of death	Death
The patient is alive at last follow-up	Date of last follow-up	Censored