Observational Study Information

Acronym / Title	PARABO - **Pa**in evaluation in **Ra**dium-223 (Xofigo®) treated mCRPC patients with **bo**ne metastases – a non-interventional study in nuclear medicine centers
Protocol version identifier	1.0
Date of last version of protocol	12 September 2014
IMPACT study number	17550
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance	Radiopharmaceuticals (V10XX03), Radium-223 dichloride
Medicinal product	Xofigo®
Product reference	EU/1/13/873/001
Procedure number	N/A
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Research question and objectives	This observational prospective single arm cohort study is designed to assess pain and bone pain related quality of life of metastatic Castration Resistant Prostate Cancer (mCRPC) patients receiving Radium-223 in a real life nuclear medicine practice setting. In addition, overall survival, time to next tumor treatment (TTNT), time to first symptomatic skeletal event (SSE), course of blood counts, and safety will be assessed.
Country(-ies) of study	Germany
Author	Dr. Ingo Bernard Bayer Vital GmbH, Medical Department Building K56, 51368 Leverkusen, Germany

Marketing authorization holder

Marketing authorization holder(s)	Bayer Pharma AG 13342 Berlin Germany
MAH contact person	Dr. Ingo Bernard Bayer Vital GmbH, Medical Department Building K56, 51368 Leverkusen, Germany

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1 Table of contents

2 List of abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer (clinical trial)
BPI-SF	Brief Pain Inventory – Short Form
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CRPC	Castration-Resistant Prostate Cancer
DMP	Data Management Plan
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FACT-BP	Functional Assessment of Cancer Therapy Quality of Life Measurement in patients with bone pain
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
HEOR	Health Economics and Outcomes Research
HR	Hazard Ratio
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board

LPFV	Last Patient First Visit
MAH	Marketing Authorization Holder
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OS	Overall Survival
PASS	Post-Authorization Safety Study
PSA	Prostate Specific Antigen
QoL	Quality of Life
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SSE	Symptomatic Skeletal Event
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEAE	Treatment Emergent Adverse Event
TTNT	Time To Next Treatment
WHO DD	World Health Organization Drug Dictionary

3 Responsible parties

3.1 Sponsor / MAH

Function: Qualified person responsible for pharmacovigilance (QPPV)

Name: Michael Kayser

Title: Qualified Person for Pharmacovigilance (QPPV)

Address: Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany

Function: Study safety lead

Name: Jürgen Gellert

Title: Local Pharmacovigilance

Address: Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

Function: Study medical expert

Name: Ingo Bernard, MD

Title: Medical Advisor Oncology

Address: Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

Function: Study conduct responsible

Name: Matthias Walther, Ph.D.

Title: Assistant Project Leader Local NIS

Address: Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

Function: Study statistician

Name: Yoriko De Sanctis

Title: Global Integrated Analysis Project Lead

Address: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

Function: Study data manager

Name: Daniel Wolf

Title: Global Clinical Data Manager Non-Interventional Studies

Address: Bayer HealthCare Germany, Bldg. K9, 51366 Leverkusen, Germany

Function:	Study epidemiologist
Name:	Jihong Zong, MD, PhD
Title:	Head TA Oncology
Address:	Bayer HealthCare Pharmaceuticals Inc., Global Epidemiology, 100 Bayer Blvd, Whippany, NJ 07981, USA

Function:	Study health economics and outcomes research (HEOR) responsible
Name:	Katja Dräxler
Title:	Market Access Manager HEOR
Address:	Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

3.2 Collaborators / Committees

Contact details of investigators and other site personnel participating in the study are kept in a study tracking database which is available upon request.

Administrative changes of responsible persons will be documented by updating the respective lists, but do not require formal protocol amendments.

4 Abstract

Acronym / Title	PARABO - **Pa**in evaluation in **Ra**dium-223 (Xofigo®) treated mCRPC patients with **bo**ne metastases – a non-interventional study in nuclear medicine centers
Protocol version identifier	1.0
Date of last version of protocol	12 September 2014
IMPACT study number	17550
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
Author	Dr. Ingo Bernard Bayer Vital GmbH, Medical Department Building K56, 51368 Leverkusen, Germany
Rationale and background	Prostate cancer is the most common non-cutaneous malignancy in men in Germany. In advanced prostate cancer, the most common site of metastases is the skeletal system which is involved in more than 90% of the castration-resistant prostate cancer patients. The development of bone metastases is a serious threat to the patients' quality of life and survival, with survival being impacted by the number of metastases. Approximately 50% of patients with bone-metastatic prostate cancer die of prostate cancer within 30 months and 80% within 5 years. Patients with castration resistant prostate cancer usually suffer from very painful bone metastases with severe impact on their quality of life. This study called PARABO is to assess pain and bone pain related quality of life of metastatic Castration Resistant Prostate Cancer (mCRPC) patients receiving Radium-223 in a real life nuclear medicine practice setting. In addition, overall survival, time to next tumor treatment, time to first symptomatic skeletal event, course of blood counts, and safety will be assessed.
Research question and objectives	The primary objective of this study is to evaluate pain response during Radium-223 treatment of mCRPC patients in a real life nuclear medicine practice setting.

	The secondary objectives in this study are: • To evaluate the change of pain and bone pain related quality of life over time during treatment phase. • To evaluate pain control rate. • To evaluate pain progression rate • To evaluate time to first pain progression. • To evaluate time to first opioid use. • To evaluate covariates on pain response of mCRPC patients during treatment phase. • To evaluate pain response based on extent of bone metastases at baseline • To evaluate the relation between bone uptake in known lesions and pain palliation (only in patients with bone scan prior to start of treatment and a second scan during or within 6 weeks after the end of Radium-223 treatment). • To evaluate Radium-223 treatment patterns • To evaluate the course of blood counts in patients with different extent of disease and in the whole patient population. • To determine treatments and time to subsequent mCRPC treatment (TTNT). • To determine the time to first symptomatic skeletal event (SSE). • To determine overall survival (OS). • Treatment-emergent adverse events (TEAE) (up to 30 days after last administration of Radium-223).
Study design	This study is a prospective, non-interventional, multi-center, single arm cohort study conducted in nuclear medicine clinics and practices throughout Germany. It is planned to enroll 300 patients with Castration Resistant prostate cancer with bone metastases.
Population	The study population will consist of castration resistant prostate cancer patients with bone metastases treated with Radium-223.
Variables	The investigator collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects

	treatment related data during treatment visits and follow-up visits. The patient questionnaires BPI-SF and FACT-BP will be used for pain and quality of life assessment before each treatment with Radium-223.
Data sources	Treating physician or designated medical person, Radium- 223 administering physician, medical records, routine measurements (e.g. tumor assessment), other physicians, patient questionnaires.
Study size	To reach a precision of < 20% for the primary outcome pain response, 300 patients have to be included, based on the following assumptions: 70% of patients will be evaluable for the primary analysis of pain response at a post-baseline assessment and 30% to 70% of patients show a pain response. 300 patients is a realistic estimate to be enrolled in a two-year enrollment period, based on current patient numbers and available sites for the treatment. With this sample size and a pain response rate of 65% a precision of < 20 % can be reached assuming subgroups to be at least of 1/2 of this size.
Data analysis	Statistical analyses will be primarily of explorative and descriptive nature. Whenever reasonable, data will be stratified by subgroups (i.e. age, other baseline characteristics). Patients receiving at least one dose of Radium-223 will be considered valid for safety analysis set. Analyses of pain or QoL will be performed for patients with evaluable patient questionnaires (BPI-SF, FACT-BP, respectively) at baseline and at least one post baseline visit. The incidence proportion will be provided, along with the exact 95% confidence interval. A clinically increase or decrease in opioid use will be taken into account as will be defined in the SAP. The primary analysis of pain response will be summarized in the population of patients with a score >1 (0="no pain") for the baseline measurement of the 'Worst Pain'-item of the BPI-SF. Pain, including subgroups considered as covariates, and quality of life assessments will be summarized descriptively including mean and change from baseline. An analysis of covariance model will be used to assess changes in pain severity. Time to event variables (TTNT, SSE, OS) will be summarized using Kaplan-Meier estimates. Median event times together with the 25th and 75th percentiles and associated 95% confidence intervals will be presented. All therapies documented will be coded using the World Health

	Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version. Incidence of treatment emergent and drug-related AEs will be presented. Additional subcategories will be based on event intensity and relationship to study drug. It is planned to have one interim analysis 6 months after LPFV. This analysis will use uncleaned data and will primarily focus on pain and QoL assessment. The final analysis will be performed after end of the study which is the date the analytical dataset is completely available.
Milestones	Start of data collection: 01 December 2014 End of recruitment: 30 November 2016 End of data collection: 31 May 2019 Final report of study results: 28 February 2020

5 Amendments

None

6 Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrollment do not require amendments to the protocol.

Table 1: Milestones

Milestone	**Planned date**
Start of data collection	01 December 2014
End of recruitment (LPFV)	30 November 2016
Interim analysis	6 months after LPFV (31 May 2017)
End of data collection	31 May 2019
Database cleaned	31 August 2019
Final report of study results	28 February 2020
Registration in the EU PAS register	expected Q4 2014

7 Introduction: Background and Rationale

Prostate cancer is the most common non-cutaneous malignancy in men in Germany. For 2012, 68,260 new cases are estimated (EU: 359,940) and 12,550 died from the disease (EU: 71,020) [1]. The estimated age-standardized rate for prostate cancer incidence in Germany is 114.1 per 100.000 (EU: 110.8) [1]. Incidence rates increase sharply beyond the age of 50 years. For men aged 50-54 years, the incidence rate is 82 per 100,000 men; ten years later, at age 60-64 years, the rate is more than five times higher at 432 per 100,000, and at 70-74 years the rate is almost nine times higher at 722 per 100,000 [2]. Based on our growing and aging population, it is expected that by the year 2030, the burden of prostate cancer will increase to approximately 89,000 new cases and 17,000 new deaths in Germany (EU: 485,000 and 103,000, respectively) [3].

Prostate cancer is unique amongst solid tumors in that the greatest threat to a patient's survival and quality of life is posed by bone metastases rather than visceral involvement. Indeed, nearly all treatments of the advanced stage are directed toward eradicating or limiting osseous metastases or palliating their side effects [4]. Cellular invasion and migration, cell matrix adhesion or cell-to-cell adhesions, interaction with endothelial cells, regulation of growth factors, and stimulation of osteoclasts and osteoblasts are thought to contribute to development of skeletal metastases [5]. Once prostate cancer becomes metastatic, survival of patients depends on the extent of the disease and the site of metastases. The most common site of metastases for advanced prostate cancer is the skeletal

system which is involved in more than 90% of the castration-resistant prostate cancer (CRPC) patients [6, 7].

Prostate cancer cells are stimulated by androgens, in particular testosterone. Conventional androgen deprivation therapy (ADT) in patients with bone metastases aims to reach castration levels of testosterone (i.e. ≤ 50 ng/mL or 1.7 nmol/L) which can be initially effective controlling the metastases in the bone. However, the majority of patients soon become castration resistant, i.e. progression occurs even at castration levels of testosterone [8]. At this stage, the disease can interchangeably be referred to as either CRPC or the older term hormone-refractory prostate cancer (HRPC) [9]. The commonly accepted term "CRPC" is used throughout this document. Already early stages of CRPC with bone metastases are associated with substantial pain and with rising levels of prostate-specific antigen (PSA) as seen in 35% and 90% of patients, respectively. The extent of PSA control after initial ADT affects prognosis: After 7 months of ADT, patients with PSA < 0.2 ng/ml (undetectable) have a better prognosis than patients with PSA ≥ 4 ng/ml [10].

In normal bone tissue, homeostasis is carried out by the balanced interplay between osteoclasts and osteoblasts which are cell types specialized in bone decomposition and bone formation, respectively. In the presence of malignant neoplasms and following hematological dissemination of tumor cells into the bone, bone metastases develop as a result of a pathologic interaction between tumor cells on the one hand and osteoblasts as well as osteoclasts on the other hand.

The development of bone metastases is a serious threat to the patients' quality of life and survival, with survival being impacted by the number of metastases. Approximately 50% of patients with bone-metastatic prostate cancer die of prostate cancer within 30 months, and 80% within 5 years [11]. The associated complications present a substantial disease and economic burden [12]. Untreated patients face severe morbidity, including bone pain, bone fractures, compression of the spinal cord and hematological consequences of bone marrow involvement such as anemia. As presence of bone metastases represents a major clinical problem for patients with metastatic castration-resistant prostate cancer (mCRPC), specific treatment options for this condition are needed. Control of bone metastases is expected to lead to improved symptoms and quality of life as well as prolonged overall survival.

Radium-223 selectively targets bone metastases with high-energy, short-range alpha-particles. A phase III, double-blind, randomized trial, ALSYMPCA (**Alp**haradin in **Sym**ptomatic **P**rostate **Ca**ncer), was started in 2008 [13]. A total of 921 patients with CRPC and symptomatic bone metastases who were receiving best standard of care and were post-docetaxel or unfit for or declined docetaxel were randomized (2:1) to receive 6 injections of Radium-223 dichloride (50 kBq/kg intravenous) or matching placebo every 4 weeks. The primary endpoint was overall survival. Main secondary efficacy endpoints were time to first skeletal-related event and various biochemical end points. Based on data of an interim analysis (n=809), the study was unblinded in July 2011, since Radium-223 significantly improved OS, compared to placebo (the median OS was 14.0 vs. 11.2 months, respectively; HR=0.70; p=0.002). The updated analysis (performed in June 2012; n=921) also showed that Radium-223 significantly improved OS compared to placebo (median OS 14.9 vs. 11.3 months, respectively; HR=0.70; p<0.001). Symptomatic skeletal events (SSE) were lower in the Radium-223 arm, and time to first SSE was significantly delayed (the median time to SSE was 15.6 months, versus 9.8 months, respectively; HR= 0.66; p<0.001). A low incidence of myelosuppression was observed, with grade 3/4 events of neutropenia (3%) and thrombocytopenia (6%). Adverse events of any grade were described in 93% of the subjects who received radium-223 dichloride; versus 96% in the placebo arm (grade 3/4

adverse events were described for 56% and 62%, respectively). Radium-223 dichloride was authorized in the European Union as Xofigo® in November 2013.

Sub-analysis from ALSYMPCA revealed in addition to the improvement in overall survival a pronounced potential for pain reduction, prolonged time to use of external beam radiation therapy (EBRT) for pain palliation and time to opioid use [14]. The distinct reduction of local symptoms from bone metastases delayed substantially the distortion of quality of life (QoL) compared with placebo [15]. This pronounced reduction in tumor related symptoms is an important benefit for patients in the castration resistant stage of prostate cancer where cure is not an option anymore but good symptom palliation the main focus of any treatment.

The effect of Radium-223 on pain and QoL preservation in mCRPC patients was, as described, to some extent demonstrated in the pivotal Phase 3 ALSYMPCA trial. However, this trial was conducted in a closely defined patient population according to strict inclusion and exclusion criteria. This non-interventional prospective study is to further examine the effect of Radium-223 on pain palliation and bone pain related QoL in mCRPC patients in more detail and in a more heterogeneous patient population under routine daily practice conditions in Germany.

To assess pain, the "Brief pain inventory short form" (BPI-SF) will be used. BPI-SF is a short, self-administered questionnaire with 11 items, which was designed to evaluate the intensity of, and the impairment caused by pain. All BPI-SF items are scored using rating scales. Four items measure pain intensity (pain now, average pain, worst pain, and least pain) using 0 ("no pain") to 10 ("pain as bad you can imagine") numeric rating scales, and 7 items measure the level of interference with function caused by pain (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life) using 0 (no interference) to 10 (complete interference) rating scales [16].

For QoL assessment, the questionnaire "Functional Assessment of Cancer Therapy Quality of Life Measurement in patients with bone pain" (FACT-BP) will be used. The FACT-BP consists of 16 items including general functioning and physical and bone pain and uses a 0-4 Likert-scale; recall period of the questionnaire is 7 days.

8 Research questions and objectives

This observational prospective single arm cohort study is designed to assess pain and bone pain related quality of life of metastatic Castration Resistant Prostate Cancer (mCRPC) patients receiving Radium-223 in a real life nuclear medicine practice setting in Germany. In addition, overall survival, time to next tumor treatment (TTNT), time to first symptomatic skeletal event (SSE), course of blood counts, and safety will be assessed.

8.1 Primary objective

The primary objective of this study is to evaluate pain response during Radium-223 treatment of mCRPC patients in a real life nuclear medicine practice setting.

8.2 Secondary objective(s)

The secondary objectives in this study are:

- To evaluate the change of pain and bone pain related quality of life over time during treatment phase.

- To evaluate pain control rate.
- To evaluate pain progression rate
- To evaluate time to first pain progression.
- To evaluate time to first opioid use.
- To evaluate covariates on pain response of mCRPC patients during treatment phase.
- To evaluate pain response related to the extent of bone metastases at baseline
- To evaluate the relation between bone uptake in known lesions and pain palliation (only in patients with bone scan prior to start of treatment and a second scan during or within 6 weeks after end of Radium-223 treatment).
- To evaluate Radium-223 treatment patterns
- To evaluate the course of blood counts in patients with different extent of disease and in the whole patient population.
- To determine treatments and time to subsequent mCRPC treatment (TTNT).
- To determine the time to first symptomatic skeletal event (SSE).
- To determine overall survival (OS).
- Treatment-emergent adverse events (TEAE) (up to 30 days after last administration of Radium-223).

9 Research methods

9.1 Study design

This study is a prospective, non-interventional, multi-center, single arm cohort study conducted in nuclear medicine clinics and practices throughout Germany. Sites are selected based on the experience of the attending physician with the indication and the treatment with Radium-223. It is planned to enroll 300 patients with CRPC with bone metastases for whom the attending physician decided according to his/her medical practice to treat the patient with Radium-223. Treatment with Radium-223 should follow the approved product information.

For each patient, the investigator will document data in standardized case report forms at initial, follow-up and final visits during treatment phase. Data will be collected using electronic case report forms (eCRF). The observation period for each patient enrolled in this study is the time from start of therapy with Radium-223 to death, withdrawal of consent, loss to follow-up or end of this study (maximum of 2 years after last administration of Radium-223), whichever comes first in time.

The medication is used within the routine clinical practice setting. Commercially available product will be used to treat the patients.

9.1.1 Primary endpoint(s)

The primary endpoints are:

- **Pain response** as determined by the worst pain item on the BPI-SF patient questionnaire. A clinically meaningful pain response is defined as an improvement of two points from the baseline BPI-SF worst pain score [17] at any post-baseline assessment.

9.1.2 Secondary endpoint(s)

The secondary endpoints are:

- **Changes of pain over time** by evaluating the worst pain item as well as the subscale scores for pain severity and pain interference as determined by patient responses on the BPI-SF questionnaire. The worst pain item and subscales will be presented separately for each post-baseline assessment.
- **Changes in bone pain related quality of life** as determined by patient responses on the bone pain specific FACT-BP questionnaire. The FACT-BP score will be presented separately for each post-baseline assessment.
- **Pain control rate** as determined by the worst pain item on the BPI-SF patient questionnaire. Pain control is defined as no increase by two points from the baseline BPI-SF worst pain score.
- **Pain progression rate** as determined by the worst pain item on the BPI-SF patient questionnaire. Pain progression is defined as an increase by two points from the baseline BPI-SF worst pain score at any post baseline assessment.
- **Time to first pain progression** is defined as the time between the first injection of Radium-223 until an increase in the BPI-SF worst pain item by at least two points.
- **Time to first opioid use** in patients who did not take opioids at study entry is defined as the time from first injection of Radium-223 until first intake of opioid analgesics.
- **Evaluation of covariates on pain response** of mCRPC patients during treatment with Radium-223. The following covariates will be analyzed:
    - opioid use
    - assessment of extent of bone metastases (<6, 6-20, > 20, superscan)
    - location of bone metastases
    - level of alkaline phosphatase at baseline (<150 mU/l, 150-300 mU/l, and >300 mU/l)
    - PSA level at baseline (<50 µg/l, 50-200 µg/l, and >200 µg/l)
    - WHO pain score at baseline (WHO-Score 0+1 and WHO-Score 2+3)
    - pretreatment with chemotherapy (yes/no)
    - pretreatment with deep androgen ablation by treatment with abiraterone or enzalutamide (yes/no)
    - extent of bone uptake in known lesions (only faint, higher uptake, and strong uptake compared to surrounding bone)

- **Relation between bone uptake in known lesions and pain palliation** (only in patients with bone scan prior to start of treatment and a second scan during or within 6 weeks after end of Radium-223 treatment)
- For **Radium-223 treatment patterns** dosage and number of injections of Radium-223 will be analyzed.
- **Course of blood counts** in patients with different extent of disease and in the whole patient population will be presented as percentage of patients below limit for further injections according to the local product information
- **Treatment-emergent Adverse Events** (**TEAE) -** Patients will be monitored for TEAE using the NCI-CTCAE Version 4.03. Detailed information collected for each TEAE will include: a description of the event, duration, whether the TEAE was serious, intensity, relationship to Radium-223, action taken, clinical outcome.
- **Time to next tumor treatment(s) (TTNT)** is defined as the time from the first application of Radium-223 until start of next mCRPC treatment including e.g. chemotherapy and/or hormonal treatment.
- **Time to first symptomatic skeletal event (SSE)** is defined as the time between the first injection of Radium-223 until the occurrence of first SSE defined as the first use of external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathological vertebral or non-vertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention
- **Overall survival** is defined as the time interval from the start of Radium-223 therapy to death, due to any cause. Patients alive at the end of the study will be censored at the last date known to be alive. Date and cause of death will be collected.

9.1.3 Strengths of study design

This is a prospective, non-interventional, multi-center, single arm cohort study of CRPC patient with bone metastases who will receive Radium-223 from routine clinical practice settings. This study will include patients in a real life scenario and thus from a more diversified and less selected patient population than in a clinical trial setting, using fewer eligibility criteria to be as much representative to the general CRPC patients with bone metastases as possible.

9.2 Setting

The study will be conducted in nuclear medicine clinics and practices throughout Germany. Data will be collected from approximately 300 patients. The observation period for each patient enrolled in this study is the time from start of therapy with Radium-223 until death, withdrawal of consent, loss to follow-up or regular end of the study which is defined as two years after the last administration of Radium-223 (whatever comes first in time).

9.2.1 Eligibility

Male patients with a diagnosis of CRPC with symptomatic bone metastases without known visceral metastases will be enrolled after the decision for treatment with Radium-223 has been made by the attending physician according to his/her medical practice.

9.2.2 Inclusion criterion/criteria

- Male patients diagnosed with CRPC with symptomatic bone metastases without known visceral metastases
- Decision to initiate treatment with Radium-223 was made as per investigator's routine treatment practice.
- Signed informed consent

9.2.3 Exclusion criterion/criteria

- Patients participating in an investigational program with interventions outside of routine clinical practice

9.2.4 Withdrawal

Each patient has the right to refuse further participation in the study at any time and without providing any reasons. A patient's participation is to be terminated immediately upon his/her request. While fully respecting the patient's rights, the investigator should seek to obtain the reason and record this on the Case Report Form (CRF).

In this observational study, withdrawal from the study is independent of the underlying therapy. On the other hand, premature end of therapy does not automatically imply end of documentation: Without withdrawal from the study, follow-up after end of therapy continues for two years, until death or until loss to follow-up (whatever comes first in time).

9.2.5 Replacement

Patients will not be replaced after drop out.

9.2.6 Representativeness

No further selection than outlined in Sections 9.2.1 – 9.2.3 should be made and patients should be enrolled consecutively in order to avoid any selection bias. With respect to site selection this study could have potential limited representativeness (at convenience sample) as we would be looking for sites with Radium-223 availability (nuclear medicine licensed facility) and experience with prostate cancer management and treatment. Currently, there are 105 nuclear medicine licensed facilities in Germany (August 2014). For sites participating in the study it is planned to include 8 to 10 patients per site.

9.2.7 Visits

Information on the patients, outcomes and other variables is recorded using Electronic Data Capture (EDC) by the treating physician (nuclear medicine physician or any other physician licensed in the administration of radioisotopes) or designated medical person at different time points. After the patient and treating physician have agreed on a treatment decision, the patient is informed about the study and has to sign an informed consent in order to participate. Baseline information is recorded with the status before the first Radium-223 administration during patient visit. For each treatment cycle, information from patient medical records is documented and entered to EDC system by the physician or designated medical person. These visits occur during routine practice, the study protocol does not define exact referral dates.

Baseline/First treatment visit

Once a patient is found eligible for inclusion, the investigator will inform the patient about the study. This will include discussing the consent form and asking the patient to read and – when agreeing to participate – sign the informed consent.

Typical information to be collected at the baseline/first treatment visit includes:

- Date of first treatment visit
- Demography
- Vital signs
- Medical history
- Prostate cancer history
- Concomitant diseases
- Opioid use and other concomitant medication
- Concomitant anti-cancer therapy
- WHO pain score
- ECOG status
- Bone scan
- Patient questionnaires on pain (BPI-SF) and QoL (FACT-BP), filled out by the patient prior to the first injection of Radium-223
- Laboratory parameters including ALP, PSA, and blood counts
- Dose of Radium-223 administered
- Adverse Events

Further treatment visits

Further treatment visits occur during routine praxis, typically every four weeks according to the approved label of Radium-223. Information to be collected at further treatment visits includes:

- Date of treatment visit
- Patient questionnaires on pain (BPI-SF) and QoL (FACT-BP), filled out by the patient prior to each injection of Radium-223
- Dose of Radium-223 administered
- WHO pain score
- ECOG status
- Changes in pain medication or other concomitant medication
- Changes in concomitant anti-cancer therapy
- Bone Scan, if available

- Laboratory parameters including ALP, PSA, and blood counts
- Adverse events
- Symptomatic skeletal events

Follow-up visit after end of treatment

If within routine clinical practice, data will be collected from a follow-up visit approximately one month after end of treatment. Typical information to be collected at this follow-up visit after treatment includes:

- Date of visit
- Patient questionnaires on pain (BPI-SF) and QoL (FACT-BP) filled out by the patient
- WHO pain score
- ECOG status
- Changes in pain medication
- Changes in anti-cancer therapy
- Bone Scan, if available
- Laboratory parameters including ALP, PSA, and blood counts
- Adverse events up to 30 days after last treatment
- Symptomatic skeletal events

Long-term follow-up

For long term follow-up either the patient or treating physician can be contacted by phone, mail or email every three months after end of treatment until death, patient's withdrawal, loss to follow-up, or end of study (whatever comes first in time) for a maximum of two years. Typical information to be collected at long-term follow-up includes:

- Date of follow-up
- Survival status
- Opioid use after last administration of Radium-223 yes/no, if yes, date of first use (only in patients without prior opioid use)
- Symptomatic skeletal events
- Further anti-cancer therapy

End of Observation

The reason for end of observation is documented which could occur at end of study, if the patient died, withdrew his consent or is lost to follow up. In case of death date of death and primary cause of death have to be documented.

9.3 Variables

The investigator collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects treatment related data during treatment visits and follow-up visits. The investigator documents the study-relevant data for each patient in the case report form (CRF). The CRF is available upon request (see Table 4: List of stand-alone documents, Annex 1)

Table 2: Tabulated overview on variables collected during the study

Variables	Baseline and first treatment	Further Treatment visits	Follow-up after end of treatment	Long-term follow-up	End of observation
Date of visit	X	X	X	X	X
Patient informed consent	X				
Demography	X				
Vital Signs	X				
Co-morbidities (medical history, concomitant diseases)	X				
Prostate cancer history (initial diagnosis, diagnostic and therapeutic procedures)	X				
WHO pain score	X	X	X		
Performance Status (ECOG)	X	X	X		
Questionnaires BPI-SF and FACT-BP	X	X	X		
Location of bone pain	X	X	X		
Number and location of skeletal lesions (bone scan)*	X	X	X		
Exposure/treatment (dose of Radium-223)	X	X			
Concurrent diagnostic and therapeutic procedures for mCRPC	X	X			
Laboratory parameters including ALP, PSA, blood counts	X	X	X		
Opioid use	X	X	X	X***	
Concomitant medication	X	X			
Adverse Events	X	X	X**		
Symptomatic skeletal events		X	X	X	
Further treatment for mCRPC		X	X	X	
Survival assessment				X	
Reason for end of observation					X

*If available, an additional bone scan together with an assessment of bone uptake of Radium-223 can be documented independently from visits.

**Up to 30 days after last treatment with Radium-223.

***Only opioid use yes/no and date of first use

9.3.1 Variables to determine the primary endpoint(s)

The variables for primary objectives are:

- Pain severity will be measured using the worst pain score of the BPI-SF questionnaire. The BPI-SF will be administered prior to each injection of Radium-223 and, if within routine clinical practice, at a follow-up visit approximately one month after the last injection of Radium-223.

9.3.2 Variables to determine the secondary endpoint(s)

The outcome variables for secondary objectives are:

- Change of pain over time: In addition to pain severity, the subscales of the BPI-SF questionnaire will be evaluated: **The total pain severity subscale** of the BPI-SF is based on the sum of the four items least, worst, average, and current pain. **The pain interference subscale** of the BPI-SF is based on the seven pain interference items.
- Quality of Life: Bone pain related QoL will be measured by evaluation of the total score of the FACT-BP questionnaire. The questionnaire will be filled out together with the BPI-SF prior to each injection of Radium-223 and, if within routine clinical practice, at a follow-up visit approximately one month after the last injection of Radium-223.
- Pain control rate, pain progression rate, and time to first pain progression will be measured using the worst pain score of the BPI-SF questionnaire.
- Evaluation of covariates on pain response:
    - opioid use
    - number of known bone metastases (<6, 6-20, > 20, superscan) at baseline based on the latest bone scintigraphy before the first injection of Radium-223 (not older than 8 weeks)
    - location of bone metastases based on bone scintigraphy
    - level of alkaline phosphatase at baseline (<150 mU/l, 150-300 mU/l, and >300 mU/l)
    - PSA level at baseline (<50 µg/l, 50-200 µg/l, and >200 µg/l)
    - WHO pain score at baseline (WHO-Score 0+1 and WHO-Score 2+3)
    - pretreatment with chemotherapy (yes/no)
    - pretreatment with deep androgen ablation by treatment with abiraterone or enzalutamide (yes/no)
    - bone uptake in known lesions (only faint, higher uptake, and strong uptake compared to surrounding bone)
- location of bone pain
- Radium-223 treatment patterns will be analyzed using dosage, number of treatments and time between treatments
- Course of blood counts

- Treatment-emergent Adverse Events (TEAE) including a description of the event, duration, whether the TEAE was serious, intensity, relationship to Radium-223, action taken, clinical outcome. Patients will be monitored for TEAEs using the NCI-CTCAE Version 4.03.
- Tumor treatment(s) starting after the first application of Radium-223
- Symptomatic skeletal event (SSE) (external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathological vertebral or non-vertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention)
- Date and cause of death

9.3.3 Demography

For demographic / socio-demographic assessment, the following data will be recorded:

- Year of birth
- Race
- Basic patient characteristics (height, weight)

9.3.4 Co-morbidities (medical history, concomitant diseases)

Any relevant medical finding that was present before start of therapy with Radium-223, independent on whether or not they are still present, has to be documented in the Medical History/Concomitant Diseases section.

9.3.5 Prior and concomitant medication

All medication taken in addition to the product for any indication (either initiated before study start or during the study) is termed concomitant medication.

Information to be collected for medication except for opioid use includes: trade name or INN, start date, stop date/ongoing, total daily dose, unit, and indication.

Opioid use will be documented on a separate form. Information to be collected include trade name or INN, start date, stop date/ongoing, dose, unit, frequency, application route. In addition, the use of pain medication within 24 h of completing the BPI-SF will be collected.

9.3.6 Exposure / treatment

Information to be documented at each Radium-223 administration includes:

- Date
- Number of injection cycle
- Dose
- Unit (kBq/kg)
- Reasons for any significant delay/interruption/discontinuation of treatment

9.3.7 Assessment of therapy

Not applicable

9.3.8 Visits

- Date of visit

9.3.9 Medical History of prostate cancer

Findings meeting the criteria listed below are considered to be relevant to the study indication and have to be documented:

- Prostate cancer classification
    - date of initial diagnosis
    - Gleason score
    - status of primary tumor at study entry
    - progression/relapse
    - date of castration resistance
    - date of initial diagnosis of bone metastases
- prior diagnostic or therapeutic procedures associated with mCRPC
    - surgery/biopsy
    - systemic anti-cancer therapy
    - radiotherapy
    - blood transfusions
- Number of metastases and extent of disease
- Baseline ECOG performance status

9.4 Data sources

The investigator collects historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment related data, results of tumor assessments and other disease status information, also documented in the medical record, during visits that take place in routine practice. For patient reported outcomes questionnaires filled out by the patient during routine visits are used. For any adverse events that occur, information is directly obtained from the patient. In case a patient is seen by more than one physician for his/her disease (e.g. the patient is monitored by a physician other than the initial investigator), the initial investigator should make every effort to collect information on any visits (including results) that have taken place outside the investigator's site due to the patient's disease, for example by interviewing the respective physician or patient or by obtaining an accompanying letter with detailed information and results.

9.5 Study Size

Aim of the sample size consideration is to assess the precision of the estimate for the pain response rate (the primary outcome) which is defined by the width of the 95% confidence interval with a given sample size. Assuming that at least 70% of patients will be evaluable for the primary analysis of pain response at a post-baseline assessment and 30% to 70% of patients show a pain response, at least 300 patients have to be included to reach a precision of < 20%. In the following table, the different scenarios are shown for actual pain response ranging from 30% to 70%.

Table 3: Width of the 95% CI for the pain response rate, assuming 210 evaluable patients

Actual pain response	Lower Limit of 95% CI	Upper Limit of 95% CI	Width of 95% CI
0.7	0.638	0.762	0.124
0.65	0.585	0.715	0.13
0.6	0.534	0.666	0.132
0.55	0.483	0.617	0.134
0.5	0.432	0.568	0.136
0.45	0.383	0.517	0.134
0.4	0.334	0.466	0.132
0.35	0.285	0.415	0.13
0.3	0.238	0.362	0.124

300 patients is a realistic estimate to be enrolled in a two-year enrollment period, based on current patient numbers and available sites for the treatment. With this sample size and a pain response rate of 65% a precision of < 20 % can be reached assuming subgroups to be at least of 1/2 of this size (i.e. 105 patients). From a clinical point of view, this precision is regarded as meaningful, taking the variance of pain measurements into account.

Calculations were performed with nQuery 7.

The sample size could be increased if the number of patients not evaluable for pain response proves to be higher than the expected 30%.

9.6 Data management

A Contract Research Organization (CRO) will be selected and assigned for EDC system development. The CRF will be part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request.

Patient questionnaires will be collected via paper forms which will be entered into the study database by the CRO.

Each patient is identified by a unique central patient identification code. This code is only used for study purposes. The patient code consists of a combination of a country code, site number and patient number. For the duration of the study and afterwards, only the study team is able to identify the patient based on the patient identification code.

The Study Database (SDB) contains all (pseudonymous) study data. The development of this application and the development and setup is done by applying Good Automated Manufacturing Practice (GAMP) standards, fulfilling the FDA 21 CFR Part 11 and EU EudraLex V4 Annex 11 regulations. A set of SOPs and guidelines are used during the study lifecycle project for supporting all study phases from specification, development, study start, deployment and change management and up to study termination.

Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP), which is available upon request (see Table 4: List of stand-alone documents, Annex 1).

For information on quality control, refer to section 9.8.

9.7 Data analysis

9.7.1 Statistical considerations

Statistical analyses will be primarily of explorative and descriptive nature.

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock. The SAP is available upon request (see Table 4: List of stand-alone documents, Annex 1).

Patients receiving at least one dose of Radium-223 will be considered valid for safety analysis set.

Analyses of pain or QoL will be performed for patients with evaluable patient questionnaires (BPI-SF, FACT-BP, respectively) at baseline and at least one post baseline visit. A clinically increase or decrease in opioid use will be taken into account. E. g. all patients without opioid intake as well as patients taking opioids will be included in analyses until an increase in opioid intake. Further details will be defined in the SAP.

Other analyses will be performed for the safety analysis set unless otherwise defined.

Whenever reasonable, data will be stratified by subgroups (i.e. age, other baseline characteristics).

All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version.

It is planned to have one interim analysis at the time of 6 months after LPFV. This analysis will use uncleaned data and will primarily focus on pain and QoL assessment. The final analysis will be performed after end of the study which is the date the analytical dataset is completely available.

9.7.2 Analysis of demography, disease details, prior and concomitant medication and other baseline data

Demography and baseline characteristics will be described with summary statistics. Concomitant medication will be coded using WHO's drug dictionary.

9.7.3 Analysis of treatment data

Summary statistics will be provided for the treatment duration, the number of treatments, starting dose and average dose, the number of patients with dose modification (interruption, delay and discontinuation), number of dose modifications, and reasons for dose modifications.

9.7.4 Analysis of primary outcome(s)

The primary analysis of pain response will be summarized in the population of patients with a score >1 (0="no pain") for the baseline measurement of the 'Worst Pain'-item of the BPI-SF. For each post-baseline assessment, the incidence proportion will be provided, along with the exact 95% confidence

interval. Pain response is defined as an improvement of two points from the baseline BPI-SF worst pain score at any post-baseline assessment, which is considered clinically meaningful [17].

Further details will be given in the SAP.

9.7.5 Analysis of secondary outcome(s)

- Change of pain over time: The responses to each of the BPI-SF items and the following two dimensions which are aggregated from BPI-SF items will be summarized descriptively:
    - Pain severity index:

      It uses the sum of the four items on the pain intensity. All four severity items must be completed for aggregating the pain severity index.
    - Pain interference index:

      It uses the sum of the seven pain interference items. The pain interference index is scored as the mean of the item scores multiplied by seven, given that at least four of the seven items have been completed.

  Summary statistics, including mean and change from baseline, will be provided for each assessment time point. For the summary of each post-baseline assessment, patients will be excluded if there is no corresponding post-baseline measurement.
- For bone pain related quality of life assessment summary statistics including mean and change from baseline will be provided for each assessment time point of the FACT-BP questionnaire. For the summary of each post-baseline assessment, patients will be excluded if there is no corresponding post-baseline measurement.
- Pain control rate will be summarized. Pain control is defined as no increase by two or more points from the baseline measurement of the 'Worst Pain'-item of the BPI-SF (Question 3) at any post-baseline assessment.
- Pain progression rate will be summarized. Pain progression is defined as two or more points increase from the baseline measurement of the 'Worst Pain'-item of the BPI-SF (Question 3) at any post-baseline assessment.
- Time to first pain progression will be summarized by Kaplan-Meier (KM) estimates.
- Pain response will be additionally summarized descriptively for the subgroups defined in 'evaluation of covariates on pain response' in Section 9.1.2.

  An analysis of covariance model will be used to assess changes in pain severity, as measured by the worst pain score on the BPI-SF, at each post-baseline assessment time point. The baseline worst pain score will be used as a covariate in each analysis of covariance model.
- The relation between bone uptake in known lesions and pain palliation will be analyzed (only in patients with bone scan prior to start of treatment and at least one further documented bone scan during or after end of Radium-223 treatment).
- The course of blood counts will be analyzed. Incidence of blood counts below limit for further injections according to the local product information in patients with different extent of disease

and in the whole patient population will be calculated. The incidence proportion will be provided, along with the exact 95% confidence interval.

- Time to event variables (TTNT, SSE, OS) will be summarized using Kaplan-Meier estimates. Median event times together with the 25th and 75th percentiles and associated 95% confidence intervals will be presented. Censoring rules will be defined in the SAP.
- Incidence of treatment emergent and drug-related AEs will be presented using the NCI-CTCAE Version 4.03. Additional subcategories will be based on event intensity and relationship to study drug.

Further details will be given in the SAP.

9.7.6 Analysis of safety data

See analysis of secondary outcomes.

9.7.7 Analysis of other data

N/A

9.7.8 Bias, confounding and effect-modifying factors

In general data collected in this study may suffer from biases (e.g. interviewer bias, either by systematic differences in data recording or different interpretation of information on exposure or outcome for different patients, reporting as well as selection bias). Besides, prospective studies are prone to bias from loss to follow-up or change in data collection methods over time. To decrease the reporting bias source data verification will be performed in at least 10% of the sites. In order to reduce selection bias, a representative sample of sites will be included in the study. Sites will be selected according to several criteria, main criteria for site selection will be: availability of suitable patients and an equal geographical distribution. Investigators should select patients to be documented in the study only based on eligibility according to inclusion and exclusion criteria, i.e. each patient diagnosed with mCRPC and starting treatment for the disease with Radium-223 should be asked for participation in a consecutive manner. No further selection should be applied.

Primary and secondary outcome variables and safety data will be analyzed with regard to different baseline factors. However, unknown and unmeasured risk factors for the outcome variables will exist and might lead to confounding when comparing results in different subgroups and when comparing study results with historical results from clinical studies.

9.8 Quality control

9.8.1 Data quality

Before study start at the sites, all investigators will be sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators will have the chance to discuss and develop a common understanding of the study protocol and the CRF.

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer.

All outcome variables and covariates will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried and the data will be validated. A check for multiple documented patients will be done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The same plan will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request (see Table 4: List of stand-alone documents, Annex 1).

National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for capturing patient documentation (eCRF) will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) [18]. The documentation is available upon request.

9.8.2 Quality review

In a subset of patients (at least 10% of all patients) source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors will access medical records on site for data verification. Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request (see Table 4: List of stand-alone documents, Annex 1).

9.8.3 Storage of records and archiving

The sponsor will make sure that all relevant documents of this study including CRFs and other patient records will be stored after end or discontinuation of the study for at least 15 years. Other instructions for storage of medical records will remain unaffected.

The investigators participating in the study have to archive documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended to also store documents for a retention period of at least 15 years.

Statistical programming performed to generate results will be stored at the sponsor's site for at least 15 years.

9.8.4 Certification/qualification of external parties

N/A

9.9 Limitations of the research methods

This prospective observational cohort study provides an opportunity to collect data of real-life patient benefit and safety information that can be analyzed and disseminated in a timely manner. However this study is a single arm cohort study without an active comparison group. Thus, in addition to subgroup analyses within this study, the results can only be compared with historical data from clinical studies, which is prone to bias and confounding as these data are generally not collected using the same way and the same or similar information may not be available.

9.10 Other aspects

N/A

10 Protection of human subjects

10.1 Ethical conduct of the study

This study is an observational study where Radium-223 is prescribed in the customary manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012 [19]). Recommendations given by other organizations will be followed as well (e.g. EFPIA [20], ENCePP [21]). ICH-GCP guidelines will be followed whenever possible.

In addition, the guidelines on good pharmacovigilance practices (GVP [22] [23]) will be followed; the relevant competent authorities of the EU member states will be notified according to Volume 9A [24].

10.3 Independent ethics committee (IEC) or institutional review board (IRB)

Documented approval from appropriate IECs/IRBs will be obtained for all participating sites prior to study start. When necessary, an extension, amendment or renewal of the IEC / IRB approval must be obtained and also forwarded to the sponsor. The IEC / IRB must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC / IRB is organized and operates according to applicable laws and regulations.

10.4 Patient information and consent

Before documentation of any data, informed consent is obtained by the patient in writing. The investigator must have the IECs / IRB written approval / favorable opinion of the written informed consent form and any other written information to be provided to patients prior to the beginning of the observation.

10.5 Patient insurance

In this study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the investigators and, respectively, the institutions involved provide sufficient protection for both patient and investigator.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10.6 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names should neither be provided to the sponsor nor the CRO. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the investigator.

11 Management and reporting of adverse events/adverse reactions

11.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product [25].

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- Off label use, occupational exposure, lack of drug effect, medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event
- Product exposure via mother/ father (exposure during conception, pregnancy, childbirth and breastfeeding)
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)
- Any combination of one or more of these factors

As mentioned above no causal relationship with a product is implied by the use of the term "adverse event".

An Adverse Reaction (AR) is defined as a response to a medicinal product which is noxious and unintended. An AR is any AE judged as having a reasonable suspected causal relationship to Radium-223.

An AE is serious (SAE) if it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important.

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is 'sudden death' where no cause has been established. In this instance, 'sudden death' should be regarded as the AE and 'fatal' as its reason for being 'serious'.

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

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as serious, unless the admission is:

- planned before subject's inclusion in the study (i.e. elective or scheduled surgery) or
- ambulant (shorter than 12 hours) or
- part of the normal treatment or monitoring of the studied disease (i.e. not due to a worsening of the disease)

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The father was exposed to a medicinal product prior to conception

Other medically important serious event: any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

11.2 Collection

Starting with the first application of Radium-223, all non-serious adverse events (AE) must be documented on the AE Report Form or in the CRF / EDC system using the NCI-CTCAE version 4.03 and forwarded to the sponsor within 7 calendar days of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within 24 hours of awareness).

If a pregnancy occurs during the study (exposition via the father), although it is not a serious adverse event, it should be documented and forwarded to the sponsor within the same time limits as a serious adverse event. The result of a pregnancy will be followed-up according to applicable Bayer SOPs. Any data on abnormal findings concerning either the mother or the baby are collected.

For each AE, the recruiting physician must assess and document the seriousness, duration, relationship to product, action taken and outcome of the event.

The documentation of any AE / SAE ends with the completion of the treatment phase of the patient including 30 days after the last administration of Radium-223.

As long as the patient has not received any Radium-223 AEs /SAEs do not need to be documented as such in this observational study. However, they are part of the patient's medical history.

For any serious drug-related AE occurring after the treatment phase plus 30 days, the standard procedures that are in place for spontaneous reporting have to be followed.

11.3 Management and reporting

Non-serious AEs

The outcome of all reported AEs (resolution, improvement etc.) will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with Radium-223 that qualify for expedited reporting will be submitted to the relevant authorities according to EU PV legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU, Module VI [22]) and according to national regulations by the sponsor; however, all investigators must obey local legal requirements.

For non-serious ARs occurring under non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the CRF / EDC system will be forwarded immediately (within 24 hours of awareness) to the pharmacovigilance country person being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant authorities according to national regulations will be done by the sponsor for SAEs occurring under Radium-223 treatment; however, all investigators must obey local legal requirements.

For any serious drug-related AE occurring after the treatment phase plus 30 days, the standard procedures that are in place for spontaneous reporting have to be followed.

For SAEs that occurred while administering non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

11.4 Evaluation

Whenever new important safety information is received, e.g. case reports from an investigator, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case reports, refer to section 11.2 and 11.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

12 Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov" and in the EMA PASS register (ENCEPP register). Results will be disclosed in a publicly available database within the standard timelines.

The results of this study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the sponsor. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines [26], STROBE [27]). No individual treating physician may publish on the results of this study, or their own patients, without prior approval from the sponsor.

13 List of references

[1] J. Ferlay, E. Steliarova-Foucher, J. Lortet-Tieulent, S. Rosso, J. W. W. Coebergh, H. Comber, D. Forman and F. Bray, "Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012," *Eur J Cancer,* vol. 49, no. 6, pp. 1374-403, April 2013.

[2] "GLOBOCAN," [Online]. Available: http://globocan.iarc.fr/Pages/age-specific_table_sel.aspx. [Accessed June 2014].

[3] "GLOBOCAN," June 2014. [Online]. Available: http://globocan.iarc.fr/Pages/burden_sel.aspx.

[4] M. J. Morris and H. I. Scher, "Clinical approaches to osseous metastases in prostate cancer.," *Oncologist,* vol. 8, no. 2, pp. 161-73, 2003.

[5] N. Pandit-Taskar, M. Batraki and C. Divgi, "Radiopharmaceutical therapy for palliation of bone pain from osseous metastases," *J. Nucl. Med.,* vol. 45, no. 8, pp. 1358-65, 2004.

[6] I. Tannock, M. Gospodarowicz, W. Meakin, T. Panzarella, L. Stewart and W. Rider, "Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response," *J. Clin. Oncol.,* vol. 7, no. 5, pp. 590-7, 1989.

[7] D. P. Petrylak, C. M. Tangen, M. H. Hussain, P. M. J. Lara, J. A. Jones and M. E. Taplin, "Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer," *N. Engl. J. Med.,* vol. 351, no. 15, pp. 1513-20, 2004.

[8] F. Saad, "Therapeutic approach to castration-resistant prostate cancer," *Eur. Urolog. Rev.,* vol. 3, no. 2, pp. 15-7, 2008.

[9] S. Kasper and M. S. Cookson, "Mechanisms leading to the development of hormone-resistant prostate cancer," *Urol. Clin. North. Am.,* vol. 33, no. 2, pp. 201-10, 2006.

[10] M. Hussain, B. Goldman, C. Tangen, C. S. Higano, D. P. Petrylak, G. Wilding and et al., "Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: data from Southwest Oncology Group Group Trials 9346 (Intergroup Study 0162) and 9916," *J. Clin. Oncol.,* vol. 27, no. 15, pp. 2450-6, 2009.

[11] M. S. Soloway, S. W. Hardeman, D. Hickey, J. Raymond, B. Todd, S. Soloway and et al., "Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan.," *Cancer,* vol. 61, no. 1, pp. 195-202, 1988.

[12] K. L. Schulman and J. Kohles, "Economic burden of metastatic bone disease in the U.S.," *Cancer,* vol. 109, no. 11, pp. 2334-42, 2007.

[13] C. Parker, S. Nilsson, D. Heinrich, S. I. Helle, J. M. O'Sullivan, S. D. Fossa and et al., "Alpha emitter radium-223 and survival in metastatic prostate cancer," *N. Engl. J. Med.,* vol. 369, no. 3,

pp. 213-23, 2013.

[14] C. Parker, D. Heinrich, D. Bottomley and et al., "Effects of radium-223 dichloride (RA-223) on health related quality of life (QOL) outcomes in the phase 3 ALSYMPCA study in patients with castration resistant prostate cancer and bone metastases (abstract 2878)," in *Presented at: European Cancer Congress (ECCO/ESMO/ESTRO), Poster Session; Genourinary Malignancies - Prostate Cancer*, Amsterdam, The Netherlands, 2013.

[15] S. Nilsson, O. Sartor, O. Bruland and et al., "Pain analyses from the phase 3 ALSYMPCA study with radium-223 dichloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (abstract 5038)," in *Presented at: 49th Annual Meeting of the American Society of Clinical Oncology, General Poster Session, Genitourinary (Prostate) Cancer*, Chicago, IL (USA), 2013.

[16] C. S. Cleeland, "The Brief Pain Inventory; User Guide 2009.," 2009. [Online]. Available: http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/sysmptom-assessment-tools/BPI_UserGuide.pdf. [Accessed June 2014].

[17] S. D. Mathias, R. D. Crosby, Y. Qian, Q. Jiang, R. Dansey and K. Chung, "Estimating minimally important differences for the worst pain rating of the Brief Pain Inventory-Short Form," *J Support Oncol.,* vol. 9, no. 2, pp. 72-8, 2011.

[18] FDA, Code of Federal Regulations. Title 21, Volume 1. 21CFR11: Electronic records; electronic signatures. 62 FR 13464, Mar. 20, 1997. Revised, 01 Apr 2012.

[19] EU, "Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC of the European Parliament and of the Council," *Official Journal of the European Union,* 20 Jun 2012.

[20] EFPIA, Code on the Promotion of Prescription-Only Medicines to and Interactions with Healthcare Professionals, Oct 2007.

[21] EMA, ENCePP guide on methodological standards in pharmacoepidemiology. EMA/95098/2010, 05 Nov 2010.

[22] EMA, Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products; EMA/873138/2011; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf, 22 Jun 2012.

[23] EMA, Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies; EMA/330405/2012; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf, 09 Jul 2012.

[24] EU, "Eudralex - Volume 9A of the Rules Governing Medicinal Products in the European Union: the Guidelines on Pharmacovigilance for Medicinal Products for Human Use; http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm," 2008.

[25] ICH, ICH Harmonized Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2D), Nov 2003.

[26] C. Graf, W. P. Battisti, D. Bridges, V. Bruce-Winkler, J. M. Conaty, J. M. Ellison, E. A. Field, J. A. Gurr, M. E. Marx, M. Patel, C. Sanes-Miller and Y. E. Yarker, "International Society for Medical Publication Professionals. Research Methods & Reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines," *BMJ*, 2009.

[27] E. von Elm, D. G. Altman, M. Egger, S. J. Pocock, P. C. Gøtzsche and J. P. Vandenbroucke, "STROBE-Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies. J Clin Epidemiol. 2," *J Clin Epidemiol.*, 2008.

Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Number	Document Name / Reference number	Date	Title
1	XF1412_List_of_active_physicians final	Will be available at end of recruitment	List of all active physicians
2	XF1412_CRF	tbd	CRF
3	XF1412_DMP	Will be available at time ready to enroll	Data Management Plan
4	XF1412_SAP	Will be available before study database lock	Statistical Analysis Plan
5	XF1412_QRP	Will be available at time ready to enroll	Quality Review Plan

* Draft versions are indicated by date and <draft> in brackets. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage.

Annex 2: ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

Study title:
PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	14
1.1.2 End of data collection[2]	☒	☐	☐	14
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	14
1.1.6 Final report of study results.	☒	☐	☐	14

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	16
2.1.2 The objective(s) of the study?	☒	☐	☐	16-17
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	16-17
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	17
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	17-19
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	28

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	19
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	13
4.2.2 Age and sex?	☒	☐	☐	19
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	19
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19-20

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	24
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the product?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	28-29

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	24-25
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☐	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	30
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	26
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	26
8.1.3 Covariates?	☒	☐	☐	24
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, product quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	25
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	24
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	24
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	28
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	28
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	26-27

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	28-30
10.3 Are descriptive analyses included?	☒	☐	☐	28-30
10.4 Are stratified analyses included?	☒	☐	☐	28-30
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	31
11.3 Are methods of quality assurance described?	☒	☐	☐	30-31
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Management of missing data will be specified in the DMP.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	30
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	30-31

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	26-27
12.3 Does the protocol address other limitations?	☒	☐	☐	31

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	31-32
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	32-33

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	14

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	36
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	36

Comments:

Name of the main author of the protocol: Ingo Bernard

Date: / /

Signature: _____

Annex 3: Signature pages

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Protocol version identifier	1.0
Date of last version of protocol	12 September 2014
IMPACT study number	17550
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added after registration
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03) Radium-223 dichloride (Xofigo®)
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Qualified person responsible for pharmacovigilance (QPPV)
Name	Michael Kayser
Title	European Qualified Person for Pharmacovigilance (QPPV)
Address	Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 30th Sept. 2014 Michael Kayser

Signature Page - Study Safety Lead

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Protocol version identifier	1.0
Date of last version of protocol	12 September 2014
IMPACT study number	17550
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added after registration
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03) Radium-223 dichloride (Xofigo®)
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study Safety Lead
Name	Jürgen Gellert
Title	Local Pharmacovigilance
Address	Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 16.9.2014 , _____

Signature Page - Study Medical Expert

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Protocol version identifier	1.0
Date of last version of protocol	12 September 2014
IMPACT study number	17550
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added after registration
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03) Radium-223 dichloride (Xofigo®)
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study medical Expert
Name	Ingo Bernard, MD
Title	Medical Advisor Oncology
Address	Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 12. Sep. 2014. I. Bernard

Signature Page - Study Conduct Responsible

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Protocol version identifier	1.0
Date of last version of protocol	12 September 2014
IMPACT study number	17550
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added after registration
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03) Radium-223 dichloride (Xofigo®)
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study conduct responsible
Name	Matthias Walther, Ph.D.
Title	Assistant Project Leader Local NIS
Address	Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

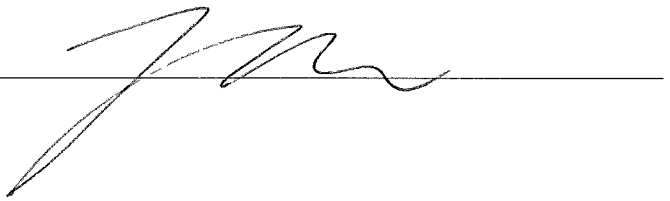
The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 17.09.2014, M. Walther

Signature Page - Study Statistician

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Protocol version identifier	1.0
Date of last version of protocol	12 September 2014
IMPACT study number	17550
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added after registration
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03) Radium-223 dichloride (Xofigo®)
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study statistician
Name	Yoriko De Sanctis
Title	Global Integrated Analysis Project Lead
Address	Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 9/29/2014, 

Signature Page - Study Data Manager

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Protocol version identifier	1.0
Date of last version of protocol	12 September 2014
IMPACT study number	17550
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added after registration
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03) Radium-223 dichloride (Xofigo®)
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study Data Manager
Name	Daniel Wolf
Title	Global Clinical Data Manager Non-Interventional Studies
Address	Bayer HealthCare Germany, Bldg. K9, 51366 Leverkusen, Germany

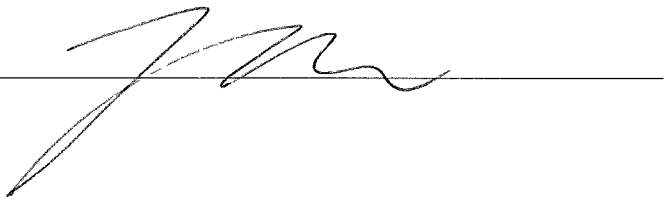
The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 30.09.2014, D. Wolf

Signature Page - Study Statistician

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Protocol version identifier	1.0
Date of last version of protocol	12 September 2014
IMPACT study number	17550
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added after registration
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03) Radium-223 dichloride (Xofigo®)
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study statistician
Name	Yoriko De Sanctis
Title	Global Integrated Analysis Project Lead
Address	Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 9/29/2014, 

Signature Page - Study Health Economics and Outcomes Research (HEOR) Responsible

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Protocol version identifier	1.0
Date of last version of protocol	12 September 2014
IMPACT study number	17550
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added after registration
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03) Radium-223 dichloride (Xofigo®)
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study health economics and outcomes research (HEOR) responsible
Name	Katja Dräxler
Title	Market Access Manager HEOR
Address	Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: Leverkusen, 30/09/2015