Observational Study Information

Title	REASSURE - Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version identifier	Version 3.0
Date of last version of protocol	05 May 2014
IMPACT study number	16913
Study type	☒ PASS ☐ non-PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride
Medicinal product	Xofigo®
Product reference	EU/1/13/873/001; NDA 203971
Procedure number	N/A
Marketing authorization holder(s)	Bayer Pharma AG, Bayer Healthcare Pharmaceuticals Inc.
Research question and objectives	This observational prospective single arm cohort study is designed to assess the incidence of second primary malignancies among patients with metastatic Castration Resistant Prostate Cancer (mCRPC) receiving Radium-223 in routine clinical practice. In addition, safety, pain, and overall survival will be assessed.
Country(-ies) of study	US, Canada, EU (countries from other regions might be added)
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Marketing authorization holder

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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.

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2. List of abbreviations

AE	Adverse Event
ADT	Androgen Deprivation Therapy
ALAT	Alanine Transaminase
ALP	Alkaline Phosphatase
ALSYMPCA	ALpharadin in SYMptomatic Prostate CAncer
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ASAT	Aspartate Transaminase
BIPS	Bremen Institute for Prevention Research and Social Medicine
BMI	Body Mass Index
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
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
EAIR	Exposure-adjusted incidence rate
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
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-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
FU	Follow-up
G-CSF	Granulocyte colony-stimulating factor

GAMP	Good Automated Manufacturing Practice
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transpeptidase
GMA	Global Medical Affairs
GPP	Good Publication Practice
GSL	Global Safety Lead
GVP	Good Pharmacovigilance Practice
HCPCS	Healthcare Common Procedure Coding System
HEOR	Health Economics and Outcomes Research
HMO	Health Maintenance Organization
HRPC	Hormone-Refractory Prostate Cancer
ICD	International Classification of Disease
ICD-9	International Classification of Disease, Ninth Revision
ICD-10	International Classification of Disease, Tenth Revision
ICH	International Conference of Harmonization
ICH-GCP	International Conference of Harmonization - Good Clinical Practice
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
KM	Kaplan-Meier
KP	Kaiser Permanente
KPSC	Kaiser Permanente Southern California
LCL	Lower Confidence Limit
LDH	Lactate Dehydrogenase
M	Month
MAH	Marketing Authorization Holder
mCRPC	Metastatic Castration Resistant Prostate Cancer
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NDC	National Drug Code
NIS	Non-Interventional Study

NNH	Number Needed to Harm
OS	Overall Survival
PSA	Prostate-specific Antigen
PASS	Post-Authorization Safety Study
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PYR	Person-Year at Risk
QoL	Quality of life
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
REASSURE	Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Southern California
SD	Standard Deviation
SDB	Study Database
SEER	Surveillance, Epidemiology and End Results
SSE	Symptomatic Skeletal Events
SOPs	Standard Operation Procedures
SMR	Standardized Mortality Ratio
SPM	Second Primary Malignancy
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
ULC	Upper Confidence Limit
US	United States
USA	United States of America
WBC	White Blood Cell
WHO	World Health Organization

3. Responsible parties

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3.2 Collaborators / Committees

Contact details of investigators and other site personnel for each country and site participating in the study is kept in a central study tracking database and is available upon request.

Information on the Steering Committee Members is kept as stand-alone document and is available upon request.

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

4. Abstract

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version identifier	Version 3.0
Date of last version of protocol	05 May 2014
IMPACT study number	16913
Study type	☒ PASS ☐ non-PASS Joint PASS: ☐ YES ☒ NO
Author	Mona M Wahba, MD, MSM

	Bayer HealthCare Pharmaceuticals Inc. Whippany, New Jersey, USA
Rationale and background	Prostate cancer is the most common non-cutaneous malignancy in men worldwide. Once prostate cancer becomes metastatic, the survival of the patient 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. 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 suffer usually from very painful bone metastases with severe impact on their quality of life (QoL). This observational study called REASSURE is to evaluate the short and long term safety profile of Radium-223, which selectively targets bone metastases with high-energy, short-range alpha-particles. REASSURE will assess the safety and tolerability of Radium-223 and the risk of developing second primary cancers among castration resistant prostate cancer patients receiving Radium-223 in the routine clinical practice setting. In addition overall survival and pain-related data will be collected.
Research question and objectives	The primary objectives of this study are: • To assess the incidence of developing second primary malignancies in mCRPC patients treated with Radium-223 in the routine clinical practice setting. • To assess the incidence of treatment-emergent serious adverse events (SAEs) (collected up to 30 days after last administration), drug -related adverse events (AEs) collected up to 30 days after last administration) and incidence of drug-related SAEs (up to 7 years after the last administration). • To assess bone marrow suppression. The secondary objectives of this study are: • To determine the Overall Survival (OS) in mCRPC patients treated with Radium-223 in the routine clinical setting. • To evaluate pain over time using the "Brief pain inventory short form" (BPI-SF) questionnaire.
Study design	This observational prospective single arm cohort study. The study will be conducted in routine clinical practice settings. It is planned to enroll 1,334 patients with Castration Resistant

	Prostate Cancer (CRPC) with bone metastases. The decision to treat with Radium-223 will be agreed between the physician and the patient independently and prior to study information. Treatment with Radium-223 should follow the approved local product information. The study will be initiated in the US and EU according to health authority approval timelines. Enrollment should start in 2014 and the recruitment is expected to last until the beginning of 2016. The observation period for each patient enrolled in this study will be the time from the start of therapy with Radium-223 to death, withdrawal of consent, lost to follow-up or end of this study (maximum of 7 years after last administration) for each individual patient, whichever comes first in time. Appropriate external secondary data source(s) will be identified through the conduct of observational cohort study (ies), independent from the REASSURE study, to serve as reference group(s) for the evaluation of second primary malignancies identified in mCRPC patients. The occurrence of second primary malignancies identified in mCRPC patients treated with Radium-223 and enrolled in the REASSURE study will be compared with corresponding information on patients in the external reference group(s).
Population	The study population will consist of CRPC patients with bone metastasis treated with Radium-223.
Variables	The following variables will be evaluated: • Second primary malignancies (as reported as SAE) • Treatment-emergent SAEs (data will be collected up to 30 days after last administration) • Drug-related SAEs (data will be collected up to 7 years after last administration) • Drug related treatment-emergent adverse events (data will be collected for treatment period up to 30 days after last administration) • Bone marrow suppression • Overall survival, defined as the time interval from the start of Radium-223 therapy to death due to any cause • Worst pain score based the BPI-SF assessments • Pain interference score based the BPI-SF assessments
Data sources	Treating physician or designated medical person, medical records, routine measurements (e.g. tumor assessment), Radium-223 administering physician (if applicable), other physicians, patient questionnaires. For the external reference group(s), appropriate secondary data source(s) will be evaluated and identified.

Study size	For this study, data will be collected to assess the incidence of developing second primary malignancies among mCRPC patients receiving Radium-223 in the routine clinical practice setting. It is expected, that approximately 1,334 patients will be enrolled into the study which accounts for 10% loss to follow-up from 1,200 patients). Based on the current data from the phase III study ALSYMPCA and SEER data from Brenner DJ et al, the incidence proportion of second primary malignancy is approximately in the range of 1.1% to 6.9%. The follow-up periods for the patients varied from approximately 3 years (ALSYMPCA) to > 10 years for SEER data. With 1,200 patients, if the observed incidence proportion is between 1.1% and 6.9%, the width of a 95% confidence interval for the rate of second primary malignancy (based on the exact binomial distribution) will be approximately 0.0131 (i.e. approximately 1.3%) to 0.0296 (i.e. approximately 3%).
Data analysis	Demographic data, baseline cancer characteristics, concomitant diseases, concomitant medication, BPI-SF of the included patients will be described with summary statistics such as mean, SD, minimum 25 and 75 percentiles, median, maximum for continuous variables, and category counts and frequencies (percentages) for categorical variables. Development of second primary malignancy will be summarized using the incidence proportion (i.e. number of patients with event divided by the number of patients at risk) and in-addition, the exposure-adjusted incidence rate (EAIR), which is defined as the number of patients with specific event divided by the total person-time of observation or at risk will be summarized. The corresponding exact 95% confidence intervals will be given as well. Descriptive summaries of Kaplan-Meier (KM) estimates and KM curves will be presented for overall survival. Adverse events will be summarized using MedDRA and the NCI-CTCAE coding system. The incidence proportion and EAIR will be estimated along with the corresponding exact 95% confidence interval. Due to the long follow-up period two interim analyses are planned for this study. For the comparison with external reference group, incidence of second primary malignancies in mCRPC patients treated with Radium-223 from the REASSURE study will be compared with corresponding information on patients with mCRPC identified in the external secondary data source(s).

Milestones	Start of data collection:	Q3 2014
	End of recruitment:	Q4 2015
	End of data collection:	12/2023
	Final report of study results:	09/2024

5. Amendments and updates

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	Q3 2014
End of recruitment	Q4 2015
End of data collection	12/2023
Interim report 1	09/2017
Interim report 2	09/2019
Registration in the EU PAS register	expected: Q2/2014
Final report of study results	09/2024

7. Introduction: Background and Rationale

Prostate cancer is the most common non-cutaneous malignancy in men worldwide. In 2008, worldwide an estimated total of 899,000 men (EU: 323,000; US: 186,000) had prostate cancer; worldwide, 258,000 died from the disease (EU: 71,000; US: 28,000) (1). The crude incidence rate is estimated around 135 cases for every 100,000 men. Incidence rates increase sharply beyond the age of 50 years, peaking in the age category of ≥ 75 years of age. For men aged 55-59 years, the incidence rate is 161 per 100,000 men; ten years later, at age 65-69 years, the rate more than triples to 538 per 100,000, and by 75-79 years the rate is almost five times higher at 781 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 1.7 million new cases and 499,000 new deaths worldwide (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 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 metastasis (5). Once prostate cancer becomes metastatic, the survival of the patient 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 occur 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 one hand and osteoblasts as well 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 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, BC1-06, ALSYMPCA (**Al**pharadin in **Sym**ptomatic **P**rostate **Ca**ncer) trial 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 [IV]) or matching placebo every 4 weeks. The primary endpoint was overall survival. Main secondary efficacy endpoints were time to first skeletal-related event, time to total alkaline-phosphatase (ALP) and total ALP response. Based on data of an interim analysis (n=809), the study was unblinded in July 2011, since radium-223 dichloride significantly improved OS, compared to placebo (the median OS was 14.0 vs. 11.2 months, respectively; HR= 0.695; p=0.00185). Symptomatic skeletal events (SSE) were lower in the radium-223 dichloride arm, and time to first SSE was significantly

delayed (the median time to SSE was 13.6 months, versus 8.4 months, respectively; HR= 0.610; p= 0.00046). A low incidence of myelosuppression was observed, with grade 3/4 events of neutropenia (1.8%) and thrombocytopenia (6.2%). Adverse events of any grade were described in 88% of the subjects who received radium-223 dichloride; versus 94% in the placebo arm (grade 3/4 adverse events were described for 51% and 59%, respectively). The updated analysis (performed in June 2012; n=921) also showed that radium-223 dichloride significantly improved OS compared to placebo (median OS 14.9 vs. 11.3 months, respectively; p=0.00007; HR=0.695).

Quality of life (QoL) results from the ALSYMPCA study showed that Radium-223 better preserved QoL versus placebo (FACT-P total score; p=0.006) (14). Post hoc analyses of pain parameters and pain-related QoL revealed that in addition to prolonging survival, Radium-223 reduces pain and opioids use in patients with CRPC and bone metastases. Radium-223 significantly prolonged median time to external beam radiation therapy for bone pain, significantly prolonged time to opioid use and decreased pain measured by patient-reported pain-related QoL score (15).

The ALSYMPCA pivotal phase III study was conducted in a controlled patient population according to strict inclusion/exclusion criteria. A total of 173 study centers in 19 countries (Australia, Belgium, Brazil, Canada, Czech Republic, France, Germany, Hong Kong, Israel, Italy, Netherlands, Norway, Poland, Singapore, Slovakia, Spain, Sweden, United Kingdom, United States of America [USA]) were initiated to participate in the study, of which 136 centers enrolled, i.e., randomized, subjects into the study. However, in the post-approval clinical practice setting, patients receiving Radium-223 are usually more heterogeneous with various co-morbid conditions.

Approximately 50 % of patients with bone-metastatic prostate cancer die of prostate cancer within 30 months, and 80% within 5 years (11). As of December 1st 2012, less than 200 ALSYMPCA patients were alive in different periods of follow up and 22 patients have been followed up for 3 years. The mean age of patients enrolled in ALSYMPCA study was 70 years.

As per the same cut-off date of December 1st 2012, the incidence proportion for second primary malignancy in patients who had received Radium-223 is approximately 1.1% (7/625=1.12%). The follow up period for these patients was approximately 3 years.

In ALSYMPCA, there were a total of 5 patients in the Radium-223 arm (n=600) and 3 patients in the placebo arm (n= 301) who had a second primary malignancy (cut off July 2011) (16). Additionally 2 patients receiving Radium-223 (one of them originally on placebo had crossover to receive Radium-223) and 2 patients in the placebo arm reported a second primary malignancy (cut off December 2012) (17). Therefore, as of December 2012, on a total of 625 patients exposed to Radium-223 (including 25 patients initially on placebo who had crossover to Radium-223), 7 had reported a second primary malignancy. The second primary malignancies in those patients were 4 skin cancers, 1 bladder cancer, 1 lymph node metastases (not from prostate cancer) and 1 lymphangiosis carcinomatosa.

None of the reported cases of second primary malignancies identified have been assessed as being related to Radium-223 (short latency period).

Data from the Surveillance Epidemiology and End Results (SEER) Program cancer registry (1973-1993) (18) indicated that of a total of 51,584 men with prostate cancer who had received radiotherapy, 3549, i.e. 6.9% developed a second malignancy. Most (3171) had solid

tumors. Skin cancers were not included in the analysis. The follow up period for these patients was up to more than 10 years (between 1973 and 1993).

The proposed 7 years follow-up of the present Radium-223 study is based on the finding from the "Spiess study" that follows the health of 899 persons who received multiple injections of another short-lived alpha-particle emitter Radium-224 mainly between 1945 and 1955 for the treatment of tuberculosis, ankylosing spondylitis and some other diseases. In December 2007, 124 persons were still alive. The most striking health effect, observed shortly after (224) Ra injections, was a temporal wave of 57 malignant bone tumors. During the two most recent decades of observation, a significant excess of non-skeletal malignant diseases has become evident. Up to the end of December 2007, the total number of observed malignant non-skeletal diseases was 270 (248 specified cases of non-skeletal solid cancers and 22 other malignant diseases, among these 16 malignant neoplasms of lymphatic and hematopoietic tissue, six without specification of site) compared to 192 expected cases. The pick of development of secondary tumors was observed between 7 and 8 years (19).

In response to the FDA and EMA post-marketing requirements, MAH will further assess the safety of Radium-223 through the conduct of an international prospective observational single arm cohort study to study the occurrence of second primary malignancies in patients treated with Radium-223: The REASSURE study (Radium-223 alpha Emitter Agent in Safety Study in mCRPC population for long-teRm Evaluation.

Due to the nature of the disease, stage of the prostate cancer and the uniqueness of the treatment with Radium-223, it would be challenging to identify an active comparison group within the REASSURE study. As an optimal alternative, incidence rates on second primary malignancies in mCRPC patients treated with Radium-223 and enrolled in the REASSURE study could be indirectly compared with the corresponding reference information on second primary malignancies in mCRPC patients from external secondary data source(s), such as population based data in the US and/or EU.

A feasibility evaluation of specific appropriate external secondary data sources is currently being conducted by the MAH. Based on this evaluation, the MAH will develop separate individual study protocol(s) for population based study(ies) estimating the incidence of second primary malignancies in one or more data sources.

8. Research questions and objectives

This observational study is conducted to evaluate the short and long term safety profile of Radium-223 and assess the incidence of developing second primary malignancies among prostate cancer patients receiving Radium-223 in the routine clinical practice setting.

8.1 Primary objective(s)

The primary objectives of this study are:

- To assess the incidence of all second primary malignancies (including myelodysplatic syndrome (MDS)/acute myeloid leukemia (AML) and osteosarcoma) in mCRPC patients treated with Radium-223 in the routine clinical practice setting.
- To assess the incidence of treatment-emergent serious adverse events (SAEs) (collected up to 30 days after last administration), drug-related adverse events (AEs)

collected up to 30 days after last administration), drug-related SAEs (up to 7 years after the last administration of Radium-223).

- To assess bone marrow suppression.

8.2 Secondary objective(s)

The secondary objectives of this study are:

- To determine the Overall Survival (OS) in patients treated with Radium-223
- To evaluate pain over time using the "Brief pain inventory short form" (BPI-SF) questionnaire (20)

9. Research methods

9.1 Study design

This study is a global, prospective, observational, multi-center, single arm cohort study. The study will be conducted in routine clinical practice settings. Site selection is done by the Bayer country medical departments. Sites are selected based only on the experience of the oncologist with the indication and the treatment with Radium-223. It is planned to enroll 1,334 patients with Castration Resistant Prostate Cancer (CRPC) with bone metastases for whom a decision has been made by the treating physician and the patient to treat with Radium-223. Treatment with Radium-223 should follow the approved local product information according to local health authority approved label.

The study will be initiated in the US, Canada, EU (countries from other regions might be added) according to health authority approval labels. The observation period for each patient enrolled in this study is the time from the start of therapy with Radium-223 to death, withdrawal of consent, lost to follow-up or end of this study (maximum of 7 years after last administration of Radium-223), whichever comes first in time. To monitor the development of second primary malignancies and potential short and long term toxicities, second primary malignancies and Radium-223-related SAEs will be collected for each patient until end of study.

In this observational study, the decision on the duration and dosage of treatment is agreed upon between the patient and the physician. However, it is highly recommended that the treating physician follows the local product information. The medication is used within the routine clinical practice setting. Commercially available product will be used to treat the patients.

Second primary malignancies incidence data from external secondary data sources will be generated to establish the reference group(s).

9.1.1 Primary Endpoint(s)

- The incidence of developing second primary malignancies

- AEs / SAEs
  - Incidence of treatment-emergent SAEs (up to 30 days after last administration).
  - Incidence of drug-related treatment-emergent adverse events (up to 30 days after last administration).
  - Incidence of drug-related SAEs (up to 7 years after last administration).
- Bone marrow suppression.

For details, please go to Section 9.3.1

9.1.2 Secondary Endpoint(s)

- The Overall Survival (OS) in mCRPC patients treated with Radium-223 in the routine clinical setting.
- The worst pain score and pain interference score over time as determined by patient responses on the "Brief pain inventory short form" (BPI-SF) questionnaire.

9.1.3 Strengths of the study design

This is an international, prospective, observational, cohort study of CRPC patient with bone metastasis who will receive Radium-223 in routine clinical practice settings. This study will include patients from a more diversified and less selected patient population than in clinical trial setting, using fewer eligibility criteria to be as much representative to the general CRPC patients with bone metastasis as possible.

9.2 Setting

The study will be conducted by Bayer Pharma AG with support of a Contract Research Organization (CRO). The study will be conducted according to local health authority approved label.

9.2.1 Eligibility

The study population will consist of CRPC patients with bone metastasis who will be treated with Radium-223.

9.2.2 Inclusion criteria

- The treatment decision to Radium-223 needs to be made independent from and before patient enrollment in the study.
- Patients with histologically or cytologically confirmed castration resistant adenocarcinoma of the prostate with bone metastases.
- Signed informed consent.

9.2.3 Exclusion criteria

- Patients previously treated with Radium-223 for any reason.
- Patients currently treated in clinical trials including other Radium-223 studies.
- Patients are planned for the systemic concomitant use of other radiopharmaceuticals for treatment of prostate cancer or for other use.

Inclusion and exclusion criteria should follow the locally approved Radium-223 product information.

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 request. The investigator should seek to obtain the reason and record this on the Case Report Form (CRF).

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 and thus to increase the likelihood of representativeness. With respect to site selection this study could have potential limited representativeness (at convenience sample) as Bayer would be looking for sites with Radium-223 availability (nuclear-medicine licensed facility) and experience with prostate cancer management and treatment.

9.2.7 Visits

Information on the patients, outcomes and other variables is recorded using Electronic Data Capture (EDC) by the treating physician (medical oncologist, urologist) or designated medical person at different time points. In certain circumstances, dosing and other related variables are recorded using EDC by the Radium-223 administering physician (nuclear medicine physician or any other physician licensed in the administration of radioisotopes). 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 in this study. 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 into EDC system by the physician or designated medical person. Paper patient questionnaires will be collected at each treatment cycle and will entered into the database by the CRO. After end of treatment, the patient information will be gathered in regular intervals (approximately 3 and 6 months, 12 months and thereafter yearly for a maximum of 7 years after last administration of Radium-223 according to local clinical practice) from patient’s record or during follow-up visits by the recruiting physician or designated person within treatment team. The visit frequency should be driven by the local standard of care at the local site.

9.3 Variables

At baseline, patients’ demographic variables and information about disease characteristics will be collected from the treating physician (including date of diagnosis, prior treatment, and tumor staging information, co-morbidities, prior medication, and concomitant medication). Treatment information and potential outcomes (second primary malignancy, other safety information and OS) are recorded by the treating physician (medical oncologist, urologist) or Radium-223 administering physician or designated medical person in an EDC system. Pain measurements are recorded starting before the first injection of Radium-223 until 6 months after last injection of Radium-223.

The follow-up will take place at approximately 3M, 6M, 12M, 24M, 36M, 48M, 60M, 72M, 84M to collect information regarding the outcomes of interest (second primary malignancy, other safety information and OS). The visit frequency should be driven by the local standard of care at the local site.

Table 2: Tabulated overview on variables collected during the study

	Baseline	Treatment (until 30 days post last dose)	6 Months FU post last dose	Long-term FU
Demography	X			
Vital Signs	X			
Prostate cancer history (classification, risk factors, ECOG, procedures)	X			
Medical history/concomitant disease	X			
Medication (prior, concomitant, subsequent)	X	X	X [a]	X [a]
Anti-cancer therapies (prior, concomitant, subsequent)	X	X	X	X
Exposure Treatment (Radium-223)		X		
Adverse Events[b]		X	X	X
Laboratory parameters	X	X	X[c]	X[c]
Pain measurements (BPI-SF)	X	X	X	

[a] Medications taken for treating of drug related SAEs/second primary malignancies Therapeutic, prevention measures and treatment modalities for bone marrow suppression will be collected.

[b] All SAEs and drug-related AEs are collected during treatment and up to 30 days after the last administration of Radium-223.
Drug related Serious Adverse Events (SAEs) are collected up to 7 years after the last administration of Radium-223.
All SAEs of second primary malignancies are collected up to 7 years after the last administration of Radium-223.
All post treatment grade 3/4 hematological toxicities are collected up to 6 months after the last administration of Radium-223.
For patients receiving subsequent chemotherapy, all AEs/SAEs of febrile neutropenia and hemorrhage will be recorded up to 6 months after the last administration of chemotherapy.

[c] For patients with a platelet count or WBC less than the lower limit of normal at 6 months post last dose of Radium- 223 are being followed until resolution at a frequency based on local clinical practice.

9.3.1 Variables to determine the primary endpoint(s)

- Second primary malignancies (reported as SAE):

  Second primary malignancies are defined as new malignancy unrelated to prostate cancer or progression of prostate cancer. All second primary malignancies will be collected irrespectively of their relationship to Radium-223. Patients will be followed up until

death, withdrawal of consent, lost to follow-up or end of the study, whichever occurs earlier. All types of malignancies including MDS/AML and osteosarcoma (which have been reported with the use of radiation) and all other malignancies (including skin cancers) will be documented. Detailed information will be collected as SAE:

- description of the event (including location and type);
- start date;
- stop date;
- treatment prior to the event (particularly any cancer related treatment and radiotherapy);
- relationship to Radium-223;
- toxicity grade;
- outcome.

- Treatment-emergent SAEs (data will be collected up to 30 days after last administration).
- Drug related treatment-emergent adverse events (data will be collected for treatment period up to 30 days after last administration).
- Drug-related SAEs (data will be collected up to 7 years after last administration)
- Bone marrow suppression, the following will be assessed:
  - Therapeutic or prevention measures, treatment modalities (e.g. blood transfusion/erythropoietin/colony growth stimulating factors) (up to 6 months after last administration of Radium-223).
  - All post treatment grade 3/4 hematological toxicities (up to 6 months after last administration of Radium-223 as AEs/SAEs):
    - description of the event;
    - start date;
    - stop date;
    - therapeutic or prevention measures, treatment modalities;
    - toxicity grade;
    - outcome;
    - relationship to Radium-223.
  - For patients with a platelet count or WBC less than the lower limit of normal at 6 months post last dose of Radium- 223 are being followed until resolution at a frequency based on local clinical practice.
  - Patients who receive subsequent cytotoxic chemotherapy will be followed for the development of febrile neutropenia and hemorrhage up to 6 months after the last administration of chemotherapy at a frequency based on local clinical practice.

9.3.2 Variables to determine the secondary endpoint(s)

- **Overall Survival (OS):**

OS 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.

- **Pain**

Pain severity will be measured using the worst pain score from the BPI-SF questionnaire. Pain interference will be measured using the pain interference score form the BPI-SF questionnaire. The BPI-SF questionnaire will be administered prior to each injection of Radium-223. The BPI-SF questionnaire will also be used at each follow-up visit until 6 months after the last injection of Radium-223.

9.3.3 Demography

For demographic assessment, the following data will be recorded:

- Year of birth
- Race (only where legally permitted)
- Ethnicity (only where legally permitted)
- Sex

Basic patient characteristics

- Weight
- Height
- Body Mass Index (BMI)
- Vital signs

9.3.4 Prostate cancer history

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

- Risk factors for cancer
- Tumor Classification
- Number of metastases and extent of disease and/or related procedures/surgeries
- Baseline ECOG performance status

9.3.5 Co-morbidities (medical history, concomitant diseases)

Co-morbidities are any medical findings, whether or not they pertain to the study indication, that was present before start of therapy with Radium-223, independent whether or not they are still present. They have to be documented in the Medical History/ Concomitant Diseases section. The patient's medical history from the last 10 years will be collected.

For any co-morbidity, the diagnosis, the start and the stop date/ongoing have to be documented.

9.3.6 Prior and concomitant medication

All medications taken before study start (initiated and stopped before study start) is termed prior medication.

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

All medications after the last dose of Radium-223 are termed subsequent medication.

Medications taken for drug-related SAEs up to 7 years post last dose of Radium-223, for Grade 3/4 hematologic toxicities up to 6 months post last dose of Radium-223, and for febrile neutropenia & hemorrhage up to 6 months post last dose of subsequent chemotherapy will also be collected.

Therapeutic and prevention measures for bone marrow suppression (blood transfusion/erythropoietin/colony growth stimulating factors) include: trade name or INN, start date, stop date/ongoing, dose, unit, frequency, indication. Information to be collected for co-medication at baseline includes: trade name or INN, start date, stop date/on-going, dose, unit, frequency, indication. Information to be collected for concomitant and subsequent medication includes: trade name or INN, start date, stop date/ongoing, dose, unit, frequency, indication. Information on prior treatments for the prostate cancer is part of the baseline information collection. Additionally, all co-medication taken at baseline and during the study will be recorded. Relevant prostate cancer therapy variables will be collected in the categories stated below:

- Prior, concomitant and subsequent cancer treatment including bisphosphonates, chemotherapy, radiotherapy, and/or re-treatment with Radium-223.
- Diagnostic radiopharmaceuticals (e.g. Technetium)

Additionally, the level of analgesic pain management will be assessed at each treatment visit, starting before the first injection of Radium-223, at each follow-up visit until 6 months after the last injection of Radium-223 based on concomitant medication data collected at these visit.

9.3.7 Exposure / treatment

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

- Dose
- Unit
- Dates (of each injection)
- Reasons for any significant delay/interruption/discontinuation

9.3.8 Assessment of therapy

N/A

9.3.9 Visits

- Date of visit/contact

9.3.9.1 Baseline

At baseline medical history, cancer history, demography, vital signs, prior medication, prior diagnostic and therapeutic procedures are documented.

9.3.9.2 Treatment phase

The dates of the administrations, the dose of Radium-223 changes in concomitant medications and anti-cancer therapy.

Safety data will be collected as specified in Section 9.3.1

Pain measurements will be documented at each treatment visit using the BPI-SF questionnaire.

The recruiting or treating physician or designated medical person or Radium-223 administering physician will be contacted by the designated CRO with reminders to follow-up if the patient received at least one treatment cycle.

9.3.9.3 Follow-up visit(s)

The follow-up will take place at approximately 3M, 6M, 12M, 24M, 36M, 48M, 60M, 72M, 84M from the last administration of Radium-223 to collect information regarding the outcomes of interest (e.g. second primary malignancy, other information on safety and OS).

Safety data will be collected as specified in Section 9.3.1

Changes in anti-cancer therapy will be documented.

Pain measurement will be assessed up to and including the 6M follow-up visit.

The designated CRO will remind physicians when collection of follow-up information is due.

9.3.10 Laboratory parameters

Following local routine medical practice, laboratory parameters will be documented, e.g. sodium, potassium, chloride, calcium, phosphate, magnesium, ASAT, ALAT, LDH, GGT, creatinine, urea, bilirubin, albumin, ALP, PSA, protein, hematocrit, hemoglobin, platelet counts, red and white blood cell counts and differential white blood cell. Laboratory abnormalities considered to be clinically significant and drug-related should be also documented on the AE page.

Hematologic evaluation of patients should be performed at baseline and prior to every dose of Radium-223 based on the approved local product information: before the first administration of Radium-223, the absolute neutrophil count (ANC) should be ≥ 1.5 x 109/L, the platelets count ≥ 100 x 109/L and hemoglobin ≥ 10 g/dL. Before subsequent administrations of Radium-223, the ANC should be ≥ 1 x 109/L and the platelet count ≥ 50 x 109/L.

For patients with a platelet count or WBC less than the lower limit of normal at 6 months post last dose of Radium- 223 are being followed until resolution at a frequency based on local clinical practice.

9.4 Data sources

9.4.1 REASSURE data sources

Treating physicians (medical oncologist, urologist) or designated medical person will collect historic and on study data from the medical records, routine measurements (e.g. tumor assessment), other treating physicians. Radium-223 administering physicians in certain circumstances may also collect from similar sources dosing data and other related data. Patients will be asked to answer patient questionnaires.

9.4.2 External reference secondary data sources

A feasibility assessment is ongoing for the selection of potential data source(s) to generate reference incidence data on second primary malignancies in mCRPC patients. The feasibility assessment is estimated to be completed by October 2014.

In the US, several electronic healthcare databases including commercially available claims databases and electronic medical record databases are being evaluated. The Kaiser Permanente electronic healthcare record database has been identified as a potential appropriate data source to serve as the reference group. Other US data sources are also under evaluation.

In Europe, an evaluation of data sources including The Health Improvement Network (THIN) in UK, The German Pharmacoepidemiological Research Database (GePaRD) via the Bremen Institute for Prevention Research and Social Medicine (BIPS) in Germany, and the Swedish National Registers is also undergoing.

9.5 Study Size

The sample size estimation for the proposed observational study is challenging because the probability of developing second primary malignancies varies for different cancer types among prostate cancer survivors. For this study, accordingly, data will be collected on all second primary malignancies and their potential relationship to Radium-223 will be evaluated.

Approximately 1,334 patients will be enrolled into the study (which accounts for 10% loss to follow-up from 1,200 patients). Based on the current data from the phase III study ALSYMPCA, and SEER data from Brenner DJ et al., the incidence proportion of second primary malignancy is approximately in the range of 1.1% to 6.9%.

Table 3 shows the width of a 95% confidence interval for the rate of second primary malignancy (based on the exact binomial distribution) for different observed incidence proportion with 1200 patients:

Table 3: Incidence and corresponding 95% confidence limits

Incidence (%)	UCL	LCL	Width (%)
1.0	0.52	1.74	1.22
1.1	0.64	1.95	1.31
5.0	3.84	6.39	2.55
6.9	5.55	8.50	2.96
10.0	8.36	11.84	3.48

With 1,200 patients, if the observed incidence proportion is between 1.1% and 6.9%, the width of a 95% confidence interval for the rate of second primary malignancy (based on the exact binomial distribution) will be approximately 0.0131 (i.e. approximately 1.3%) to 0.0296 (i.e. approximately 3%). The sample size calculation is based on an estimated 10% for the loss to follow up. The sample size could be increased if loss to follow up rate proves to be higher than expected.

9.6 Data management

A CRO will be selected and assigned for EDC system development. All CRFs 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.

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 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.

9.6.1 Dataflow

Participating physicians or designated medical person will use the EDC system to enter the data. Patient questionnaires will be collected via paper forms which will be entered into the study database. Quality control of entered data will include range, coding, missing and date checks as well as cross-reference (consistency) checks between variables. Accuracy of data transcription from source (medical records) to the EDC would be done by source data verification.

9.6.2 Database freeze/lock

For each interim analysis and for the final analysis the database is frozen at a predefined time point. The database will be 'cleaned' in approximately 4 weeks of the database freeze. After the final freeze, no additional incoming data is entered in the database – this database will represent the final data source for all analyses. Duplicate copies are made of each database, so that all calculations can be repeated if necessary.

For information on quality control, refer to Section 9.8.

9.7 Data analysis

9.7.1 Statistical considerations

Statistical analyses will be primarily explorative and descriptive. All statistical issues including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). Wherever reasonable, evaluation will be stratified by subgroups (i.e. age, other baseline characteristics).

Patients who receive at least one dose of Radium-223 will be considered valid for safety and included in the full analysis set.

Summary statistics such as mean, standard deviation (SD), minimum, 25 and 75 percentiles, median, maximum will be calculated for continuous variables. Frequencies (percentages) will be calculated for categorical variables.

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 World Health Organization (WHO)'s drug dictionary.

9.7.3 Analysis of treatment data

Summary statistics will be provided for the treatment duration, 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)

Second primary malignancies (reported as SAE)

Development of second primary malignancies will be summarized using incidence proportion, i.e., number of patients with event divided by the number of patients at risk. The number of patient at risk is defined as the safety population, but excludes patients who start other radiopharmaceuticals or enroll into other trials, if the patient does not develop primary second malignancies before receiving other radiopharmaceuticals or enrolls into other trials. In addition, the exposure-adjusted incidence rate (EAIR), which is defined as the number of patients with the specific event divided by the total person-time of observation or at risk, will be summarized. For patients developing a second primary malignancy, the exposure time will be truncated at the time when the second primary malignancy is reported. For both the incidence proportion and EAIR, the corresponding exact 95% confidence interval will be provided.

Sensitivity analysis will be performed to include patients who start other radiopharmaceuticals.

The annualized incidences rate to be presented with median time to follow up.

In addition, descriptive summaries of Kaplan-Meier (KM) estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% confidence interval (CI) and median with 95% CI) and KM curves will be presented for time to development of second primary malignancy. Patients who start other radiopharmaceuticals or enroll into other trials will be censored when they start other radiopharmaceuticals or enroll into other trials.

AEs / SAEs

These following events will be summarized using the MedDRA and the CTCAE (Version 4.03) coding system.

Adverse events will be categorized and summarized according to relation, seriousness, CTCAE grade, discontinuation of therapy, action taken and outcome. The incidence proportion and EAIR will be summarized, along with the exact 95% confidence interval.

- Incidence of treatment-emergent SAEs (up to 30 days after last administration).
- Incidence of drug-related treatment-emergent adverse events (up to 30 days after last administration).
- Incidence of drug-related SAEs (up to 7 years after last administration).

Bone marrow suppressions

The following will be provided:

- Proportion of patients who take therapeutic or prevention measures, treatment modalities (e.g. blood transfusion/erythropoietin/colony growth stimulating factors).
- Incidence of post treatment grade 3/4 hematological toxicities (up to 6 months after last administration of Radium-223 as AEs/SAEs).

  It will be summarized by CTCAE category and the worst grade. The incidence proportion will be provided, along with the exact 95% confidence interval.

  Information for therapeutic or prevention measures, treatment modalities will also be summarized.
- Incidence of abnormal platelet count or WBC.

  It will be summarized by period (up to 30 days after last administration, and after 30 days after last administration to 6 months after last administration) and the worst grade.
- Incidence of febrile neutropenia and hemorrhage for patients who receive subsequent cytotoxic chemotherapy.

Further details will be described in the SAP.

9.7.5 Analysis of secondary outcome(s)

9.7.5.1 Overall survival (OS)

Descriptive summaries of KM estimates and KM curves will be presented for OS. Patients alive at the end of the study will be censored at the last date known to be alive.

Further details will be described in the SAP.

9.7.5.2 Pain assessment

For the BPI-SF pain assessments, summary statistic, including mean and change from baseline, for the pain severity and pain intensity and the items make up these indices will be provided for each assessment time point. In addition, 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.

Further details will be described in the SAP.

9.7.6 Comparison with external reference secondary data sources

Incidence of second primary malignancies in mCRPC patiens treated with Radium-223 in the REASSURE study will be compared with corresponding information on patients with mCRPC identified in external secondary data source(s).

Site specific incidences on cancer diagnosis will be analyzed by comparing the observed number of cases for second primary malignancies in the REASSURE cohort with corresponding expected number based on cancer incidence rated derived from the external reference secondary data source(s). The expected numbers will be ascertained by individually computed person-years at risk for the entire REASSURE cohort. The time recorded will start at date of first injection of Radium-223 and will end at the time of second primary malignancy occurrence, the date of death or the end of study follow up (data collection is estimated to be completed at December, 2023), whichever comes first. Age (by 5-year age groups) will be accounted for in the analysis. The ratio of the observed and expected number of cases by means of Standardized Morbidity Ratio will be used as the measure of the increased or decreased incidence rates, accompanied by an exact 95% confidence interval assuming the observed number of second primary malignancy cases.

Upon the completion of the feasibility assessment for the selection of external secondary data source(s), separate individual study protocol(s) using external secondary data source(s) will be developed independently from the REASSURE protocol. This/these protocol(s) will include more details on the statistical analysis approach for comparison of data on second primary malignancies in mCRPC patients from the REASSURE study with the corresponding information from external secondary data sources.

The proposed study(ies) will be performed and completed according the timelines that will be provided upon the completion of the feasibility assessment for the external secondary data source(s).

The indirect comparison of REASSURE data with the external secondary data source(s) will be performed following the completion of the REASSURE study and in accordance with timelines of its study report.

9.7.7 Analysis of safety data

All safety variables are indicated as primary outcome.

9.7.8 Bias, confounding and effect-modifying factors

In this observational study, careful attention should be paid to describing the patient population, and caution should be applied to the interpretation of results, especially when making comparisons to previous studies, and/or making comparisons across subgroups, as there may be confounding factors, measured or unmeasured.

In addition, as a result of the relatively long follow-up time and challenges to evaluation and documentation of the occurrence of a second primary malignancies some patients may not have complete follow-up and/or the time to development of the second primary malignancies may not be completely known. Therefore, careful attention should be applied to the interpretation of the summary measures to be estimated, including incidence proportion and EAIR.

9.7.9 Interim Analysis

It is estimated that it will take approximately 1.5 years for completion of enrollment. Two interim analyses will be planned based on the milestones for this study.

9.7.10 Loss of follow-up

A low “loss to follow-up rate” will be essential for the validity of the study, especially in this patient population with a chronic disease and fragile overall survival chances.

In order to minimize loss to follow-up a multi-faceted follow-up process will be established. Level 1 activity includes the electronic follow-up CRF and – in case of no response – up to two electronic reminder letters to the treating physician. If Level 1 activities does not lead to a response, multiple attempts are to be made to contact the treating medical oncologist, urologist or designated medical person by phone (Level 2). The aim is to keep the total loss to follow-up at the end of the study as low as possible It is assumed that a loss-to follow-up rate of less than 10% for the US and less than 5% for Europe can be achieved.

Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the treating physician should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. This excerpt expresses the need for physicians associated with this study to make a first-hand effort to contact patients who are lost-to-follow-up (21).

The designated CRO should be notified in case of the change of the treating physician and Radium-223 administering physician (if applicable) and all efforts to receive information of the new site/physician should be made.

9.8 Quality control

9.8.1 Data quality

Before study start at the sites, all physicians participating in the study will be sufficiently trained by Bayer or the designated CRO on the background and objectives of the study and ethical as well as regulatory obligations. Treating physicians and Radium-223 administering physician (if applicable) will have the chance to discuss and develop a common understanding of the study protocol and the CRF.

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

Prior to submission of the electronic CRF, all pages should be filled out completely. A check for plausibility will be performed while data is being entered. Missing or implausible data will be queried directly online. Data from the CRF must be verifiable against source documents. Data from patient questionnaires will be entered in the study database. Checks for multiple documented patients will be done. All details of the above analyses will be described in detail in the data management plan. For quality purposes, it is planned to conduct monitoring in order to verify/validate data and to increase data quality. Source documents and patient data will be verified in up to 10% of all sites involved in this study.

Adverse Events and Serious Adverse Events will be handled in the same way as the other data reported in the CRF. However, in addition the SAEs will be entered into the safety database for coding, medical assessment and for reporting to authorities according to national regulatory requirements. Coding of Adverse Events, medical history and signs and symptoms will be performed according to MedDRA and coding of concomitant medications, prior anti-cancer therapy and further therapy will be performed according to WHO-Drug dictionary.

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.

A final database will be declared when all data has been entered, the data entry verified, the data validated and a final SAE reconciliation took place.

National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for patient documentation will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) (22). 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.

9.8.3 Storage of records and archiving

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

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 safety and effectiveness 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. The results generated from this study will need to be compared with those derived from the reference group(s). Although the reference group(s) can provide information for understanding the results observed in REASSURE, it has its own weakness as these data are generally not collected using the same way and the same or similar information may not be available.

In addition, this study could experience a higher than expected loss of follow-up because of the long follows up period. However due to the advanced stage of the mCRPC and the average age of the treated population the probability of 7 years survival is very low.

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 usual 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, FDA and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012 (23)). Recommendations given by other organizations will be followed as well (e.g. EFPIA(24), ENCePP (25)). ICH-GCP guidelines will be followed whenever possible (26).

In addition, the guidelines on good pharmacovigilance practices (GVP) will be followed; the relevant competent authorities of the EU member states will be notified according to Volume 9A (27).

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

Review of the study protocol will be obtained at ethics committees or review boards in the participating countries (USA and EU) as required by local law. Non-interventional studies are not within the scope of the European Clinical Trial Directive (2001/20/EC). Accordingly, clinical trial applications to individual European national authorities will not be filed. However, regional regulatory approval within certain European member states will be obtained as required by national regulations. All relevant data protection laws in the participating continents and countries will be followed. When necessary, an extension, amendment or renewal of the IEC/IRB approval will be obtained.

10.4 Patient information and consent

Before documentation of any data, informed consent is obtained by the patient in writing. In countries where required by law or regulation, the IECs/IRB written approval/favorable

opinion of the written informed consent form and any other written information to be provided to patients must be obtained 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 and the study has no interventional character. 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 enrolling and treating physicians and Radium-223 administering physicians and, respectively, the institutions involved provide sufficient protection for both patient and investigator.

10.6 Confidentiality

Bayer as well as the designated CRO ensure adherence to applicable data privacy protection regulation. Data are transferred to Bayer 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 designated CRO is obligated to ensure that no documents contain such data. Study findings stored on a computer will be stored in accordance with local data protection laws.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names will not be supplied to the sponsor. 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.

11. Management and reporting of adverse events/adverse reactions

11.1 Definitions

The observation period / reporting of adverse events for a patient in this study starts with screening.

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to 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 (26).

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
- Any combination of one or more of these factors
- An effect related to lack of drug effect,
- An effect related to medication errors,
- Medication error, overdose, drug abuse, drug misuse or drug dependency itself event, as well as any resulting
- An effect related to off-label use or occupational exposure
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)
- Drug exposure via mother / father (exposure during conception, pregnancy, childbirth and breastfeeding)

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

Hospitalizations will not be regarded as adverse events, if they:

- were planned before inclusion in the study,
- are ambulant (shorter than 12 hours),
- are part of the normal treatment or monitoring of the studied disease, i.e. they were not due to a worsening of the disease.

A drug related AE is any AE judged by the treating physician or Radium-223 administering physician (if applicable) as having a reasonable suspected causal relationship to Radium-223. It is defined as a response to a medicinal product, which is noxious and unintended.

An AE is serious 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
- Results in a congenital anomaly or birth defect in an offspring
- 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 automatically considered as Serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours, or
- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), or
- The admission is not associated with an adverse event (i.e. social hospitalization for purposes of respite care).

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 subject 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 administration of Radium-223, all drug-related non-serious Adverse Events (AE) must be documented on the AE Report Form or on the CRF 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).

For each AE/SAE, the recruiting physician must assess and document the seriousness, duration, causal relationship to study drug, action taken and outcome of the event.

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

As long as the patient has not received any Radium-223, AEs /SAEs do not need to be documented as the patient is considered ineligible.

After the treatment period, all SAEs judged as being drug-related by the treating physician or Radium-223 administering physician (if applicable) have to be documented until 7 years from last treatment or until death, withdrawal of consent, or lost to follow-up, whichever occurs earlier. However, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other second primary malignancy must be reported as SAEs at any time, and regardless of the causality assessment.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed on behalf of the treating physician or Radium-223 administering physician (if applicable).

11.3 Management and reporting

Drug-related non-serious Adverse Events (AE) 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) and according to national regulations by the sponsor; however, all treating physicians or Radium-223 administering physicians (if applicable) must obey local legal requirements.

Serious AEs

All SAEs will be forwarded immediately (within 24 hours of awareness) to the pharmacovigilance country person at Bayer being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented until study end. Where required, the designated CRO 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 treating physicians or Radium-223 administering physicians (if applicable) must obey local legal requirements.

For SAEs that occurred while administering non-Bayer drugs, the designated CRO 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 GPV safety database.

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.

For this mandated PASS, progress reports will be submitted with each PSUR to the competent authorities. Interim reports will be written depending on analysis performed by the designated CRO.

The results of this study are intended to be published in a peer-reviewed journal and as abstracts/presentations at national and international congresses. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP Guidelines (28), STROBE (29)). No individual treating physician or Radium-223 administering physician (if applicable) may publish on the results of this study, or their own patients, without prior approval from Bayer.

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Annex 1. List of stand-alone documents

Table 4: List of stand-alone documents

Number	Document reference number	Date	Title
1	16913_List of active physicians_final	Will be available at end of recruitment	List of all active physicians
2	16913_ CRF_draft	30 April 2014	CRF draft
5	16913_ DMP	Will be available at time of ready to enroll	Data Management Plan
6	16913_ SAP	Will be available before study database lock	Statistical Analysis Plan
7	16913_QRP	Will be available at time of ready to enroll	Quality Review Plan

Annex 2. ENCePP checklist for study protocols

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]	☒	☐	☐	13
1.1.2 End of data collection[2]	☒	☐	☐	13
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	13
1.1.5 Registration in the EU PAS register	☒	☐	☐	13
1.1.6 Final report of study results.	☒	☐	☐	13

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
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:

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?	☒	☐	☐	17,18
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)	☒	☐	☐	26

[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.

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	17
4.2.2 Age and sex?	☒	☐	☐	22
4.2.3 Country of origin?	☒	☐	☐	17
4.2.4 Disease/indication?	☒	☐	☐	17
4.2.5 Co-morbidity?	☒	☐	☐	22
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)	☒	☐	☐	18

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)	☒	☐	☐	23
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?	☐	☐	☒	

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?	☒	☐	☐	20-22
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)	☐	☒	☐	
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.)	☒	☐	☐	25
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.)	☒	☐	☐	25
8.1.3 Covariates?	☐	☒	☐	
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)	☒	☐	☐	25
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	☐	☒	☐	
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)	☒	☐	☐	31
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	31
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?	☒	☐	☐	25

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?	☒	☐	☐	27
10.3 Are descriptive analyses included?	☒	☐	☐	27-29
10.4 Are stratified analyses included?	☐	☐	☐	
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:

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
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	25
12.3 Does the protocol address other limitations?	☒	☐	☐	31

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13 1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	32
13 2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	32
13 3 Have data protection requirements been described?	☒	☐	☐	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?	☒	☐	☐	13

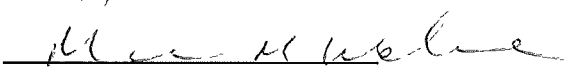
Comments

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 Mona M. Wahba

Date 5/5/2014

Signature 

Annex 3. Signature pages

Title	Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version identifier	3.0
Date of last version of protocol	05 May 2014
IMPACT study number	16913
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer Pharma AG, 13342 Berlin, Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
Function	Global Pharmacovigilance
Name	Michael Kayser
Title	Qualified Person for Pharmacovigilance (QPPV)
Address	Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: May 6, 2014, Michael Kayser

Title	Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version identifier	3.0
Date of last version of protocol	05 May 2014
IMPACT study number	16913
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer Pharma AG, 13342 Berlin, Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 06-MAY-2014 , Nils Opitz

Title	Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version identifier	3.0
Date of last version of protocol	05 May 2014
IMPACT study number	16913
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer Pharma AG, 13342 Berlin, Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 5/5/2014, Mona M Wahba

Title	Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version identifier	3.0
Date of last version of protocol	05 May 2014
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Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer Pharma AG, 13342 Berlin, Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 6 May 2014, 

Title	Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
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EU PAS register number	To be added after registration
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer Pharma AG, 13342 Berlin, Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
Function	Global Non-Interventional Studies
Name	Karin Achilles
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 06.05.'14 , _____

Title	Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version identifier	3.0
Date of last version of protocol	05 May 2014
IMPACT study number	16913
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer Pharma AG, 13342 Berlin, Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
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Address	Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 5/5/2014, _____

Title	Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
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Marketing authorization holder(s)	Ex-USA: Bayer Pharma AG, 13342 Berlin, Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 06.05.2014, Daniel Wolf

Title	Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version identifier	3.0
Date of last version of protocol	05 May 2014
IMPACT study number	16913
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Marketing authorization holder(s)	Ex-USA: Bayer Pharma AG, 13342 Berlin, Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
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Title	Study Epidemiologist
Address	Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: May 5, 2014, Jihong Zong

Title	Radium-223 alpha Emitter Agent in Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version identifier	3.0
Date of last version of protocol	05 May 2014
IMPACT study number	16913
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer Pharma AG, 13342 Berlin, Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
Function	Global Health Economics and Outcomes Research
Name	Paul Cislo
Title	Global HEOR Specialty Medicine Responsible
Address	Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: May 5th, 2014, Paul A Cislo