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Official Title:	REASSURE - Radium-223 alpha Emitter Agent in nonintervention Safety Study in mCRPC popUlation for longteRm Evaluation
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Post Authorization Safety Study (PASS) Information

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	Version 5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☒ PASS ☐ non-PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS7187
Active substance	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride
Medicinal product	Xofigo®
Product reference	EU/1/13/873/001; NDA 203971
Procedure number	N/A
Study Initiator and Funder	Bayer AG, Germany; Bayer Healthcare Pharmaceuticals Inc., USA Effective January 01, 2017 Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumed all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures have changed.
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	Argentina, Austria, Belgium, Canada, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Luxembourg, Mexico, Netherlands, Portugal, Spain, Sweden, United Kingdom, United States
Author	PPD Bayer Consumer Care AG PPD, Switzerland

Marketing authorization holder

Marketing authorization holder(s)	Ex-USA: Bayer AG, Kaiser-Wilhelm-Allee 1 51373 Leverkusen Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
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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.

1. Table of contents

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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
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
GAMP	Good Automated Manufacturing Practice
GCP	Good Clinical Practice

GePaRD	The German Pharmacoepidemiological Research Database
GGT	Gamma-glutamyl Transpeptidase
GPP	Good Publication Practice
GSL	Global Safety Lead
GVP	Good Pharmacovigilance Practice
HEOR	Health Economics and Outcomes Research
HR	Hazard Ratio
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
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
MRP	Medical Review Plan
N/A	Not Applicable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NIS	Non-Interventional Study
OS	Overall Survival
PSA	Prostate-specific Antigen
PASS	Post-Authorization Safety Study
PSUR	Periodic Safety Update Report

QoL	Quality of life
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
REASSURE	Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Southern California
SD	Standard Deviation
SEER	Surveillance, Epidemiology and End Results
SSE	Symptomatic Skeletal Events
SOPs	Standard Operation Procedures
SPM	Second Primary Malignancy
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
THIN	The Health Improvement Network
TTP	Time To Progression
UK	United Kingdom
UCL	Upper Confidence Limit
US	United States
USA	United States of America
WBC	White Blood Cell
WHO	World Health Organization

3. Responsible parties

3.1 Initiator /MAH

Role: PPD
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3.2 Collaborators / Committees

Contact details of physicians 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 and date	Version 5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☒ PASS ☐ non-PASS Joint PASS: ☐ YES ☒ NO
Author	PPD Bayer Consumer Care AG PPD, Switzerland
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 usually suffer from very painful bone metastases with severe impact on their quality of life (QoL). There is also little or limited information on the timing of progression and management of progression in the clinical setting for this patient population. Time to progression has been and continues to be of interest as a potential surrogate marker in other solid tumors. This study provides an opportunity to collect and review these data in the clinical setting. The purpose of 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, pain-related data, disease progression data and data on all bone fractures and bone associated events will be collected. At the request of regulatory authorities, this study was

	implemented in order to contribute information on the safety of treatment with Radium-223 in patients with castration resistant prostate cancer with bone metastases.
Research question and objectives	The primary objectives of this study are: • To assess the incidence of developing second primary malignancies in metastatic castration-resistant prostate cancer (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. • To assess the incidence of bone fractures and bone associated events (e.g. osteoporosis).
Study design	This is an 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 CRPC with bone metastases. The decision to treat with Radium-223 will be agreed upon between the physician and the patient independently and prior to providing the patient study information. Treatment with Radium-223 should follow the approved local product information. The study will be initiated in the US, Canada, the EU and Latin America according to health authority approval timelines. Enrollment should start in 2014 and the recruitment is expected to last until the end of 2017. 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. 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 (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 • Progression, defined as the first progression from the start of Radium-223 therapy • Treatment post progression • Bone fractures and bone associated events (reported as AEs).
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, 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 (CI) 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, and 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 a specific event divided by the total person-time of observation or at risk, will be summarized. The corresponding exact 95% CIs will be given as well. Descriptive summaries of Kaplan-Meier (KM) estimates and KM curves will be presented for overall survival. Descriptive summaries only will be provided for progression (first progression after initial treatment with Radium-223). Adverse events will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) and the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) coding system. The incidence proportion and EAIR will be estimated along with the corresponding exact 95% CI. Due to the long follow-up period, two interim analyses are planned for this study. For the comparison with external reference groups, 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 sources.

Milestones	Start of data collection (FPFV): 20 Aug 2014 (actual) End of recruitment (LPFV): 31 Dec 2017 (actual) Planned end of data collection (LPLV) *: Dec 2024 Planned final report of study results**: Jun 2025 * max. 7 years after LP last treatment or after LP documented End of Observation, whatever comes first ** 6 months after LPLV

5. Amendments and updates

Amendment Number	Reason for Amendment	New version number	Effective Date
AM01	To include collection of data to allow assessment of time to progression and treatment post progression in the study setting. To update the protocol with timeline and administrative changes	v 4.0	18 January 2016
AM02	The ongoing randomized phase III study ERA-223 examines Radium-223 dichloride versus placebo in combination with abiraterone plus prednisone in prostate cancer patients. The ERA-223 study was unblinded based on the Independent Data Monitoring Committee (IDMC) recommendation following an ad hoc independent analysis where more treatment emergent fractures, symptomatic skeletal event free survival (SSE-FS), and total death events were observed in the active treatment arm compared to the placebo arm. The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed preliminary data from the ERA-223 study and has taken action by introducing a contraindication as a temporary measure to protect patients' safety while an in-depth review of the benefit and risks of Radium-223 dichloride is ongoing. Based on this situation and to comply with the request of the clinical trial facilitation group (CTFG), the protocol amendment has been prepared with updates summary as: • Radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone. • Assessment of the incidence of bone fractures and bone associated events (e.g., osteoporosis) should be performed; • The option of starting a BHA should be considered, taking into consideration applicable guidelines. Other changes:Global LPFV was changed to	v 5.0	07 Jun 2018

	31 Dec 2017 to allow for continued enrollment in Latin America (regulatory obligation). Adoption to most current template. Administrative changes were implemented and inconsistencies corrected.		

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 (FPFV)	20 Aug 2014 (actual)
End of recruitment (LPFV)	31 Dec 2017 (actual)
End of data collection (LPLV)*	Dec 2024
Interim report 1	Sep 2017 (actual)
Interim report 2	Sep 2019
Registration in the EU PAS register	17 Aug 2014 (actual)
Final report of study results**	Jun 2025

* The observation period ends after the last patient alive has been followed up for 7 years after treatment or has died, has withdrawn consent, or was lost to follow-up.

** 6 months after LPLV

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; 10 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 5 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 in 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. 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 as osteoclasts on the other hand [11].

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. 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.

There is also little or limited information on the timing of progression and management of progression in the clinical setting for this patient population, based on a review of the literature and a search of the www.clinicaltrials.gov data base (only 39 studies reported, with few completed and those being of a small sample size). Approximately 50% of patients with bone-metastatic prostate cancer die of prostate cancer within 30 months, and 80% within 5 years [13]. Time to progression has been and continues to be of interest as a potential surrogate marker in other solid tumors [14] [15] [16].

The active moiety of Xofigo, a bone-targeted radiopharmaceutical, is the isotope Radium-223 (as Radium-223 dichloride) that mimics calcium and selectively targets bone, specifically

areas of bone metastases, with high-energy, short-range alpha-particles. Xofigo is indicated for the treatment of castration-resistant prostate cancer patients with bone metastases [17].

A Phase III, double-blind, randomized, BC1-06, ALSYMPCA (**Al**pharadin in **Sym**ptomatic **P**rostate **Ca**ncer) trial was started in 2008 [18]. 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 (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 significantly improved OS compared to placebo (the median OS was 14.0 vs. 11.2 months, respectively; hazard ratio [HR] = 0.695; p=0.00185). Symptomatic skeletal events (SSE) were lower in the Radium-223 arm, and time to first SSE was significantly delayed (the median time to SSE was 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 patients who received Radium-223; 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 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 (Functional Assessment of Cancer Therapy-Prostate [FACT-P] total score; p=0.006) [19]. Post hoc analyses of pain parameters and pain-related QoL revealed that in addition to prolonging survival, Radium-223 reduced 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 [20].

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.

As of the updated analysis for safety (cut-off 10 October 2014), 479 patients (77.5%) in the Radium-223 group, 224 patients (74.4%) in the placebo group, and 15 patients (62.5%) in the crossover group died during the 3-year follow-up period [17].

Overall, treatment-emergent SAEs were experienced by fewer patients (47.2%) in the Radium-223 group than patients in the placebo group (61.1%) or the crossover group (62.5%); total number of events was 685, 393, and 21 for the Radium-223 group, the placebo group, and the crossover group, respectively. The most common (≥ 5% in either group) treatment emergent SAEs were consistent with the disease itself such as malignant neoplasm progression (10.8%, Radium-223; 12.6%, placebo; 8.3%, crossover); bone pain (10.2%,

Radium-223; 16.6%, placebo; 4.2%, crossover); anemia (8.2%, Radium-223; 8.3%, placebo; 4.2%, crossover); and spinal cord compression (3.5%, Radium-223; 5.3%, placebo; 4.2%, crossover). All other treatment-emergent SAEs occurred in < 5% of patients. No significant differences in individual treatment-emergent SAEs were reported for patients between the treatment groups.

Since efficacy of Radium-223 solution for injection is achieved by distribution of Radium-223 to bone with high metabolic activity such as bone metastases, and localized internal radiation, the possibility of long-term radiation effects to adjacent bone marrow and normal bone tissue was specifically evaluated during the follow-up period.

Post-treatment follow-up of adverse events was performed in ALSYMPCA. Only AEs considered treatment related by the investigator were reported in the period from 12 weeks after last injection in the ALSYMPCA study. In total, 27 patients in the Radium-223 group, 8 patients in the placebo group, and 2 patients in the crossover group reported related post-treatment AEs. Anemia was reported by 11 patients in the Radium-223 group and 5 patients in the placebo group. Thrombocytopenia was reported by 3 patients in the Radium-223 group, and by none in the placebo group. Neutropenia was reported for 2 patients in the Radium-223 group, no patient in the placebo group, and 1 patient in the crossover group. Leukopenia was reported for 2 patients in the Radium-223 group. Neutropenic sepsis and pancytopenia was reported by 1 patient in the crossover group. Aplastic anemia was reported by 1 subject in the Radium-223 dichloride group (1/27, 3.7%). Cardiopulmonary failure was reported by 1 patient (0.3%, 1/301) in the placebo group, and no patient in the Radium-223 dichloride group or the crossover group. Multi-organ failure was reported by 1 patient in the Radium-223 dichloride group [17].

Long-term toxicity was assessed in ALSYMPCA. From Follow-up Visit 1 and onwards, specific diseases were assessed including acute myelogenous leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer, or primary cancer in other organs. The following cases were reported as post-treatment follow-up AEs: a case of bladder cancer (Radium-223 patient at Follow-up Visit 1); squamous cell carcinoma of the left hand (placebo patient at Follow-up Visit 2); skin cancer (placebo patient at Follow-up Visits 7 and 8); squamous cell carcinoma of the skin (crossover patient at Follow-up Visit 1); adenocarcinoma rectum and adenocarcinoma sigmoideum (placebo patient at Follow-up Visit 4); lymph node metastases not originating from prostate cancer (Radium-223 patient at Follow-up Visit 6); and meningioma (crossover patient at Follow-up Visits 2). Aplastic anemia (Radium-223 patient at Follow-up Visits 5 and 6) was also reported as Post-treatment follow-up AE/SAE. All events were regarded as not related to study drug by the investigator [17].

In summary, the safety and tolerability of Radium-223 did not show new or unexpected changes in the safety profile in ALSYMPCA [17].

Data from the Surveillance Epidemiology and End Results (SEER) Program cancer registry (1973-1993) [21] 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 year 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) Radium-223 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 peak of development of secondary tumors was observed between 7 and 8 years [22].

In response to the Food and Drug Administration (FDA) and European Medicine Agency (EMA) post-marketing requirements, the Marketing Authorization Holder (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 non-intervention 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 was conducted by the MAH. 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.

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), and 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 [23].
- To assess the incidence of bone fractures and bone associated events (e.g. osteoporosis).

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 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 and Latin America (Argentina, Austria, Belgium, Canada, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Luxembourg, Mexico, Netherlands, Portugal, Spain, Sweden, United Kingdom, United States) 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. Radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone. The option of starting a bone health agent (BHA) including bisphosphonates or denosumab should be considered, taking into consideration applicable guidelines.

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 AEs (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 10.3.1

9.1.2 Secondary Endpoint(s)

- The 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 BPI-SF questionnaire.
- Bone fractures and bone associated events (e.g. osteoporosis), regardless of investigator assessment of causality, based on AEs.

9.1.3 Strengths of the study design

This is an international, prospective, observational, cohort study of CRPC patients 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 representative to the general CRPC patients with bone metastasis as possible.

9.2 Setting

The study will be conducted by Bayer 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

In this observational study, withdrawal from the study is independent of the underlying therapy and will not affect the patient's medical care. Each patient may withdraw from the study at any time and without giving a reason. If a patient wants to terminate the study participation, no further data will be collected. However, the patient will be asked whether he agrees that the data collected so far can be used. In case the patient does not agree, his data will be deleted from the study database and will not be used for any study-related analysis. In case a patient would like to withdraw the consent given earlier, he should inform his doctor and the site should document the withdrawal and the extent of withdrawal in the eCRF as well as in the patient's medical records.

9.2.5 Replacement

Patients will not be replaced after drop out.

9.2.6 Representativeness

No further selection than outlined in Sections 10.2.1-10.2.3 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, tumor staging information, co-morbidities, prior medication, and concomitant medication). Treatment information and potential outcomes (second primary malignancy, other safety information, OS, and progression (defined as first progression after initial treatment with Radium-223) 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 3 months (M), 6M, 12M, 24M, 36M, 48M, 60M, 72M, and 84M to collect information regarding the outcomes of interest (second primary malignancy, other safety information, OS, and progression). 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 therapy[b] (prior, concomitant, subsequent)	X	X	X	X
Exposure Treatment (Radium-223)		X		
Adverse Events[c]		X	X	X
Laboratory parameters	X	X	X[d]	X[d]
Progression[e]		X	X	X
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 up to 6 months after the last dose administration.

[b] Anti-cancer therapy includes antihormonals, chemotherapy, radiotherapy, immunotherapy, bone health agents (e.g.bisphosphonates / denosumab) and/or re-treatment with Radium-223. See

Section 10.3.6.

[c] 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.
AEs of bone fractures and bone associated events 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.

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

[e] Only the first progression post treatment needs to be collected.

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 first. 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 an SAE as follows:

  - 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 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.
- Patients with a platelet count or white blood cell count (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):**

Overall survival is defined as the time interval from the start of Radium-223 therapy to death due to any cause. Patients whose death is not confirmed at the time of data-cut 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. Completion of the BPI-SF questionnaire by the patient is voluntary.

- **Bone fractures and bone associated events**

Incidence of bone fractures and bone associated events (e.g. osteoporosis), regardless of investigator assessment of causality, reported as AEs.

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)
- 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 Eastern Cooperative Oncology Group (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 are to be documented in the Medical History/ Concomitant Diseases section of the CRF. The patient's medical history from the last 10 years prior to the start of the study (defined as Baseline visit) will be collected.

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

9.3.6 Prior and concomitant medication

All medications taken before study start (initiated and stopped before study start [defined as Baseline visit]) are termed prior medications.

All medications taken in addition to the study drug for any indication (either initiated before study start [Baseline] or during the study) are termed concomitant medications.

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

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 and 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) are to include: trade name or

International Nonproprietary Name (INN), start date, stop date/ongoing, dose, unit, frequency, and indication.

Information to be collected for co-medication at baseline includes: trade name or INN, start date, stop date/on-going, dose, unit, frequency, and indication. Information to be collected for concomitant and subsequent medication includes: trade name or INN, start date, stop date/ongoing, dose, unit, frequency, and 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 related treatment including antihormonals (e.g. LHRH analogues, antiandrogens, abiraterone, enzalutamide), chemotherapy (e.g.docetaxel, cabazitaxel), radiotherapy, immunotherapy (incl. sipuleucel-T), bone health agents (bisphosphonates, denosumab) and/or re-treatment with Radium-223.
- Therapeutic radiopharmaceuticals

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 visits.

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

Not applicable (N/A)

9.3.9 Visits

- Date of visit/contact

9.3.9.1 Baseline

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.

At baseline, medical history, cancer history, demography, disease characteristics, vital signs, prior and concomitant medication, prior diagnostic and therapeutic procedures are documented. Following local routine medical practice, laboratory parameters will be documented.

Level of analgesic pain management will be assessed, starting before the first injection of Radium-223, based on concomitant medication data collected at these visits.

9.3.9.2 Treatment phase

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

Data on progression will be collected. Changes in anti-cancer therapy will be documented.

Safety data will be collected as specified in Section 10.3.1 and Section 10.3.2.

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

Level of analgesic pain management will be assessed at each treatment visit, based on concomitant medication data collected at these visits.

Paper patient questionnaires (BFI-SF) will be collected at each treatment cycle and will be entered into the database by the CRO.

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, and 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 10.3.1 and Section 10.3.2.

Data on progression will be collected. Changes in anti-cancer therapy will be documented.

Pain measurement will be assessed up to and including the 6M follow-up visit. Level of analgesic pain management will be assessed at each follow-up visit until 6 months after the last injection of Radium-223 based on concomitant medication data collected at these visits.

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.

The designated CRO will remind physicians/sites when collection of follow-up information is due with email documentation reminder.

9.3.10 Laboratory parameters

Following local routine medical practice, laboratory parameters will be documented, e.g. sodium, potassium, chloride, calcium, phosphate, magnesium, aspartate transaminase (ASAT,) alanine transaminase (ALAT), lactate dehydrogenase (LDH), gamma-glutamyltranspeptidase (GGT), creatinine, urea, bilirubin, albumin, ALP, PSA, protein,

hematocrit, hemoglobin, platelet counts, red and white blood cell counts, and differential white blood cell count. 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 platelet 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 to be followed until resolution at a frequency based on local clinical practice.

9.3.11 Progression

Progression is defined as first progression after initial treatment with Radium-223. The type of progression (as assessed by the physician) will be collected. This may include symptomatic skeletal events (SSEs), prostate specific antigen level (PSA), radiological imaging, or other unequivocal clinical progression.

Progression defined as SSE includes any of the following: the use of EBRT to relieve skeletal symptoms, new pathological bone fractures (vertebral or non-vertebral), occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention.

Progression defined as increase of PSA level and/or radiological progression is solely based on physician's assessment.

Progression does not include second primary malignancies, tumor-related death, or death from any cause.

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), and 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 was performed for the selection of potential data source(s) to generate reference incidence data on second primary malignancies in mCRPC patients. Three population-based studies on the background rates of second primary malignancies were conducted in Germany, Sweden and in the US.

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 ongoing.

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 for 1,200 patients). Based on the current data from the Phase III study ALSYMPCA and SEER data [21], 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 (CI) for the rate of second primary malignancy (based on the exact binomial distribution) for different observed incidence proportion with 1,200 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

LCL=lower confidence limit; UCL=upper confidence limit

With 1,200 patients, if the observed incidence proportion is between 1.1% and 6.9%, the width of a 95% CI 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 Standard Operation Procedures (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 10.8.

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, and 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. In addition, the 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% CI will be provided.

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

In addition, descriptive summaries of KM estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% 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% CI.

- 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

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.

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

  Information for therapeutic or prevention measures, treatment modalities will also be summarized.

- Incidence of abnormal platelet count or WBC.

  This 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 means and change from baseline, for the pain severity and pain intensity and the items that 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.

9.7.5.3 Bone fractures and bone associated events

For bone fractures and bone associated events, the incidence proportion and EAIR will be summarized, along with the exact 95% CI.

Fracures will be identified based on MedDRA coding system.

9.7.6 Comparison with external reference secondary data sources

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

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% CI assuming the observed number of second primary malignancy cases.

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

Safety variables are indicated as primary or secondary outcomes.

Analyses of further variables will be detailed in the SAP, as appropriate.

9.7.8 Analysis of other data

Descriptive summaries of KM estimates and KM curves will be presented for time to progression (TTP) (Section 10.3.11 for definition of progression). Time to progression is defined as the time interval from the day of the first dose to the date of first progression. Second primary malignancies and death will not be counted in the analysis for progression. Patients who do not have a progression at the end of the study will be censored at the date of their last evaluable assessment.

Further details will be described in the SAP.

9.7.9 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.

9.7.10 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.

9.7.11 Loss of follow-up

A patient is considered “lost to follow-up” if during the course of the study no further follow-up data can be retrieved and/or if at the time of End of Observation no further data collection is possible.

A low “lost 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. The aim is to keep the total loss to follow-up at the end of the study as low as possible.

The designated CRO will remind physicians/sites when collection of follow-up information is due with email documentation reminder. The local conduct responsible is in the loop for the reminder, and will follow-up and coordinate with the sites afterwards. Site personnel should apply due diligence – within the applicable standard patient care procedures – to contact patients to ascertain the reason for lost-to-follow-up.

In case the site personnel obtains knowledge that the patient is lost to follow-up due to transfer to another hospital, a hospice or has died, site personnel should apply due diligence to retrieve information required for the End of Observation documentation (e.g. second primary malignancies) or date of death, if applicable. Although a patient 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 [24].

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.

Adverse events and SAEs 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 AEs, 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 DMP. The same plan will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request.

Medical Review of the data will be performed according to the Medical Review Plan (MRP). The purpose of the Medical Review is to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on the Medical review will be described in the MRP, which is available upon request.

A final database will be declared when all data have been entered, the data entry verified, the data validated, and a final SAE reconciliation has taken 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) [25]. The documentation is available upon request.

9.8.2 Quality review

Quality review will be done in two steps: in the first step the site's training status will be assessed via standardized telephone interviews. In the second step, source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the OS protocol and verification with source documents.

Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request (see Table 4, Annex 1).

9.8.3 Storage of records and archiving

The initiator of the study 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 [26]). Recommendations given by other organizations will be followed as well (e.g. European Federation of Pharmaceutical Industries and Associations [EFPIA] [27], European Network of Centers in Pharmacoepidemiology and Pharmacovigilance [ENCePP] [28]). International Conference of Harmonisation - Good Clinical Practice [ICH-GCP] guidelines will be followed whenever possible [29].

In addition, the guidelines on good pharmacovigilance practices (GVP module VI [30] and since the study qualifies as a PASS, GVP module VIII [31], [32]) will be followed.

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

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

10.4 Patient information and consent

Before documentation of any data, informed consent is obtained by the patient in writing. 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 physician.

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 patient will be kept confidential and will not be made publicly available. Patient names will not be supplied to the initiator. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the initiator. Study findings stored on a computer will be stored in accordance with local data protection laws.

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

11. Management and reporting of adverse events/adverse reactions

11.1 Definitions

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 [29].

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 event
- 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 (hospitalization 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 patient 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 patient and may require intervention to prevent another serious condition.

Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

Progression of the underlying disease itself does not qualify as an AE. However, if progression of the underlying disease leads to signs and symptoms that fulfill the criteria of seriousness, these should be documented as SAEs. In this case progression of the underlying disease should be mentioned in the comment section of the AE report form.

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 Bayer within 7 calendar days of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within 1 business day 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 treatment related AE/SAE ends with the completion of the treatment phase (including 30 days after last administration of Radium-223) of the patient.

All post treatment grade 3/4 hematological toxicities are collected up to 6 months after the last administration of Radium-223.

As long as the patient has not received any Radium-223, AEs /SAEs do not need to be documented as 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, primary bone cancer or any other second primary malignancy must be reported as SAEs at any time, and regardless of the causality assessment. All bone fractures and bone associated events such as osteoporosis need to be reported as either AE(s) or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

If a pregnancy occurs in a female partner of a study patient during the study, although it is not a serious adverse event itself, it should be documented and forwarded to Bayer within the same time limits as a serious adverse event. The result of a pregnancy will be followed-up according to applicable Bayer SOPs.

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).

Patients with a platelet count or white blood cell count (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.

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 Bayer; 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 Bayer 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 a physician, 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 EU PAS register at "http://www.encepp.eu/encepp_studies/indexRegister.shtml". Results will be disclosed in a publicly available database within the standard timelines.

For this mandated PASS, progress reports will be submitted with each Periodic Safety Update Report (PSUR) or in the agreed frequency and content 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. Good Publication Practice [GPP] Guidelines [33], Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] [34]). 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	living document available from NIS Base system	List of all active physicians
2	16913_REASSURE_CRF_V10.0_20180322	22 Mar 2018	CRF
3	16913_REASSURE_DMP_V1.0_signed	14 Aug 2014	Data Management Plan
4	16913_REASSURE_SAP IA1 V1.0	8 Nov 2016	Statistical Analysis Plan
5	16913_REASSURE_QRP_V 3.0_20170731	31 Jul 2017	Quality Review Plan
6	16913_REASSURE_Medical Review Plan V3.0_final	18 Jan 2018	Medical Review Plan
7	Reassure SC members		List of Steering Committee Members

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 3); adopted by the ENCePP Steering Group on 01/07/2016.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☒	☐	--
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	--
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	--

Comments:

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	7
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7, 9.1
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.1, 9.3, 9.7
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	--
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.2

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	7
	4.2.2 Age and sex?	☒	☐	☐	9.2
	4.2.3 Country of origin?	☒	☐	☐	9.1
	4.2.4 Disease/indication?	☒	☐	☐	7, 9.2
	4.2.5 Duration of follow-up?	☒	☐	☐	9.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	--

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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 drug?	☐	☐	☒	--

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.1, 9.1.2, 9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒☐	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	--
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	--

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☒	☐	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☒	☐	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.7.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.7.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

Section 9.7.9 addresses bias in general

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3, 9.4.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3, 9.4.1
9.1.3 Covariates?	☐	☒	☐	--
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4.1
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☒	☐	--
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.8.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.4, 9.8.1
9.3.3 Covariates?	☐	☒	☐	--
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	--

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.1
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.3 Are stratified analyses included?	☒	☐	☐	9.7.1

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8.1
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☐	
12.1.2 Information bias?	☐	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.5
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.3

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.3 Have data protection requirements been described?	☒	☐	☐	10.6

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Section 5, App. 4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: PPD

Date: 20/09/2018

Signature: PPD

Annex 3. Signature pages

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS7187
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer AG, Kaiser-Wilhelm-Allee 1; 51373 Leverkusen; Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
Role	PPD
Name	PPD PPD

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

Date, Signature: 27-Aug-2018, PPD

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS7187
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer AG, Kaiser-Wilhelm-Allee 1; 51373 Leverkusen; Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
Role	PPD
Name	PPD

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

Date, Signature: 20-Aug-2018, PPD

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS7187
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
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Role	PPD
Name	PPD

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

Date, Signature: 20/Aug/2018, PPD

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
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Role	PPD
Name	PPD

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

Date, Signature: Aug 27, 2018 PPD

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
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Role	PPD
Name	PPD

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

Date, Signature: 25-Oct-2018 , PPD

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS7187
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer AG, Kaiser-Wilhelm-Allee 1; 51373 Leverkusen; Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
Role	PPD
Name	PPD

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

Date, Signature: 20 Aug 2018 , PPD

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
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Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer AG, Kaiser-Wilhelm-Allee 1; 51373 Leverkusen; Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
Role	PPD
Name	PPD

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

Date, Signature: 20-AUG-2018 PPD

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS7187
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer AG, Kaiser-Wilhelm-Allee 1; 51373 Leverkusen; Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
Role	PPD
Name	PPD

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

Date, Signature: 26 Aug-2018 PPD

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	5.0, 26 APR 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS7187
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer AG, Kaiser-Wilhelm-Allee 1; 51373 Leverkusen; Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
Role	PPD
Name	PPD

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

Date, Signature: Aug 28, 2018 PPD

Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Protocol version and date	5.0, 20 Aug 2018
IMPACT study number	16913
Study type / Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS7187
Active substance (medicinal product)	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride (Xofigo®)
Marketing authorization holder(s)	Ex-USA: Bayer AG, Kaiser-Wilhelm-Allee 1; 51373 Leverkusen; Germany USA: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ, USA
Role	PPD
Name	PPD

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

Date, Signature: 04 SEPTEMBER 2018, PPD

Annex 4. Description of Amendments

Table 5: Description of Amendments

AM01: 18 January 2016

Protocol Section	Description
General	General formatting, defining abbreviations and updating abbreviations list, correcting spelling, grammar, and terms for consistency was performed throughout. Changed terms from subject to patient, sponsor to initiator, and investigator to physician to comply with terminology convention for non-interventional studies.
Header	Changed logo and Bayer HealthCare to Bayer logo
Title	Corrected for consistency to include non-intervention throughout.
Author	Author changed from PPD to PPD throughout
Section 3: Responsible Parties	Updated to indicate change of contacts: PPD : from PPD to PPD PPD : from PPD to PPD, and PPD : from PPD to PPD
Section 4: Abstract	Added to Rationale and Background time to progression will be assessed and that the study was being conducted at the request of regulatory authorities. Corrected for consistency with study design by removing "non-interventional" as the statement already includes observational. Added progression and treatment post progression to variables and data analysis.
Section 6: Milestones	Updated end of recruitment and added date of EU PAS registration.
Section 7: Introduction: Background and Rationale	Added missing reference for bone tissue homeostasis. Added text and reference for rationale of collecting timing of progression. Updated ALSYMPCA data with text from updated Investigator's Brochure.
Section 9.3: Variables	Added progression and definition of first progression. Added progression to Table 2 and corrected footnote a.
Section 9.3.2: Variables to determine the secondary endpoint(s)	Added that completion of BPI-SF questionnaire is voluntary.
Section 9.3.5: Co-	Added clarification of study start.

AM01: 18 January 2016

Protocol Section	Description
morbidities (medical history, concomitant diseases)	
Section 9.3.6: Prior and concomitant medications	Added clarification of study start.
Section 9.3.9.1: Baseline	Reordered text for clarity and ensured all variables being assessed were captured and consistent with CRF and elsewhere in text.
Section 9.3.9.2: Treatment Phase	Added that data on progression and changes in anti-cancer therapy will be documented. Moved text for clarity and ensured all variables being assessed were captured and consistent with CRF and elsewhere in text.
Section 9.3.9.3: Follow-up visit(s)	Added that data on progression will be collected. Moved text for clarity and ensured all variables being assessed were captured and consistent with CRF and elsewhere in text.
Section 9.3.11: Progression	New section added to address time to progression and defining progression may be defined by the physician, including SSEs, PSA, RECIST 1.1, or other types of progression. Definition of progression by SSE and PSA added; use of PCWG 2 or 3 for other progression, specifically bone lesions. Defined what is not considered progression: second primary malignancies, tumor-related death, or death from any cause.
Section 9.7.8: Analysis of other data	New section added to address time to progression, defining progression TTP as time interval from day of first dose to date of first progression, and how data will be analyzed (descriptive summaries of KM and KM curves). Second primary malignancies and death will not be counted in the analysis for progression.
Section 9.7.11: Loss of follow-up	Text deleted that was no longer applicable: "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." "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."
Section 9.8.1 Data Quality	Text added for Medical Review Plan to comply with updated protocol template.
Section 11 Management and reporting of adverse events/adverse reactions'; subsection	Deleted "worsening of a sign or symptom of the condition under treatment or of a concomitant illness" as progression is not an adverse event in this study. Added text to this section to further clarify.

AM01: 18 January 2016

Protocol Section	Description
11.1: Definitions	
Section 11.2: Collection	Text added reporting and recording requirements regarding pregnancy in a female partner of a study patient per applicable Bayer SOPs.
Section 13: List of references	New references added to support new text in introduction and rationale.
Annex 1: List of stand-alone documents	Table 4: Amendment and Medical Review Plan added.
Annex 3: Signature pages	Title corrected; version and date updated; signatories updated as appropriate.
Annex 4: Description of Amendments	New annex added for amendment.

AM02: 07 June 2018

Protocol Section	Description
General	Protocol was updated to reflect changes in timelines(actual), to adopt the most current template, to add administrative changes and to remove inconsistencies. Enrollment was terminated in all countries except for Argentina, Colombia, and Mexico in Mar 2017. Global LPFV was changed to Q4 2017 (31 Dec 2017) to allow for continued enrollment in Latin America only (regulatory obligation). Reporting of all bone fractures and bone associated events (e.g. osteoporosis) was added as either AE(s) or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment, through the long-term follow-up. Additionally, the following was specified: Radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone. The option of starting a BHA should be considered, taking into consideration applicable guidelines.
Title page	Update of version and date, addition of EU PAS register number, study phase, change in name of study initiator, change in countries of study, change in author and MAH contact person
Section 3: Responsible	Updated to indicate change of contacts:

AM02: 07 June 2018

Protocol Section	Description
Parties	PPD : from PPD to PPD PPD : from PPD to PPD , PPD : from PPD to PPD and PPD PPD : from PPD to PPD PPD : from PPD to PPD PPD : from PPD to PPD PPD : from PPD to PPD and PPD : from PPD to PPD
Section 4: Abstract	Addition of study phase, update of version and date, change in author, addition of evaluation of bone fractures in the section on background and rationale, in the section on research question and objectives and in the section variables, change in countries of study and dates for study milestones (end of recruitment and data collection, final report of study results)
Section 6: Milestones	Change in dates for study milestones (end of recruitment and data collection, final report of study results)
Section 8.1 Primary objective	Correction of text by adding “serious” to “To assess the incidence of treatment-emergent serious adverse events (TESAEs)”
Section 8.2 Secondary objectives	Addition of “To assess the incidence of bone fractures and bone associated events (e.g. osteoporosis)”
Section 9.1	Addition of Latin America and country specifications (Argentina, Austria, Belgium, Canada, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Luxembourg, Mexico, Netherlands, Portugal, Spain, Sweden, United Kingdom, United States). Addition of “Radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone. The option of starting a bone health agent (BHA) including bisphosphonates or denosumab should be considered, taking into consideration applicable guidelines.”
Section 9.1.2 Secondary Endpoints	Addition of a secondary endpoint: • Bone fractures and bone associated events (e.g. osteoporosis), regardless of investigator assessment of causality, based on AEs.
Section 9.2.4	Update of the section according to current template and process.

AM02: 07 June 2018

Protocol Section	Description
Withdrawal	
Section 9.3: Variables	Update of footnotes to Table 2 to reflect collection of data for bone fracture and bone associated events
Section 9.3.2: Variables to determine the secondary endpoint(s)	Correction of description of censoring for overall survival to "Patients whose death is not confirmed at the time of data-cut will be censored at the last date known to be alive." Addition of variable bone fracture and bone associated events
Section 9.3.3: Demography	"Sex" was deleted
Section 9.3.6 Prior and concomitant medication	Update of relevant prostate cancer therapy variables collected in the categories stated.
Section 9.3.9.2 Treatment phase	Addition of reference to Section 9.3.2
Section 9.3.9.3 Follow-up visits	Addition of reference to Section 9.3.2 Addition of "email documentation reminder."
Section 9.3.11. Progression	Updates of definitions
Section 9.4.2 External reference secondary data sources	Update of date on external sources
Section 9.7.4 Analysis of primary outcome	Deletion of definition of "number of patients at risk" Deletion of specification of sensitivity analysis. Deletion of "(up to 6 months after last administration of Radium-223 as AEs/SAEs)" concerning incidence of post treatment grade 3/4 hematological toxicities.
Section 9.7.5 Analysis of secondary data	Addition of Section 9.7.5.3 Bone fractures and bone associated events "For bone fractures and bone associated events, the incidence proportion and EAIR will be summarized, along with the exact 95% CI. AEs will be summarized using the MedDRA and the CTCAE (Version 4.03) coding system. AEs will be categorized and summarized according to relation, seriousness, CTCAE grade, discontinuation of therapy, action taken, and outcome."

AM02: 07 June 2018

Protocol Section	Description
Section 9.7.6 Comparison with external reference secondary data sources	Deletion of "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)."
Section 9.7.7 Analysis of safety data	Addition of "or secondary" Addition of "Analyses of further variables will be detailed in the SAP, as appropriate."
Section 9.7.11 Loss to follow-up	Updated text on loss to follow up
Section 9.8.1 Data quality	Deleted part of the text on monitoring
Section 9.8.2 Quality review	Updated text on quality review
Section 10.2 Regulatory authority approvals/authorizations	Updated based on new template and added text on GVP modules.
Section 10.3 IEC and IRB	Updated text on IEC/IRB approval
Section 10.6 Confidentiality	Added text (on investigator maintaining patient records) from latest template
Section 11.2 Collection	Added text on the collection of AEs based on all bone fractures and bone associated events. Added text about "platelet count or white blood cell count (WBC) less".
Section 12 Plans for disseminating and communicating study results	Addition of details on the EU PAS register and PSUR submission

AM02: 07 June 2018

Protocol Section	Description
Annex 1: List of stand-alone documents	Table 4: Update of the documents, dates and document reference numbers.
Annex 2: ENCePP checklist of study protocols	Update of ENCePP checklist to revision 3, 01/07/2016
Annex 3: Signature pages	Title updated; version and date updated; EU PAS register number added, signatories updated as appropriate.
Annex 4: Description of Amendments	Annex for amendment updated with the specifications of Amendment 02.