Post Authorization Safety Study (PASS) Information

Acronym / Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Protocol version identifier	4.0
Date of last version of protocol	30 April 2018
IMPACT study number	18043
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Radiopharmaceuticals (V10XX03), Radium-223 dichloride
Medicinal product	Xofigo®
Product reference	EU/1/13/873/001
Procedure number	N/A
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Research question and objectives	This observational prospective single arm cohort study is designed to examine overall survival, symptomatic skeletal event free survival and quality of life of metastatic Castration Resistant Prostate Cancer (mCRPC) patients receiving Radium-223 under real life conditions. In addition, time to next tumor treatment (TTNT), mobility, quality of life and self-care (Moses-Questionnaire), independence in activities of daily living and safety will be examined.

Country(-ies) of study	Germany
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Marketing authorization holder

Marketing authorization holder(s)	Bayer Pharma AG, 13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
MAH contact person	Dr. Juliane Brendel Bayer Vital GmbH, Medical Department Building K56, 51368 Leverkusen, Germany

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

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

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2 List of abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse Event
BHA	Bone Health Agent
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer (clinical trial)
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CRPC	Castration-Resistant Prostate Cancer
DMP	Data Management Plan
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
ES	External Supplier
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy Quality of Life Measurement in prostate cancer patients
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
HEOR	Health Economics and Outcomes Research
HR	Hazard Ratio
ICH	International Conference of Harmonization
IDMC	Independent Data Montoring Committee

IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
Katz	Katz Index of Independence in Activities of Daily Living (ADL)
LPFV	Last Patient First Visit
MAH	Marketing Authorization Holder
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MOSES	ICF-oriented, adaptive physician assessment instrument of mobility, self-care, and domestic life
N/A	Not Applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OS	Overall Survival
PASS	Post-Authorization Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PSA	Prostate Specific Antigen
QoL	Quality of Life
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SSE	Symptomatic Skeletal Event
SSE-FS	Symptomatic Skeletal Event Free Survival
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEAE	Treatment Emergent Adverse Event
TTNT	Time To Next Treatment
WHO DD	World Health Organization Drug Dictionary

3 Responsible parties

3.1 Sponsor / MAH

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3.2 Collaborators / Committees

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

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

4 Abstract

Acronym / Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
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Author	Dr. Juliane Brendel Bayer Vital GmbH, Medical Department Building K56, 51368 Leverkusen, Germany
Rationale and background	Prostate cancer is the most common non-cutaneous malignancy in men in Germany. In advanced prostate cancer, the most common site of metastases is the skeletal system which is involved in more than 90% of the castration-resistant prostate cancer (mCRPC) 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 mCRPC are usually of higher age and may suffer in addition from different age-related comorbidities. These comorbidities will usually reduce their ability to stand efficacious systemic treatment options like chemotherapy if the disease is in an advanced stage with systemic spread. Radium-223-dichloride is a new treatment option with specific targeting to bone lesions for patients with mCRPC with favorable toxicity profile compared with chemotherapy. A distinct overall survival advantage and significant extended time to first symptomatic skeletal event was demonstrated in a large phase III study (ALSYMPCA) in docetaxel pretreated as well as in untreated patients suffering from mCRPC with symptomatic

	bone metastases and no known visceral metastases treated with best supportive care in combination with Ra-223-dichloride or placebo. But data of routine use outside clinical trials or in combination with new drugs with deep androgen ablation are limited. This study is designed to evaluate the overall survival (OS), symptomatic skeletal event free survival (SSE-FS) and safety in relation to comorbidities (assessed by Cumulative Illness Rating Scale-Geriatric (CIRS-G)) and concomitant or sequential use with new drugs with deep androgen signal ablation like abiraterone or enzalutamide. The preservation of quality of live and ability for self-care and participation in daily living activities is of major importance in patients with advanced stage of cancer, like patients with mCRPC. The quality of life will therefore be explored as patient reported outcome using the validated questionnaires FACT-P. An independent rater will judge the independence in activities of daily living by using the Katz-Index and body function in dimensions of "mobility", "self-care" and "domestic life" by using the MOSES questionnaire based on the International Classification of Functioning, Disability and Health (ICF) passed by the World Health Organization (WHO).
Research question and objectives	The primary objective of this study is to evaluate the overall survival during Radium-223 dichloride treatment of mCRPC patients in a real life setting by the treating urologists and oncologists in Germany. The secondary objectives in this study are: • To explore symptomatic skeletal event free survival (SSE-FS) • To examine the incidence of treatment-emergent adverse events (TEAE) (up to 30 days after last administration of Radium-223) • To calculate the incidence of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment and 5 year follow-up period • To explore treatments and time to subsequent mCRPC treatment (TTNT). • To examine the quality of life as patient reported

	outcome using the validated questionnaires FACT-P. • To explore the independence in activities of daily living by using the Katz-Index. • To explore body function in the dimension of "mobility", "self-care" and "domestic life" by using the MOSES questionnaire.
Study design	This study is a prospective, non-interventional, multi-center, single arm cohort study conducted in departments of urology or oncology throughout Germany. It is planned to enroll at least 75 patients with mCRPC with bone metastases in primary data collection.
Population	The study population will consist of mCRPC patients with symptomatic bone metastases without known visceral metastases for whom the attending physician decided according to his/her medical practice to treat the patient with Radium-223 dichloride.
Variables	The investigator collects data on patient's history (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects treatment related data during treatment visits and follow-up visits. The patient questionnaires FACT-P will be used for quality of life assessment at each visit. The treating physician as investigator will assess the independence in activities of daily living (Katz-index) and body function (MOSES questionnaire).
Data sources	Treating physician in Urology or Oncology or designated medical person, Radium-223 administering physician, medical records, routine measurements (e.g. tumor assessment), other physicians, and patient questionnaires.
Study size	The estimates for the expected number of deaths, and the precision of estimates for median OS for a sample size of 75 patients assume an exponentially distributed OS with a median of 20 months, an enrolment period of 36 months, a follow-up period of 60 months after the last Radium-223 injection/treatment of the last enrolled patient (and thus a total observation period of 102 months) and a 10% loss-to-follow-up rate per year.
Data analysis	Statistical analyses will be primarily of explorative and descriptive nature. All analyses will be provided for the complete study population, as well as separately for the chemotherapy

	naïve vs non naïve study population. Patients receiving at least one dose of Radium-223 will be considered valid for safety analysis set. Time to event variables (OS, SSE-FS, TTNT) will be summarized using Kaplan-Meier estimates. Median event times together with the 25th and 75th percentiles and associated 95% confidence intervals will be presented. Analyses of QoL will be performed for patients with evaluable patient questionnaires (FACT-P) at each visit. Descriptive statistics (e.g. means, mean changes) will be provided for each assessment time point. All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version. Incidence of treatment emergent and drug-related AEs will be presented. Additional subcategories will be based on event intensity and relationship to study drug. The study analyses will be descriptive and no formal hypothesis testing will be performed
Milestones	Start of data collection: Q2/2015 End of recruitment: Q2/2018 End of data collection: Q4/2023 Final report of study results: Q3/2024

5 Amendments

Amendment Number	Reason for Amendment	New version number	Effective Date
AM01	• Reduction of sample size from 500 patients to 250 planned patients due to previously unexpected delays in enrolment. • Extension of enrollment period from 24 months to 40 months. • Number of patients for interim analyses reduced from 100 to 75 and from 400 to 180, respectively. The reduction of patient number and elongation of recruitment period were calculated by taking into account the patient availability under real life conditions which differs from the initial site feasibility statements significantly: Initial feasibility statements were 8 patients per site per year. A follow-up assessment 1 year after FPFV showed that the number of eligible patients was only between 0-6 per site and year in reality. More sites are planned to be opened after recruitment of the two other Xofigo® NIS PARABO and REASSURE ended recruitment in Germany (Q1/2017) to reach a site number of 100-125. The intended increase of study sites in 2017 has been taken into account for the calculation of the time needed to enroll 250 patients. With 100 sites becoming active during 2017, the aim to enroll 250 patients until Q3 2018 is from today`s point of view a realistic estimate.	V 2	23 February 2017
AM02	• Deletion of 2nd exclusion criterion to allow for enrollment of chemotherapy pretreated patients • Addition of (S)AE exception "disease progression" • Provision that all analyses will be provided for the complete study population, as well as separately for the chemotherapy naïve vs non naïve study population. The reason for this amendment is to allow the enrollment of chemotherapy pretreated patients based on the observation that the mCPRC therapy landscape in Germany has changed significantly since study start. Chemotherapy with Docetaxel in combination with conventional androgen ablation therapy will now be offered to all suitable patients with hormone sensitive metastasizing prostate cancer (about 20% of all patients). In addition	V 3	14 August 2017

	chemotherapy with Docetaxel is now increasingly used in earlier lines of therapy in suitable mCRPC patients (younger and without important comorbidities) to delay the development of a disease which is refractory to androgen receptor targeted therapies. The inclusion of chemotherapy pretreated patients more likely allows to draw conclusions about the safety and efficacy under real world conditions and not only in a subgroup of Xofigo® patients.		
AM 03	• Study was changed to a post authorization safety study (PASS) as a consequence of the fact that fractures have been classified as an "important potential risk" as one result of the interim analysis of the ERA-223 study. • Initiation of BHAs including bisphosphonates or denosumab, should be considered by investigator. • Early stop of recruitment period in Q2 2018 due to low patient enrolment. Sample size considerations were therefore adapted to a sample size of 75 patients and initially planned interim analyses were cancelled due to reduced sample size. • Prolongation of follow-up period for up to 5 years after last Radium-223 treatment. • Removal of subgroup analyses (with exception of presenting patients previously treated versus not previously treated with chemotherapy). • Addition of secondary objective to calculate incidence of pathological fractures, non-pathological fractures and bone associated events during the treatment and 5 year follow-up period. • The wording regarding the withdrawal has been updated. The reason for this amendment is a request by the PRAC to amend all study protocols in ongoing Xofigo studies based on the findings of the interim analysis of the ERA-223 study. The collection of pathological fractures, non-pathological fractures and bone associated events (e.g. osteoporosis) during the treatment and 5 year follow-up period will provide more safety insights from routine practice.	V 4	30 April 2018

6 Milestones

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

Table 1: Milestones

Milestone	Planned date
Start of data collection	01 May 2015
End of data collection	31 December 2023
Registration in the EU PAS register	Q2 2018
Database cleaned	31 March 2024
Final report of study results	30 September 2024

7 Introduction: Background and Rationale

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

Prostate cancer is unique amongst solid tumors in that the greatest threat to a patient's survival and quality of life is posed by bone metastases rather than visceral involvement. Indeed, nearly all treatments of the advanced stage are directed toward eradicating or limiting osseous metastases or palliating their side effects [4]. Cellular invasion and migration, cell matrix adhesion or cell-to-cell adhesions, interaction with endothelial cells, regulation of growth factors, and stimulation of osteoclasts and osteoblasts are thought to contribute to development of skeletal metastases [5]. Once prostate cancer becomes metastatic, survival of patients depends on the extent of the disease and the site of metastases. The most common site of metastases for advanced prostate cancer is the skeletal system which is involved in more than 90% of the metastatic castration-resistant prostate cancer (mCRPC) 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. $\leq$ 50 ng/dL or 1.7 nmol/L) which can be initially effective controlling the metastases in the bone. However, the majority of patients soon become castration resistant, i.e. progression occurs

even at castration levels of testosterone [8]. At this stage, the disease can interchangeably be referred to as either CRPC or the older term hormone-refractory prostate cancer (HRPC) [9]. The commonly accepted term "CRPC" is used throughout this document. Already early stages of mCRPC with bone metastases are associated with substantial pain and with rising levels of prostate-specific antigen (PSA) as seen in 35% and 90% of patients, respectively. The extent of PSA control after initial ADT affects prognosis: After 7 months of ADT, patients with PSA < 0.2 ng/ml (undetectable) have a better prognosis than patients with PSA ≥ 4 ng/ml [10].

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

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

Radium-223 selectively targets bone metastases with high-energy, short-range alpha-particles. A phase III, double-blind, randomized trial, ALSYMPCA (**Alp**haradin in **Sym**ptomatic **P**rostate **Ca**ncer), was started in 2008 [13]. A total of 921 patients with mCRPC and symptomatic bone metastases who were receiving best standard of care and were post-docetaxel or unfit for or declined docetaxel were randomized (2:1) to receive 6 injections of Radium-223 dichloride (50 kBq/kg intravenous) or matching placebo every 4 weeks. The primary endpoint was overall survival. Main secondary efficacy endpoints were time to first skeletal-related event and various biochemical end points. Based on data of an interim analysis (n=809), the study was unblinded in July 2011, since Radium-223 significantly improved OS, compared to placebo (the median OS was 14.0 vs. 11.2 months, respectively; HR=0.70; p=0.002). The updated analysis (performed in June 2012; n=921) also showed that Radium-223 significantly improved OS compared to placebo (median OS 14.9 vs. 11.3 months, respectively; HR=0.70; p<0.001). Symptomatic skeletal events (SSE) were lower in the Radium-223 arm, and time to first SSE was significantly delayed (the median time to SSE was 15.6 months, versus 9.8 months, respectively; HR= 0.66; p<0.001). A low incidence of myelosuppression was observed, with grade 3/4 events of neutropenia (3%) and thrombocytopenia (6%). Adverse events of any grade were described in 93% of the subjects who received Radium-223 dichloride; versus 96% in the placebo arm (grade 3/4 adverse events were described for 56% and 62%, respectively). Radium-223 dichloride was authorized for marketing in the European Union as Xofigo® in November 2013.

Sub-analysis from ALSYMPCA revealed in addition to the improvement in overall survival a pronounced potential for pain reduction, prolonged time to use of external beam radiation therapy (EBRT) for pain palliation and time to opioid use [14]. The distinct reduction of local symptoms from bone metastases delayed substantially the distortion of quality of life (QoL) compared with placebo [15]. This pronounced reduction in tumor related symptoms is an important benefit for patients in the castration resistant stage of prostate cancer where cure is not an option anymore but good symptom palliation the main focus of any treatment. It is very likely that the extended OS and TTSSE did not only preserve the QOL but also the independence in activities of daily living and body function which may itself build the basis for the perceived long-term preservation in QOL observed in patient treated with Radium-223 dichloride in ALSYMPCA. If this would be the case it is likely that the treatment with Radium-223 dichloride would save substantial costs for patient care in mCRPC patients.

The effect of Radium-223 on the independence in activities of daily living and body function in mCRPC patients was not investigated in the pivotal Phase 3 ALSYMPCA trial but data on QOL were collected in this closely defined patient population according to strict inclusion and exclusion criteria. This non-interventional prospective study is designed to further examine the effect of Radium-223 on QoL and activities of daily living and body function in mCRPC patients in more detail and in a more heterogeneous patient population under routine daily practice conditions in Germany. In contrast to the NIS PARABO, which is focused on the assessment of pain, and the NIS REASSURE, which is focused on the long-term safety for Radium-223 treated patients, this study will collect data on overall survival, time to SSE, QOL and activity of daily living in mCRPC patients. The inclusion of patients for each of the above mentioned NIS will be organized by different groups of physicians and study sites in different areas.

For QoL examination, the questionnaire “Functional Assessment of Cancer Therapy Quality of Life Measurement in patients with prostate cancer” (FACT-P) [28] will be used. The FACT-P questionnaire version 4 is a 39-item questionnaire consisting of five domains; ‘Physical well-being’, ‘Social/Family well-being’, ‘Emotional well-being’, ‘Functional well-being’ and ‘Additional concerns’ (consisting of items relating specifically to prostate cancer and/or its treatment) and uses a 0-4 Likert-scale; recall period of the questionnaire is 7 days [28]. The activities of daily living will be examined using the KATZ index [29] and body function by the MOSES questionnaire [30].

Comorbidities will be captured in all patients using the cumulative illness rating scale for Geriatrics (CIRS-G) [31, 32].

The ERA-223 study, a phase III randomized trial in prostate cancer patients examining radium-223 dichloride versus placebo in combination with abiraterone and prednisone (study number 15396, NCT02043678) was unblinded based on the Independent Data Monitoring Committee (IDMC) recommendation following an ad hoc independent analysis where more treatment emergent fractures, SSE-FS, and total deaths events were observed in the active treatment arm compared with the placebo arm. Based on the available data, the benefit-risk of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in mCRPC is considered unfavorable. The Pharmacovigilance Risk Assessment Committee (PRAC) initiated on 30 NOV 2017 a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data observed in the ERA-233 study. Therefore and in view of the seriousness of the events observed, the PRAC recommended provisional amendments to the product information to contraindicate the use of Radium-223 dichloride in combination with abiraterone plus prednisone/prednisolone. The IDMC also

recommended that during the 5 year follow up period all bone fractures and bone associated events (e.g., osteoporosis) are to be documented regardless of investigator´s causality assessment. This change of product information which was implemented in March 2018 is reflected by the changes made in the protocol with this amendment.
In order to collect comprehensive safety information across all clinical trials with Radium-223 dichloride, in the URANIS study, pathological fractures (as part of symptomatic skeletal events),non-pathological fractures and bone associated events will be assessed in all patients available for safety analysis.
Hitherto in URANIS enrolled patients treated with the combination of Radium-223 and abiraterone plus prednisone/prednisolone will be presented thoroughly and separately to further substantiate any increased risk in bone fractures in those patients.
With the new version of the product information of Radium-223 (dated March 2018), Radium-223 should not be given concurrently with abiraterone plus prednisone/prednisolone.
Based on the available data on Radium-223, the option of starting a bone health agent (BHA) should be considered, taking into consideration applicable guidelines.

8 Research questions and objectives

This observational prospective single arm cohort study is designed to evaluate overall survival (OS) of metastatic Castration Resistant Prostate Cancer (mCRPC) patients receiving Radium-223-dichloride in a real life nuclear medicine practice setting in Germany. In addition, symptomatic skeletal event free survival (SSE-FS), time to next tumor treatment (TTNT), safety, QOL, mobility and self-care, activities of daily living and body function will be explored.

8.1 Primary objective

The primary objective of this study is to evaluate the overall survival during Radium-223 dichloride treatment of mCRPC patients in a real life setting.

8.2 Secondary objective(s)

The secondary objectives in this study are:

- To explore symptomatic skeletal event free survival (SSE-FS).
- To examine the incidence of treatment-emergent adverse events (TEAE) (up to 30 days after last administration of Radium-223).
- To calculate the incidence of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment and 5 year follow-up period.
- To explore treatments and time to subsequent mCRPC treatment (TTNT).
- To examine the QoL as patient reported outcome using FACT-P.
- To explore the independence in activities of daily living by using the Katz-Index.

- To explore body function in dimensions of “mobility”, “self-care”, and “domestic life” (MOSES questionnaire)

9 Research methods

9.1 Study design

This study is a prospective, non-interventional, multi-center, single arm cohort study conducted in 125 departments of urology and oncology throughout Germany. Sites are selected based on the experience of the attending physician with the indication and the treatment with Radium-223. It is planned to enroll at least 75 patients with mCRPC with symptomatic bone metastases without known visceral metastases for whom the attending physician decided according to his/her medical practice to treat the patient with Radium-223 dichloride. Treatment with Radium-223 dichloride should follow the approved product information.

For each patient, the investigator will document data in standardized case report forms at initial, follow-up and final visits during treatment phase. Data will be collected using electronic case report forms (eCRF). The observation period for each patient enrolled in this study is the time from start of therapy with Radium-223 dichloride to death, withdrawal of consent, loss to follow-up or end of this study (maximum of 5 years after last administration of Radium-223), whichever comes first in time.

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

This study uses 2 types of data sources: primary data collection from clinical visits and secondary data based on medical charts. Medical history of mCRPC patients will be collected retrospectively from defined timepoints to capture the clinical course of disease before inclusion in the current trial.

9.1.1 Primary endpoint(s)

The primary endpoints are:

- **Overall survival** is defined as the time interval from the start of Radium-223 dichloride therapy to death, due to any cause. Patients alive at the end of the study will be censored at the last date known to be alive. Date and cause of death will be collected.

9.1.2 Secondary endpoint(s)

The secondary endpoints are:

- **Exploration of symptomatic skeletal event free survival** (SSE-FS) of mCRPC patients is defined as the time from start of treatment to the occurrence of one of the following:

  (1) An on-study SSE, which is defined as:

  - the use of external beam radiotherapy (EBRT) to relieve skeletal symptoms
  - the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)

- the occurrence of spinal cord compression
- a tumor related orthopedic surgical intervention.

(2) Death from any cause

- **Estimation of the incidence of pathological fractures** (as part of symptomatic skeletal events (SSE))**, non-pathological fractures** and **bone associated events** during the treatment and 5 year follow-up period.
- **Time to next tumor treatment(s) (TTNT)** is defined as the time from the last application of Radium-223 until start of next mCRPC treatment including e.g. chemotherapy and/or hormonal treatment.
- **Incidence of treatment-emergent adverse events (TEAE)** up to 30 days after last administration of Radium-223. Patients will be monitored for TEAE using the NCI-CTCAE Version 4.03. Detailed information collected for each TEAE will include a description of the event, duration, whether the event was serious, intensity, relationship to Radium-223 dichloride, action taken and clinical outcome.
- **Quality of life as patient reported outcome** estimated using FACT-P questionnaire. Changes in QOL as determined by patient response on the FACT-P questionnaire. Analyses of QoL will be performed for patients with evaluable patient questionnaires (FACT-P) at each visit.
- **Activities of daily living** explored according to the Katz-Index.
- **Body function** explored in dimensions of “mobility”, “self-care” and “domestic life” using the MOSES questionnaire.

9.1.3 Strengths of study design

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

9.2 Setting

The study will be conducted in up to 125 departments of urology and oncology throughout Germany. Data will be collected from at least 75 patients according to local health authority approved label. The observation period for each patient enrolled in this study is the time from start of therapy with Radium-223 until death, withdrawal of consent, loss to follow-up or regular end of observation which is defined as five years after the last administration of Radium-223 (whatever comes first in time).

9.2.1 Eligibility

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

9.2.2 Inclusion criterion/criteria

- Male patients diagnosed with castration resistant adenocarcinoma of the prostate (CRPC) with symptomatic bone metastases without known visceral metastases
- Decision to initiate treatment with Radium-223 was made as per investigator's routine treatment practice.
- Signed informed consent

9.2.3 Exclusion criterion/criteria

- Patients participating in an investigational program with interventions outside of routine clinical practice and also in all non-interventional studies focusing on Radium-223-dichloride.

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 data. 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 extend of withdrawal in the Case Report Form as well as in the patient´s medical record.

9.2.5 Replacement

Patients will not be replaced after drop out.

9.2.6 Representativeness

No further selection than outlined in Sections 9.2.1 – 9.2.3 should be made and patients should be enrolled consecutively in order to avoid any selection bias. With respect to site selection this study could have potential limited representativeness (at convenience sample) as we would be looking for sites with Radium-223 dichloride 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 (nuclear medicine physician or any other physician licensed in the administration of radioisotopes) or designated medical person at different time points. After the patient and treating physician have agreed on a treatment decision, the patient is informed about the study and has to sign an informed consent in order to participate. Baseline information is recorded with the status before the first Radium-223 dichloride administration during patient visit. Information on predefined retrospective visits will capture the clinical course of disease before inclusion in the current trial. These retrospective visits are defined as time spans of ±4 weeks at 6 months, 12 months, 18 months and 24 months prior the date of informed consent. If the documented data would be outside the

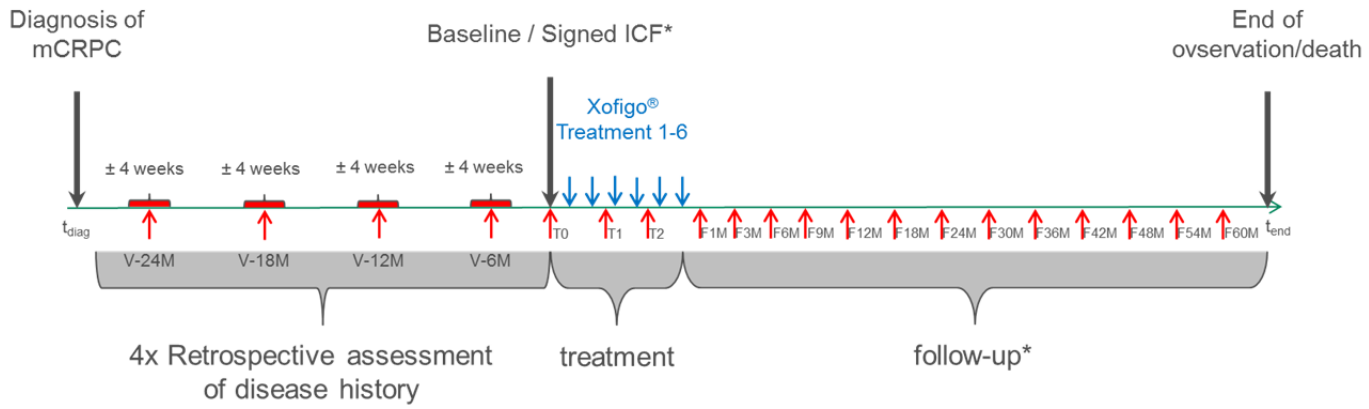
predefined ± 4 weeks for the retrospective visit, the treating physicians are encouraged to document these data under the next closest predefined visit.

Data of first and second visit during treatment will be documented after second and fourth application of Radium-223-dichloride, respectively. The further course of disease will be captured in follow-up visits after end of active treatment with Radium-223-dichloride approximately after 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after end of treatment.

For each treatment cycle, information from patient medical records is documented and entered in the EDC system by the physician or designated medical person. These visits occur during routine clinical practice, the study protocol does not define exact referral dates. The planned schedule of visits for this non-interventional trial is given as an overview on Figure 1.

Figure 1: Overview of scheduled visits

(ICF: Informed consent form; *Additional signed informed consent for prolonged follow-up period (longer than 24 months after end of treatment with Radium-223) is necessary)



Retrospective visit

The retrospective visits are defined as time spans of ±4 weeks at 6 months, 12 months, 18 months and 24 months prior the date of informed consent. It is assumed that retrospective visits will be completed within 2 month after inclusion based on available clinical documentation.

Typical information to be collected at the retrospective visits for the respective time spans includes:

- Date of visit
- Laboratory parameters including ALP, PSA and blood counts
- Prior anti-cancer therapy
- ECOG

Baseline visit

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

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

- Date of visit
- Demography
- Medical history
- Concomitant diseases
- CIRS-G index
- Prostate cancer history
- Concomitant anti-cancer therapy
- Chemotherapy status (naïve / non naïve)
- WHO pain score
- ECOG status
- Pain medication or other concomitant medication
- Patient questionnaire on QoL (FACT-P), filled out by the patient prior to the first injection of Radium-223
- Questionnaires on Activities of daily living (Katz-Index) and Body function (MOSES questionnaire)
- Laboratory parameters including ALP, PSA, blood counts
- Treating nuclear medicine physician

First and Second visit during treatment

Typical information to be collected at second treatment visit includes:

- Date of visit
- WHO pain score
- ECOG status
- Patient questionnaires on QoL (FACT-P), filled out by the patient prior to the injection of Radium-223
- Questionnaires on Activities of daily living (Katz-Index) and Body function (MOSES questionnaire)

- Changes in pain medication or other concomitant medication (including any BHA treatment)
- Changes in concomitant anti-cancer therapy
- Laboratory parameters including blood counts
- Dose of Radium-223 administered for treatment session 1-2 or 3-4
- Adverse events (including non-pathological fractures and bone associated events (e.g. osteoporosis))
- Symptomatic skeletal events (e.g. pathological fractures)
- Further treatment for mCRPC
- Survival assessment

Follow-up visit after end of treatment

If within routine clinical practice, data will be collected from a follow-up visit approximately 4 weeks after end of treatment. Further follow-up visits will be performed approximately after 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after end of treatment.

After implementation of amendment 3, not only symptomatic skeletal events but also non-pathological fractures and bone associated events are collected for all enrolled patients in the follow-up visits after end of treatment.

Typical information to be collected at this follow-up visit after treatment includes:

- Date of visit
- WHO pain score
- ECOG status
- Patient questionnaires on QoL (FACT-P)
- Questionnaires on Activities of daily living (Katz-Index) and Body function (MOSES questionnaire) during first follow-up visit
- Changes in pain medication and any BHA treatment
- Changes in anti-cancer therapy
- Laboratory parameters including blood counts
- Dose of Radium-223 administered (only at first follow up visit for treatment session 5 and 6)
- Adverse events up to 30 days after last treatment
- Symptomatic skeletal events (e.g. pathological fractures)
- All other (non-pathological) fractures and bone associated events (e.g. osteoporosis)
- Survival assessment
- Further treatment for mCRPC

End of Observation

The reason for end of observation is documented which could occur two years after the last administration of Radium-223, if the patient died, withdrew his consent or is lost to follow up. In case of death the date of death and primary cause of death have to be documented. The treating physician is encouraged to document the reason for the end of observation for all patients immediately after recognition but latest 60 months after end of treatment. A follow-up period of 60 months only applies to patients who consented to prolonged follow-up. For patients who do not consent to a prolonged follow-up period of 60 months, the reason for end of observation should be documented at the latest 24 months after end of treatment.

9.3 Variables

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

Table 2: Tabulated overview on variables collected during the study

Variables	Retrospective visit	Baseline visit	1st and 2nd visit during treatment	Follow-up after end of treatment	End of observation
Date of visit	X	X	X	X	X
Patient informed consent		X			
Demography		X			
Co-morbidities (medical history, concomitant diseases)		X			
Prostate cancer history (initial diagnosis, diagnostic and therapeutic procedures)		X			
WHO pain score		X	X	X	
Performance Status (ECOG)	X	X	X	X	
CIRS-G index		X			
FACT-P questionnaire		X	X	X	
KATZ-Index		X	X	X*	
MOSES questionnaire		X	X	X*	
Exposure/treatment (dose of Radium-223)		X	X		
Concurrent diagnostic and therapeutic procedures for mCRPC		X	X		
Laboratory parameters	X	X	X	X	
Concomitant medication (including any BHA treatment)		X	X	X**	
Any Adverse Events			X	X***	
Symptomatic skeletal events (e.g. pathological fractures)			X	X#	
All other (non-pathological) fractures and bone associated events (e.g. osteoporosis) during follow-up period				X#	
Prior anti-cancer therapy	X				
Further treatment for mCRPC			X	X	
Survival assessment			X	X	
Reason for end of observation					X

*only during first follow-up visit
**only change of pain medication and any BHA treatment
***Up to 30 days after last treatment with Radium-223.
to be documented on AE form up to 5 years follow-up period

9.3.1 Variables to determine the primary endpoint(s)

The variables for primary objectives are:

- **Overall survival** is defined as the time interval from the start of Radium-223 dichloride therapy to death, due to any cause. Patients alive at the end of the study will be censored at the last date known to be alive. Date and cause of death will be collected.

9.3.2 Variables to explore the secondary endpoint(s)

The outcome variables for secondary objectives are:

- **Symptomatic skeletal event free survival** of mCRPC patients (external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathological vertebral or non-vertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention, or death)
- **Time to next tumor treatment(s) (TTNT)** - Tumor treatment(s) after the last application of Radium-223 will be collected.
- **Incidence of treatment-emergent adverse events (TEAE)**.
- **Incidence of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures** and **bone associated events** during the treatment and 5 year follow-up period.
- **Quality of life as patient reported outcome** estimated using FACT-P.
- **Activities of daily living** assessed according to the Katz-Index.
- **Body function** assessed in dimensions of “mobility”, “self-care” and “domestic life” using the MOSES questionnaire.

9.3.3 Demography

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

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

9.3.4 Co-morbidities (medical history, concomitant diseases)

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

9.3.5 Prior and concomitant medication

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

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

9.3.6 Exposure / treatment

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

- Date
- Dose
- Unit
- Reasons for any significant delay/interruption/discontinuation of treatment

9.3.7 Assessment of therapy

Not applicable

9.3.8 Visits

- Date of visit

9.3.9 Medical History of prostate cancer

- Findings meeting the criteria listed below are considered to be relevant to the study indication and have to be documented:
  - Prostate cancer classification
    - date of initial diagnosis
    - Gleason score
    - status of primary tumor at study entry
    - progression/relapse
    - date of initial diagnosis of bone metastases
    - date of mCRPC diagnosis defined as confirmed rise of PSA despite conventional androgen ablation therapy (e.g. LHRH analoga)
  - prior diagnostic or therapeutic procedures associated with mCRPC
    - surgery/biopsy
    - systemic anti-cancer therapy including chemotherapy
    - radiotherapy
    - blood transfusions
  - Number of metastases and extent of disease
  - Baseline ECOG performance status

9.4 Data sources

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

information on any visits (including results) that have taken place outside the investigator's site due to the patient's disease, for example by interviewing the respective physician or patient or by obtaining an accompanying letter with detailed information and results.

9.5 Study size

The expected number of deaths, and the precision of estimates for median OS, for the sample sizes of 500 (original protocol) and sample sizes of 250, 150, 125 and 100, which may be defined by pretreatment with chemotherapy or chemotherapy-naïve patients (Amendment 2), are provided in the table below. These estimates for the sample size of 100, 125, 150 and 250 patients assume an exponentially distributed OS with a median of 20 months, an enrolment period of 40 months, a follow-up period of 24 months after the last Radium-223 injection/treatment of the last enrolled patient (and thus a total observation period of 70 months) and a 10% loss-to-follow-up rate per year (Amendment 2). The estimates for the sample size of 500 patients include the same assumptions, with the exception of an enrolment period of 24 months, and total observation period of 54 months, as planned in the original protocol.

Table 3: Expected number of deaths and confidence interval for median OS for different sample sizes

Sample Size	Expected Number of Deaths	Expected 95% confidence Interval for Median OS
500	331	17.5 – 22.8 months
250	173	16.5 – 24.0 months
150	104	15.5 – 25.4 months
125	87	15.1 – 25.9 months
100	69	14.6 – 26.8 months

The sample size was stepwise reduced from originally 500 to 250 patients (Amendment 1) and from 250 to an expected 75 patients as a result of the decision to terminate enrollment early (Amendment 3). This decision was taken due to the very slow enrollment rate which is not expected to be improving.

For a sample size of 75 patients and follow-up time of 5 years after last radium-223 treatment, the expected number of deaths is 52, and the expected 95% confidence interval for median OS is 13.8 – 28.0 months. These estimates assume an exponentially distributed OS with a median of 20 months, an enrollment period of 36 months, and thus a total observation period of 102 months, and a 10% loss-to-follow-up rate per year.

9.6 Data management

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

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

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

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

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

For information on quality control, refer to section 9.8.

9.7 Data analysis

9.7.1 Statistical considerations

Statistical analyses will be primarily of explorative and descriptive nature.

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

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

All analyses will be performed for the safety analysis set unless otherwise noted.

Analyses of QoL will be performed for patients with evaluable patient questionnaires (FACT-P) at each visit. A clinically relevant increase or decrease in opiate use will be taken into account and will be defined in the SAP.

Analyses of body function (Moses questionnaire) and activities of daily living (Katz-Index) will be performed for patients with evaluable questionnaires.

All analyses will be provided for the complete study population, as well as separately for the chemotherapy naïve vs non naïve study population.

All enrolled patients having received concomitant abiraterone plus prednisone/prednisolone remain in the study and will be analyzed, both within the complete study population analysis set as well as a separate subgroup.

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

The final analysis will be performed after end of the study which is the date the database has been declared to be clean. The analyses will be descriptive and no formal hypothesis testing will be performed.

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

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

Use of the anti-hormonal agents abiraterone plus predinisone/prednisolone or enzalutamide and other anti-androgens will be tabulated according to timing of use relative to Radium-223 dichloride, to include sequential use, concurrent use and layered use.

9.7.3 Analysis of treatment data

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

9.7.4 Analysis of primary outcome(s)

The primary analysis of Overall survival (OS) will be done based on recorded dates of death. OS is defined as the time interval from the start of Radium-223 dichloride therapy to death, due to any cause. Patients alive at the end of the study will be censored at the last date known to be alive.

OS will be summarized using Kaplan-Meier estimates. Median event times together with the 25th and 75th percentiles and associated 95% confidence intervals will be presented.

9.7.5 Analysis of secondary outcome(s)

- For quality of life exploration summary statistics including mean and mean change from baseline will be provided for each assessment time point of the FACT-P questionnaire. For the summary of each post-baseline assessment, patients will be excluded if there is no corresponding post-baseline measurement.
- Time to event variables (SSE FS, TTNT) will be summarized using Kaplan-Meier estimates. Median event times together with the 25th and 75th percentiles and associated 95% confidence intervals will be presented. Censoring rules will be defined in the SAP.

- Incidence of treatment emergent and drug-related AEs will be presented. Additional subcategories will be based on worst grade as reported using CTCAE and relationship to study drug.
- Incidence proportions and incidence rates of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment (reported as adverse events) and 5 year follow-up period will be presented. Fractures reported as adverse events will be identified by the MedDRA High Level Group Term of 'Fractures'. In addition, all fractures and bone associated events will be listed, along with information regarding use of the anti-hormonal agents abiraterone plus prednisone/prednisolone, enzalutamide, or use of other anti-androgens, and timing with respect to radium-223 use.

Further details will be given in the SAP.

9.7.6 Analysis of safety data

See analysis of secondary outcomes.

9.7.7 Analysis of other data

Not aplicable

9.7.8 Bias, confounding and effect-modifying factors

In general data collected in this study may suffer from biases (e.g. interviewer bias, either by systematic differences in data recording or different interpretation of information on exposure or outcome for different patients, reporting as well as selection bias). Besides, prospective studies are prone to bias from loss to follow-up or change in methods over time. To decrease the reporting bias source data verification will be performed in at least 20% of the sites. In order to reduce selection bias, a representative sample of sites will be included in the study. Sites will be selected according to several criteria, main criteria for site selection will be: availability of suitable patients and an equal geographical distribution. Investigators should select patients to be documented in the study only based on eligibility according to inclusion and exclusion criteria, i.e. each patient diagnosed with mCRPC and starting treatment for the disease with Radium-223 should be asked for participation in a consecutive manner. No further selection should be made and patients should be enrolled consecutively in order to avoid any selection bias applied.

Unknown and unmeasured risk factors for the outcome variables may exist and might lead to confounding when comparing results with results from other clinical studies. Therefore, caution should be applied when making any informal comparisons with results from other clinical studies.

9.8 Quality control

9.8.1 Data quality

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

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

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

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

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 (see Table 4, Annex 1).

National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for capturing patient documentation (eCRF) will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) [16]. The documentation is available upon request.

9.8.2 Quality review

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

9.8.3 Storage of records and archiving

The sponsor will make sure that all relevant documents of this study including CRFs and other patient records will be stored after end or discontinuation of the study for at least 10 years. Other instructions for storage of medical records will remain unaffected.

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

Statistical programming performed to generate results will be stored at the sponsor's site for at least 10 years.

9.8.4 Certification/qualification of external parties

N/A

9.9 Limitations of the research methods

This prospective observational cohort study provides an opportunity to collect data of real-life safety and effectiveness information that can be explored and disseminated in a timely manner. However, a limitation of the study is related to the reduced sample size of 75 patients, which results in less precise estimates, as compared to the earlier sample sized of 250 and 500 patients. Therefore, interpretation of results should proceed with caution, taking into consideration the reduced precision of estimates.

Since this study is a single arm cohort study without an active comparison group, caution should be applied when making any comparisons, including comparisons of subgroups within the study, and comparisons with historical results from clinical studies. This caution applies in particular to the collection of pathological and non-pathological fractures and bone associated events with special attention to those occurring under concomitant treatment with abiraterone plus prednisone/prednisolone (until amendment 3 came into force). Due to the non-controlled design with one cohort only, any observed effects in this study may not be attributed to treatment with Radium-223 alone, but will also reflect the natural course of disease. Differentiation of treatment effect and natural course of disease is not possible with this design.

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

10.2 Non-interventional design

The study is carried out in the framework of a non-interventional trial. All patient related procedures should be done according to usual local practice for the diagnostic work-up and routine treatment. The assessment of QOL and body function is now widely used as part of the quality assurance program in certified prostate cancer centers and a usual instrument for the outcome assessment in rehabilitation medicine. To collect the patient reported outcomes in the same way for all patients within the URANIS trial the FACT-P and MOSES questionnaire was selected.

Therefore it seems justified to assume these questionnaires still as non-interventional if the patient would completely voluntarily fill out the MOSES questionnaires 4 times during this study: before the first treatment with Radium-223-dichloride, 2 times under treatment (after 2 and 4 cycles of Radium-223-dichloride) and at the first follow-up visit. FACT-P questionnaire will be filled out completely voluntarily at baseline, at treatment visits and at each follow-up visit, cumulatively up to ten times.

10.3 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 [17]). Recommendations given by other organizations will be followed as well (e.g. EFPIA [18], ENCePP [19]). ICH-GCP guidelines will be followed whenever possible.

In addition, the guidelines on good pharmacovigilance practices (GVP [20] [21]) will be followed; the relevant competent authorities of the EU member states will be notified according to Volume 9A [22]. Since the study qualifies as a PASS, GVP module VIII will be followed [33].

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

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

10.5 Patient information and consent

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

Patients who are currently participating in the study when Amendment 03 becomes active will be informed about prolongation and adaption of the follow-up period and will be asked to provide written informed consent to prolonged study participation.

10.6 Patient insurance

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

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

10.7 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be

used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

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

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

11 Management and reporting of adverse events/adverse reactions

11.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product [23].

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

The AE may be:

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

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

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

An AE is serious (SAE) if it:

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

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

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

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

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

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

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

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

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

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

In oncology trials, disease progression is considered as part of the natural history of the disease and should not be reported as (S)AE.

All disease progressions are collected as additional outcome parameters (treatment outcome / tumor response).

If disease progression leads to signs and symptoms that meet the criteria for an SAE (ie, hospitalization, disability, death, or important medical event), the signs and symptoms should be reported as an SAE instead of the underlying disease progression.

11.2 Collection

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

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

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

With the exception of pathological fractures (as part of symptomatic skeletal events), non-pathological fractures and bone-associated events, the documentation of any AE/SAE ends 30 days after the last administration of Radium-223. All pathological fractures (as part of symptomatic skeletal events), non-pathological fractures and bone associated events have to be documented as (S)AE throughout the whole follow-up period up to 5 years.

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

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

11.3 Management and reporting

Non-serious AEs

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

Non-serious ARs

All non-serious ARs occurring under treatment with Radium-223 that qualify for expedited reporting will be submitted to the relevant authorities according to EU PV legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU, Module VI [20]) and according to national regulations by the sponsor; however, all investigators must obey local legal requirements.

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

Serious AEs

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

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

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

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

11.4 Evaluation

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

12 Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov" and in the 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.

The results of this study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the sponsor. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines [24], STROBE [25]). No individual treating physician may publish on the results of this study, or their own patients, without prior approval from the sponsor.

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Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Number	Document Name / Reference number	Final version and date (if available)*	Title
1	XF1503_List_of_active_physicians final	Will be available at end of recruitment	List of all active physicians
2	XF1503_CRF	Version 6.0, 06 February 2018	Case Report Form
3	XF1503_DMP	Version 1.0, 20 October 2015	Data Management Plan
4	XF1503_SAP	Will be available before study database lock	Statistical Analysis Plan
5	XF1503_QRP	Version 1.0, 26 January 2016	Quality Review Plan
6	XF1503_MRP	Version 1.0, 23 November 2016	Medical Review Plan

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

Annex 2: ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

- Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
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)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☐	☐	
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:				
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)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1

[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**
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7.5
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; 11.3

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.1 to 9.2.3
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	6; 9.2
	4.2.2 Age and sex?	☒	☐	☐	9.2.1
	4.2.3 Country of origin?	☐	☒	☐	
	4.2.4 Disease/indication?	☒	☐	☐	9.2
	4.2.5 Duration of follow-up?	☒	☐	☐	9.2; 9.2.7
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

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; 9.3.6; 9.7.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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?	☒	☐	☐	9.7.4; 9.7.5
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7.4; 9.7.5
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)	☒	☐	☐	9.1.2

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7.8
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7.8
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.7.8
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.7.8
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

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)	☒	☐	☐	9.7.1

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)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
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)	☒	☐	☐	9.3.6
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2; 9.7.5
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.2.7
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.5
9.3.3 Covariates?	☒	☐	☐	9.7.2
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
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
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)	☒	☐	☐	9.6; 9.8.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8.1; 9.8.2
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?	☒	☐	☐	9.7.8
12.1.2 Information bias?	☒	☐	☐	9.7.8
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)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4; 10.5
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10.7

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?	☒	☐	☐	5; Annex 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: _____

Date: dd/Month/year

Signature: _____

Annex 3: Questionnaires used during the trial

Katz Index of Independence in Activities of Daily Living

ACTIVITIES Points (1 or 0)	INDEPENDENCE: (1 POINT) **NO** supervision, direction or personal assistance	DEPENDENCE: (0 POINTS) **WITH** supervision, direction, personal assistance or total care
BATHING Points: _____	(1 POINT) Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	(0 POINTS) Needs help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
DRESSING Points: _____	(1 POINT) Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	(0 POINTS) Needs help with dressing self or needs to be completely dressed.
TOILETING Points: _____	(1 POINT) Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	(0 POINTS) Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING Points: _____	(1 POINT) Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.	(0 POINTS) Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE Points: _____	(1 POINT) Exercises complete self control over urination and defecation.	(0 POINTS) Is partially or totally incontinent of bowel or bladder.
FEEDING Points: _____	(1 POINT) Gets food from plate into mouth without help. Preparation of food may be done by another person.	(0 POINTS) Needs partial or total help with feeding or requires parenteral feeding.

TOTAL POINTS = _____ *6 = High (patient independent)* *0 = Low (patient very dependent)*

Slightly adapted from Katz S., Down, T.D., Cash, H.R. et al. (1970) Progress in the Development of the Index of ADL. *Gerontologist* 10:20-30. Copyright The Gerontological Society of America. Reproduced by permission of the publisher.

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

MOSES Questionnaire
Erik Farin, Annette Fleitz and Christian Frey

Changing a body position
Skip question: Can you kneel down and stand up again or squat down and stand up again without any difficulty or pain?
1CHAIR Sit on a chair and stand up again
2BED Lie down on a bed and stand up again
3SQUAT Squat down and stand up again
4FLOOR Kneel on the floor and stand up again
5BEND Bend down and pick up a small object (e.g. crumpled up paper)
6STRETCH Stretch to get a book from a high shelf
7SLIDE Slide from a chair to a bed placed next to it without standing up

Maintaining a body position
Skip question: Can you remain in a kneeling or standing position for long periods without any difficulty or pain?
8STAND Stand without interruption for a long period (e.g. waiting 20 minutes in line)
9SIT Sit on a chair for a long time (e.g. for the length of a meal)
10KNEEL Kneel on the floor for a long time (e.g. when cleaning)

Carrying objects
Skip question: Can you lift heavy objects of daily life (e.g. a full bucket of water or a case of beverages) from the floor to a table without any
difficulty or pain?
11LIFT Lift a heavy object (e.g. a 10 kg bucket of water)
12TABLE Lift a heavy object from the floor to the table (e.g. a 10 kg bucket of water)
13CARRY Carry a heavy object (e.g. a 10 kg bucket of water) 10 metres

Lower extremities
Skip question: Can you use your feet or legs to pull a heavy object (e.g. a chair) towards yourself or push it away without any difficulty or pain?
14PUSHL Push and move a light object (e.g. a ball) using your feet or legs
15PUSHH Push and move a heavy object (e.g. a chair) using your feet or legs
16PULLL Pull a light object (e.g. a crumpled piece of paper) towards yourself with your feet
17PULLH Pull a heavy object (e.g. a chair) towards yourself with your feet

Use of hands and arms
Skip question: Can you grasp small objects with your fingers and hands and pick up small objects (e.g. coins) with your fingers without any
difficulty or pain?
18GRASP Grasp and hold objects (e.g. a hammer) in your hands
19PICK Pick up small objects (e.g. coins) with your fingers
APPENDIX contd.
20BUTTON Button your clothes
21WRITE Write with a pen
22PULLF Pull objects with your fingers and hands (e.g. pull a door closed)

23PUSHF Push objects away with your fingers and hands (e.g. push a package across the table)

Walking (without equipment)
Skip question: Can you run for a short stretch or walk up a slope without any difficulty or pain?
24W20M Walk short distances (e.g. inside the home, up to 20 metres)
25W200M Walk distances in the building (up to 200 metres)
26W2KM Walk long distances (more than 2 kilometres)
27WHILL Walk up a steep slope (e.g. on a hill)
28WPATH Walk on an unlevel, rocky path
29WICY Walk along an icy path in winter
30STAIRS Climb two flights of stairs
31RUN Run a short distance

Moving about (using equipment)
Skip question: Do you use any equipment for walking such as crutches or a walker? (no further skip question)
32W20M Walk short distances (e.g. inside the home, up to 20 metres)
33W200M Walk distances in the building (up to 200 metres)
34WHILL Walk up a steep slope (e.g. on a hill)
35WPATH Walk on an uneven, rocky path
36PUBLICT Use public transportation (e.g. bus, train)
37TAXI Use a taxi
38CAR Get into a car as a passenger

Self-care
Skip question: Can you wash yourself and brush your teeth without any help and without any difficulty or pain?
39WASH Wash at the sink
40TEETH Brush your teeth
41HAIR Take care of your hair (e.g. comb, shave, style)

Dressing
Skip question: Can you put on and take off socks and underwear without any help and without any difficulties or pain?
42SHIRT Put on and take off a shirt
43SWEAT Put on and take off a sweater
44UPANTS Put on and take off underpants
45SOCKS Put on and take off socks

Eating and drinking
Skip question: Can you open jars and bottles and drink out of a bottle without any help and without any difficulty?
46BREAD Eat a slice of bread
47JAM Open a jar of jam
48GLASS Lead a glass to the mouth and drink

49BOTTLE Open a bottle of water and drink from the bottle

Acquiring the necessities of life
(No skip question)
50RENT Look for and rent a new apartment
51REFURN Refurnish the apartment when necessary
52GROCER Buy groceries

Housework
(No skip question)
53MEAL Prepare a simple meal (e.g. rice pudding)
54WASHC Wash clothes by hand if necessary
55DISHES Wash dishes in the sink
56DUST Dust
57SCRUB Scrub the floor
58WINDOW Wash windows

CIRS-G (CUMULATIVE ILLNESS RATING SCALE FOR GERIATRICS)

(nach Hock G, Nosper M., 2005)

Organsystem	1 Punkt	2 Punkte	3 Punkte	4 Punkte	Punkte
Herz	MI vor über 5 Jahren Gelegentlich Ap-Anfälle	Komp. Herzinsuffizienz mit tgl. Med. Linksherzhypertrophie Vorhofflimmern Schenkelblock Tgl. Antiarrhytmika Auffällige bradkyarde Perioden	MI innerhalb der letzten 5 Jahre Abnormer Stresstest Z.n. Bypass-OP/coronarer Angioplastik Herzinsuffizienz zw. 2 und 4	Instabile Ap Starke Aktivitätseinschränkung Hartnäckige Herzinsuffizienz	
Gefäßsystem	Kompensierte Hypertonie mit Diät Diast. Werte über 90 mmHg, keine Med. Gewichtsverlust Normales Cholesterin (unter 200 mg/dl)	1 x tgl. Med.einnahme 1 AS-Symptom (Claudatio, Angina p.) Aortenaneurysma unter 4 cm	2 oder mehr Med. tgl Linksventrikelhypertrophie 2 oder mehr AS-Symptome	Gefäß-OP/Bypass-OP wegen Problemen Aortenaneurysma über 4 cm	
Hämatopoetisches System	Hb bei Frauen über 10 unter 12 Hb bei Männern über 12 unter 14 Anämie bei chron. Erkrankung	Hb bei Frauen über 8 unter 10 Hb bei Männern über 10 unter 12 Anämie durch Eisen-, Vit.B12- oder Folsäuremangel Chron. Niereninsuffizienz, dialysepflichtig Leukozyten über 2000 unter 4000	Hb bei Frauen unter 8 Hb bei Männern unter 10 Leukozyten unter 2000	Jede Leukämie Jedes Lymphom Jede hämatopoetische Malignität	
Atmungsorgane Anmerkung: Pack years: Anzahl der gerauchten Schachteln/Tag mal der Anzahl der Raucherjahre ehem. Raucher, derzeit Nichtraucher werden niedriger eingestuft	Rezidivierende akute Bronchitis ohne Med. Chron. Bronchitis ohne Med. Asthma, nur Inhalationstherapie Raucher über 10 unter 20 Pack years	COPD Tgl. Med. oder Inhalator In den letzten 5 Jahren 2 oder mehr Pneumonien Raucher 20 bis 40 Pack years	Eingeschränkte respiratorische Kapazität Steroidtherapie Akute Pneumonie, ambulant Raucher über 40 Pack years	Benötigt Sauerstoff Respiratorische Insuffizienz Lungen-Ca Stationäre Pneumoniebehandlung	
HNO-System und Augen Anmerkung: Degenerative Augenerkrankungen (z.B. Katarakt) werden nach Sehproblemen eingeteilt	Sehkorrektur 20/40 (Snellen-Index) Chron. Sinusitis Leichte Schwerhörigkeit	Sehkorrektur 20/60 Sehbehinderung beim Lesen und Autofahren Hörgerät Vertigo mit Med. Chron. Sinusitis mit Med.	Partielle Blindheit Kann nicht mehr Zeitung lesen Hört in Gesellschaft schlecht	Funktionelle Blindheit/Taubheit Laryngektomie OP wegen Vertigo	
Oberes GIT	Hiatushernie Behandeltes Sodbrennen	Gastritis in den letzten 5 Jahren Ulcus duodenalis in den letzten 5 Jahren Tgl. H2-Blocker	Aktiver Ulcus „guiac" positiver Stuhl Dysphagie und Schluckreflexerkrankungen	Magen-Ca Perforierter Ulcus (auch früher) Malaena, Hämatochezie	
Unteres GIT	Darmträgheit unter Med. unter Kontrolle Hämorrhoiden Z.n. Hernie-OP	Tgl. Gebrauch von Laxantien Divertikulose Unbehandelte Hernie	Darmstörung in den letzten 5 Jahren Tgl. stimulierende Laxantien oder Einläufe	Hämatochezie Divertikulitis, jede Blutung Colon-Ca, Z.n. Darmverschluss	
Leber und Galle	Hepatitis vor über 5 Jahren Cholezystektomie	Leberwerte: mittel erhöht Hepatitis in den letzten 5 Jahren Cholelithiasis Tgl. Alk-Abusus in den letzen 5 Jahren	Bilirubin über 2 mg/dl Erhöhte Leberwerte (über 150% des Normalbereichs) Zugabe von Pankreasenzymen	Gallengangobstruktion Gallenblasen-Ca Cholezystitis Aktive Hepatitis	

Senioren Krebshilfe

Gemeinsam gegen Krebs im Alter

Niere Anmerkung: spez. glomeruläre od. andere Nierenerkrankungen werden nach der Behandlung mit Medikamenten und deren Erfolg eingeteilt	Pyelonephritis asymptomatisch oder Nierensteine in den letzen 5 Jahren	Kreatinin über 1,5 unter 3 ohne Med.	Kreatinin über 1,5 mit Med./über 3 häufige Pyelonephritis	Dialysepflichtig Nieren-Ca	
Urogenitalsystem	Stessinkontintenz Hysterektomie Asymptomatische BPH	ileal loops, Katheter, Nephrostomie Frauen: patholog. PAP, rez. HWI, Inkontinenz Männer: BPH mit Einengung und HWI Z.n. TUR der Prostata, Prostatektomie	Hämaturie, Z.n. Urosepsis, tgl. Inkontinenz Frauen: vaginale Blutungen, Cervix-Ca in situ Männer: Prostata-Ca in situ	Harnwegsverschluß Carcinome	
Skelettsystem	Arthrithis mit Med. In ATLs aufgrund Gelenkspathologie leicht eingeschränkt Entfernung eines Haut-Ca (nicht Melanom) Hautinfektion mit Ab-Therapie innerhalb des letzten Jahres	Tgl. Antirheumatika Tgl. Med. bei chron. Hauterkrankungen Notwendigkeit von Hilfsmitteln wegen Gelenkserkrankung Melanom ohne Metastasen Moderat begrenzte ATLs	Steroidtherapie wegen Arthritis Kompressionsfraktur wegen Osteoporose Starke Einschränkung in ATLs	Rollstuhl starke Gelenksdeformierungen Osteomyelitis Knochen-/Muskel-Ca Melanom mit Metastasen	
Neurologisches System Anmerkung: Die Schwere von Schlaganfällen wird nach dem Grad der Behinderung und nach Defiziten eingeteilt	TIA in Anamnese Häufige Kopfschmerzen mit Med.	TIA Tgl. Med. wegen chron. Kopfschmerzen oder regelmäßige Aktivitäts-einschränkungen CVA ohne signifikant bleibende Schäden Neurodegenerative Erkrankung mit milden Beschwerden	CVA mit leichten bleibenden Dysfunktionen ZNS-OP Neurodegenerative Erkrankung mit mittleren Beschwerden (Bradikinese, schlurfender Gang trotz Med.) Hemiparese und Sprachbeeinträchtigung nach Apoplex Leichte Gangstörung	CVA mit funktionellen Hemiparesen/ Aphasie Neurodegenerative Erkrankung mit schweren Beschwerden (vollständige Abhängigkeit im Alltag)	
Stoffwechsel und Mamma	DM mit Diät Adipositas mit BMI über 30 SD-Hormonersatztherapie	DM mit Insulingabe Fibrozystische Mamma-Veränderung	DM mit Retinopathie Periphere Neuropathie Blutzucker über 300 mg/dl Stat. Therapie einer Elektrolytstörung BMI über 45	Schlecht kontrollierter DM Diabetisches Koma od. Ketoazidose im letzten Jahr NNM-Hormontherapie NNM-/SD-Ca, Mamma-Ca	
Psychiatrisches Erkrankungen Anmerkung: „Delirium" überschneidet die Kat. Stoffwechsel, bei beiden werden daher 3 P. vergeben. Bei der Psyche wird dieses Symptom mit 4 P. gewertet.	Ambulante Depression-Behandlung vor über 10 Jahren Leichte psychische Beschwerden Gelegentlicher Gebrauch von Med. wegen Angstzuständen Leichte Demenz (MMSE unter 28, über 25)	Schwere Depression in den letzen 10 Jahren (DSM III-R) Jeder Psychiatrieaufenthalt Drogenmissbrauch vor über 10 Jahren	Aktuelle Depression (DSM III-R) 2 oder mehr depressive Phasen in den Letzten 10 Jahren Mittlere bis schwere Demenz (MMSE 15-20) Tgl. Gebrauch von Psychopharmaka Aktuelle Drogenabhängigkeit (DSM III-R)	Aktuelle psychische Erkrankung mit stat. Aufenthalt Intensive stat./amb. Betreuung Suizidale Depression Schwere Demenz (MMSE unter 15) Akute Psychose, Delirium Starke Drogenabhängigkeit	

Totalpunkte:	
Gesamtzahl der betroffenen Systeme:	
Zahl von Systemen mit 3 Punkten:	
Zahl von Systemen mit 4 Punkten:	

Annex 4: Description of Amendments

Amendment 01; 23 February 2017

Protocol Section	Description
General	Updated version number and date of last version of protocol as well as page numbers in inventory
EU PAS register number	Changed from “To be added after registration” to “N/A”
Observational study information: Study Initiator and Funder	Marketing authorization holder(s) was deleted and the following information war added: Please note that, effective 1st January 2017, Bayer Pharma AG transfers its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Research question and objectives	Changed the word “assessed” to “examine”.
Marketing authorization holder	The table was deleted
Table of contents	Was adapted
Section 3.1 Sponsor / MAH	Changed study conduct responsible from Christian Müller to Markus Langen. Changed title team leader local NIS to project leader local NIS. Changed the title of study data manager from Data Management Non-Interventional Studies to Senior Lead Data Manager, CDM Medical Affairs. Changed the address Bayer HealthCare Germany, Bldg. K9, 51366 Leverkusen to Pharma AG, Wuppertal, Germany Changed the name of study epidemiologist from Jihong Zong, MD to Zdravko Vassilev. Changed the head from Head TA to Head TA OPT/HEM Changed the address from Bayer HealthCare Pharmaceuticals Inc., Global Epidemiology, 100 Bayer Blvd, Whippany, NJ 07981, USA to Bayer U.S. Pharmaceuticals Division, Global Epidemiology, 100 Bayer Blvd, Whippany, NJ 07981, USA Changed the Study health economics and outcomes research (HEOR) responsible from Katja Dräxler to Michael Meinhardt
Section 4 Abstract	Changed the updated version number and date of last version of protocol The impact number 18043 was added Rational and background: Changed the word “assessed” to “explored” and orthographic mistake was corrected.

	Research question and objectives: The wording changed from “evaluate” to “explore” and from “determine” to “examine” or to “explore” and from to “assess” to “examine” or to “explore” Study design: Changed the size of planned enrolled chemotherapy naïve patients with mCRPC with bone metastases in primary data collection from 500 to 200. Study size: The enrolment period was extended from 24 to 40 month and the observational period from 54 to 70 month. The wording changed from “evaluate” to “explore” and from “determine” to “examine” or to “explore” and from to “assess” to “examine” or to “explore”. Data analysis: Changed conditions for the interim analysis and final analysis. Milestones: The End of recruitment was changed from to Q3/2018 The end of data collection was changed from to Q1/2021 The final report of study results was changed from to Q4/2021
Section 5: Amendments	The amendment AM01 was added.
Section 6: Milestones Table 1 Milestones	Interim analysis: Changed from when the active treatment with Ra-223-dichloride finished in 100 (approximately in December 2015) and 400 patients (approximately in December 2016) to when 75 (approximately in March 2017) and 180 patients (approximately in March 2018) have been enrolled. The End of data collection: Changed from to 31 March 2021 Database cleaned: Changed from to 30 June 2021 Final report of study results: 31 July 2020 to December 2021
Section 7: Introduction: Background and Rationale	Changed the word “are” to “were”, “assessment” to “examination” and “assessed” to “examined”.
Section 8: Research questions and objectives	Changed word “assessed” to “explored”.
8.2 Secondary objective(s)	The wording changed from “evaluate” to “explore” or to “examine” and from “determine” to “examine” or to “explore”.
Section 9.1 Study design	The size of planned enrolled chemotherapy naïve patients with mCRPC with bone metastases in primary data collection was changed from 500 to 250.
Section 9.1.2 Secondary endpoint	The wording of “evaluation” changed to “exploration” and “analyzed” to “examined” and “assessed” to explored”.
Section 9.2. Setting	Changed from “The study will be conducted in 125 departments of urology and oncology throughout Germany. Data will be collected from approximately 500 patients according to local health authority approved label” The study will be

	conducted in up to 125 departments of urology and oncology throughout Germany. Data will be collected from approximately 250 patients according to local health authority approved label“.
Section 9.2.1 Eligibility	Text deleted: “The inclusion of patients who have been pretreated with Radium-223-dichloride is possible, as data on retreatment with Radium-223-dichloride is limited. The analysis for this subgroup will be described in SAP in detail.”
Section 9.2.4: Withdrawal	Text about refuse further participation was updated.
Section 9.3.2 Variables to explore the secondary endpoint(s)	Title was changed from “Variables to determine the secondary endpoint(s)” to “Variables to explore the secondary endpoint(s)”
Section 9.5: Study size	Change the enrollment and follow-up period and therefore the total observation period Text was deleted.
Section 9.7.1 Statistical considerations	Text about information about the subgroup was deleted. Text added “further details will be given in the SAP.” Whenever reasonable, data will be stratified by subgroups (i.e. age, other baseline characteristics). Information about interim analyses was changed. Text deleted about objective of the interim analyses. The date of final analysis was changed. Deletion of the information about documentation of already with Radium-223-dichloride pretreated patients.
Section 9.7.4 Analysis of primary outcome(s)	Orthographic mistake was corrected.
9.7.5 Analysis of secondary outcome(s)	Changed word “assessment” to “exploration”.
Section 9.7.8 Bias, confounding and effect-modifying factors	Changed the reporting bias source data verification of the sites from 10% to 20 %. Text deleted: “A direct comparison of results from the current non-interventional study with data from pivotal clinical trials is limited due to the open-label design without control group. But nevertheless the inclusion of a large number of patients covering a wide range of clinical situations would allow to investigate the treatment with Radium-223-dichloride in the routine setting.” Text added: “Therefore, no formal comparisons of groups will be performed, and caution should be applied when making any informal comparisons, including comparisons of subgroups within the study, and comparisons with historical results from clinical studies.”
Section 9.8.1 Quality control	Text added: “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 (see Table 4, Annex 1)."
Section 9.9 Limitations of the research methods	Text was updated. Caution should be applied when making any comparisons, including comparisons of subgroups within the study, and comparisons with historical results from clinical studies
Section 9.10 Other Aspects	Section was deleted.
Annex 1: List of stand-alone documents	Changed document Name / reference number and final version date. Added 6th stand-alone document (medical review plan).
Annex 5: Signature page	Changed protocol version from 1 to 2 and date of last version of protocol from 28 January 2015 to 23 February 2017. Changed study conduct responsible from Christian Müller to Markus Langen. Changed the title from Team to Project Leader Non-interventional studies Changed the name of study epidemiologist from Jihong Zong, MD to Zdravko Vassilev Changed the title from Head TA Oncology to OPT/HEM Changed the address from Bayer HealthCare Pharmaceuticals Inc., Global Epidemiology, 100 Bayer Blvd, Whippany, NJ 07981, USA to Bayer U.S. Pharmaceuticals Division, Global Epidemiology, 100 Bayer Blvd, Whippany, NJ 07981, USA Changed the name of Study Health Economics and Outcomes Research (HEOR) from Katja Dräxler to Michael Meinhardt

Amendment 02; 14 August 2017

Protocol Section	Description
General	Updated version number and date of last version of protocol as well as page numbers in inventory
Acronym / Title	Changed text from "…of Ra-223 dichloride treated chemotherapy naïve mCRPC patients to "…of Ra-223 dichloride treated mCRPC patients", because also chemotherapy positive mCRPC patients can be enrolled.
Research question and objectives	Text was updated. Also chemotherapy positive mCRPC patients can be enrolled.
Table of contents	Was adapted
Section 3.1 Sponsor / MAH	Changed study data manager from Daniel Wolf to Christian de Vries Changed the address from Bayer Pharma AG, Wuppertal, Germany to Bayer AG, Berlin, Germany.

Section 4 Abstract	Changed the updated version number and date of last version of protocol Changed titel/Research question and objectives/Study design/Population: Changed text from "…of Ra-223 dichloride treated chemotherapy naïve mCRPC patients to "…of Ra-223 dichloride treated mCRPC patients", because also chemotherapy positive mCRPC patients can be enrolled. Research question and objectives: Changed word treatment to (pre-)treatment Study size: Changed text from: Assuming an exponentially distributed OS with a median of 20 months, enrolment period of 40 months, a follow-up period of 24 months after the last Radium-223 chloride injection/treatment (and thus a total observation period of 70 months) and 10% loss-to-follow-up rate per year, inclusion of 250 patients is expected to result in 173 deaths, and the 95% confidence interval around the median of 20 months is expected to be 16.5 – 24.0 months. To: The estimates for the expected number of deaths, and the precision of estimates for median OS (for the complete patient population of 250 as well as subgroup sample sizes of 100, 125, and 150, which may be defined by pre-treatment with chemotherapy or chemotherapy-naïve patients) assume an exponentially distributed OS with a median of 20 months, an enrolment period of 40 months, a follow-up period of 24 months after the last Radium-223 injection/treatment of the last enrolled patient (and thus a total observation period of 70 months) and a 10% loss-to-follow-up rate per year. Data analysis: Changed text from: "Statistical analyses will be primarily of explorative and descriptive nature. Whenever reasonable, data will be stratified by subgroups (i.e. age, comorbidities, treatment with cytostatics, concomitant or sequential use with new drugs with deep androgen signal ablation or other baseline characteristics)." To: "Statistical analyses will be primarily of explorative and descriptive nature. All analyses will be provided for the complete study population, as well as separately for the chemotherapy naïve vs non naïve study population. In addition, whenever reasonable, data will be stratified by subgroups (i.e. age, comorbidities, , concomitant or sequential use with new drugs with deep androgen signal ablation or other baseline characteristics)."
Section 5: Amendments	The amendment AM02 was added.
Section 6: Milestones Table 1 Milestones	Interim analysis: Changed from "when 75 (approximately in March 2017) and 180 patients (approximately in March 2018) have been enrolled" to "when 75 (approximately in September 2017) and 180 patients (approximately in May 2018) have been enrolled"
Section 7: Introduction: Background and Rationale	Changed the sentences "In contrast to the NIS PARABO, which is focused on the assessment of pain, and the NIS REASSURE, which is focused on the long-term safety for Radium-223 treated patients, this study will collect data on overall survival, time to SSE, QOL and activity of daily living in a chemotherapy naive cohort. The inclusion of different patient population for each of the above mentioned NIS will be organized by different groups of physicians and study sites

	in different areas. " to "In contrast to the NIS PARABO, which is focused on the assessment of pain, and the NIS REASSURE, which is focused on the long-term safety for Radium-223 treated patients, this study will collect data on overall survival, time to SSE, QOL and activity of daily living in mCRPC patients. The inclusion of patients for each of the above mentioned NIS will be organized by different groups of physicians and study sites in different areas."
Section 8: Research questions and objectives	Changed text from "This observational prospective single arm cohort study is designed to evaluate overall survival (OS) of chemotherapy naïve metastatic Castration Resistant Prostate Cancer (mCRPC) patients receiving Radium-223-dichloride in a real life nuclear medicine practice setting in Germany." To "This observational prospective single arm cohort study is designed to evaluate overall survival (OS) of metastatic Castration Resistant Prostate Cancer (mCRPC) patients receiving Radium-223-dichloride in a real life nuclear medicine practice setting in Germany.
8.1 Primary objective	Changed from chemotherapy naïve mCRPC patients to chemotherapy naïve mCRPC patients
8.2 Secondary objective	Changed word from "treatment to pre-treatment"
Section 9.1 Study design	Changed from "chemotherapy naïve patients with CRPC" to "patients with CRPC".
Section 9.1.2 Secondary endpoint	Changed from "Concomitant" to "Pretreatment, concomitant"
Section 9.2.3 Exclusion criterion/criteria	Deletion of exclusion criterion "Pretreatment with cytostatics (chemotherapy)"
Section 9.2.6 Representativeness	Changed from "No further selection than outlined in Sections 9.2.1 – 9.2.3 should be made and patients should be enrolled consecutively to the subgroups in a balanced way in order to avoid any selection bias." to "No further selection than outlined in Sections 9.2.1 – 9.2.3 should be made and patients should be enrolled consecutively in order to avoid any selection bias."
Section 9.2.7 Visits	Baseline visit: Added the following typical information to be collected at the baseline/first treatment visit: Chemotherapy status (naïve / non naïve)
9.3.9 Medical History of prostate cancer	Updated systemic anti-cancer therapy: including chemotherapy as prior diagnostic or therapeutic procedures associated with mCRPC
Section 9.5: Study size	Update from "Assuming an exponentially distributed OS with a median of 20 months, enrolment period of 40 months, a follow-up period of 24 months after the last Radium-223 injection/treatment of the last enrolled patient (and thus a total observation period of 70 months) and 10% loss-to-follow-up rate per year, inclusion of 250 patients is expected to result in 173 deaths, and the 95% confidence interval around the median of 20 months is expected to be 16.5 – 24.0 months." to

	"The expected number of deaths, and the precision of estimates for median OS, for the complete patient population of 250 as well as subgroup sample sizes of 100, 125, and 150, which may be defined by pre-treatment with chemotherapy or chemotherapy-naïve patients, are provided in the table below. These estimates assume an exponentially distributed OS with a median of 20 months, an enrolment period of 40 months, a follow-up period of 24 months after the last Radium-223 injection/treatment of the last enrolled patient (and thus a total observation period of 70 months) and a 10% loss-to-follow-up rate per year." Added Table 3: Expected number of deaths and confidence interval for median OS for different sample sizes
Section 9.7.1 Statistical considerations	Text updated from "Whenever reasonable, data will be stratified by subgroups (i.e. age, other baseline characteristics)." to "All analyses will be provided for the complete study population, as well as separately for the chemotherapy naïve vs non naïve study population. In addition, whenever reasonable, data will be stratified by subgroups (i.e. age, other baseline characteristics."
Section 9.7.7 Analysis of other data	Orthographic mistake was corrected.
Section 9.7.8 Bias, confounding and effect-modifying factors	Text was updated from "No further selection should be made and patients should be enrolled consecutively to the subgroups in a balanced way in order to avoid any selection bias applied." to "No further selection should be made and patients should be enrolled consecutively in order to avoid any selection bias applied."
Section 9.8.1 Quality control	Orthographic mistake was corrected.
Section 9.9 Limitations of the research methods	Text was added: "Due to the non-controlled design with one cohort only, any observed effects in this study may not be attributed to treatment with Radium 223 alone, but will also reflect the natural course of disease. Differentiation of treatment effect and natural course of disease is not possible with this design."
Section 9.10 Other Aspects	Header was added.
Section 11 Management and reporting of adverse events/adverse reactions	In oncology trials, disease progression is considered as part of the natural history of the disease and should not be reported as (S)AE. All disease progressions are collected as additional outcome parameters (treatment outcome / tumor response). If disease progression leads to signs and symptoms that meet the criteria for an SAE (ie, hospitalization, disability, death, or important medical event), the signs and symptoms should be reported as an SAE instead of the underlying disease progression.
Annex 1: List of stand-alone documents	Changed from "Table 3" to "Table 4". Changed the final version and date of document XF1503_CRF.

Annex 3: MOSES Questionnaire	Orthographic mistakes were corrected.
Annex 5: Signature page	Changed protocol version and date of protocol. Changed title of protocol. “Chemotherapy naïve” was deleted. Changed the name of study data manager from Daniel Wolf to Christian de Vries and the address.

Amendment 03; 30April 2018

Protocol Section	**Description**
General	Updated version number and date last version of protocol as well as page numbers in inventory.
Observational study information	Study type changed to Post Authorization Study (PASS)
EU PAS register number	N/A changed to Study not yet registered
Study Initiator and Funder	Tense changed to Past Tense in information on Bayer Pharma AG
Author	Changed from Dr. Jörg Pinkert to Dr. Juliane Brendel
Marketing Authorization Holder and MAH contakt person	Added due to change in study type
1 Table of contents	Adapted
2 List of abbreviations	Bone Helath Agent, Independent Data Monitoring Committee, Pharmacovigilance Risk Assessment Committee added
3.1 Sponsor/MAH	Academic title added for Study safety lead Changed Study medical expert from Jörg Pinkert to Juliane Brendel Changed Study conduct responsible from Markus Langen to Thomas Neußer Qualified Person responsible Pharmacovigilance (QPPV) added Affiliation of Study statistician changed from Bayer Health Care Pharmaceuticals Inc. to Bayer U.S. LLC Title of Study data manager changed from Senior Lead Data Manager to Principle Data Manager Academic Title and Title of Study epidemiologist changed from PHD to MD, MPH and Head TA OPT/HEM to Head TA ONC2, respectively
4 Abstract	Updated Protocol version identifier and Date of last version of protocol Study type changed from non-PASS to PASS Authorship transferred from Dr. Jörg Pinkert to Dr. Juliane Brendel CRPC corrected to mCRPC in Rationale and background Deletion of the secondary objectives concerning the exploration of covariates of

	overall survival and the exploration of covariates of symptomatic skeletal event free survival Addition of a new secondary objective (To calculate the incidence of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment and 5 year follow-up period) Adaption of enrollment target in Study design Sample size considerations in Study size adapted to a sample size of 75 patients and to reflect the adapted study timelines Text regarding the previously planned subgroup analyses and regarding the previously planned Cox regression analysis deleted in Data analysis Text regarding the previously planned interim analyses deleted in Data analysis Timing of Milestones adapted (End of recruitment in Q2 2018 instead of Q3 2018; End of data collection in Q4 2023 instead of Q1 2021; Final report of study result in Q3 2024 instead of Q4 2021)
5 Amendments	Amendment 03 was added
6 Milestones	Interim analysis: Text and dates deleted End of data collection: Changed from 31 March 2021 to 31 December 2023 Registration in the EU PAS register: Q2 2018 added Database cleaned: Changed from 30 June 2021 to 31 March 2024 Final report of study results: Changed from 31 December 2021 to 30 September 2024
7 Introduction: Background and Rationale	Castration-resistant prostate cancer (CRPC) corrected to metastatic castration-resistant prostate cancer (mCRPC), if applicable Text added regarding the use of bone targeted treatments, including bone health agents and radionuclide therapy (“Regardless of the nature and location of bone metastases, the use of bone targeted treatments, including bone health agents (BHA, e.g. bisphosphonates or denosumab) and radionuclide therapy can decrease bone pain and the risk of pathological fractures.”) Text deleted regarding Cox model to determine the influence of comorbidities on oS and time to SSE (“These comorbidities will be used later in the Cox model to determine their influence as covariates on OS and time to SSE.”) Text added to mention the results of the ERA-223 study and to explain the change in the SMPC im March 2018 (“The ERA-223 study, a phase III randomized trial in prostate cancer patients examining radium-223 dichloride versus placebo in combination with abiraterone and prednisone (study number 15396, NCT02043678) was unblinded based on the Independent Data Monitoring Committee (IDMC) recommendation following an ad hoc independent analysis where more treatment emergent fractures, SSE-FS, and total deaths events were observed in the active treatment arm compared with the placebo arm. Based on the available data, the benefit-risk of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in mCRPC is considered unfavorable. The Pharmacovigilance Risk Assessment Committee (PRAC) initiated on 30 NOV 2017 a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data observed in the ERA-233 study. Therefore and in view of the seriousness of the events observed, the PRAC recommended provisional amendments to the product information to

	contraindicate the use of Radium-223 dichloride in combination with abiraterone plus prednisone/prednisolone. The IDMC also recommended that during the 5 year follow up period all bone fractures and bone associated events (e.g., osteoporosis) are to be documented regardless of investigator´s causality assessment. This change of product information which was implemented in March 2018 is reflected by the changes made in the protocol with this amendment. In order to collect comprehensive safety information across all clinical trials with Radium-223 dichloride, in the URANIS study, pathological fractures (as part of symptomatic skeletal events),non-pathological fractures and bone associated events will be assessed in all patients available for safety analysis. Hitherto in URANIS enrolled patients treated with the combination of Radium-223 and abiraterone plus prednisone/prednisolone will be presented thoroughly and separately to further substantiate any increased risk in bone fractures in those patients. With the new version of the product information of Radium-223 (dated March 2018), Radium-223 should not be given concurrently with abiraterone plus prednisone/prednisolone. Based on the available data on Radium-223, the option of starting a bone health agent (BHA) should be considered, taking into consideration applicable guidelines.")
8.2 Secondary objective(s)	Deletion of the secondary objectives concerning the exploration of covariates of overall survival and the exploration of covariates of symptomatic skeletal event free survival Addition of a new secondary objective (To calculate the incidence of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment and 5 year follow-up period) The wording with regard to the Secondary objectives "To explore the independence in activities of daily living by using the Katz-Index" and "To explore body function in the dimension of "mobility", "self-care" and "domestic life" by using the MOSES questionnaire" was adapted to be in line with the wording in section 4 Abstract
9.1 Study design	Enrollment target was changed from 250 patients to at least 75 patients. CRPC was corrected to mCRPC. Wording regarding the observational period for each patient was adapted to the prolonged follow-up period of 5 years.
9.1.2 Secondary endpoint(s)	Deletion of the secondary endpoints concerning the exploration of covariates of overall survival and the exploration of covariates of symptomatic skeletal event free survival Addition of a new secondary endpoint (Estimation of the incidence of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment and 5 year follow-up period)
9.1.3 Strengths of study design	CRPC corrected to mCRPC
9.2 Setting	Wording adapted to the new enrollment target (at least 75 patients) and the prolonged follow-up period (five instead of two years).

9.2.1Eligibility	CRPC corrected to mCRPC
9.2.4 Withdrawal	Text adapted regarding the use of data after apatient´s withdrawal of study participation.
9.2.7 Visits	Follow-up period was prolonged. Therefore, follow-up visits 30, 36, 42, 48, 54 and 60 months after end of treatment were added. Figure 1 was adapted to reflect the prolonged follow-up period. First and Second visit during treatment: Any BHA treatment needs to be documented as concomitant medication. Wording for documentation of non-pathological fractures and bone associated events (e.g. osteoporosis) and Symptomatic skeletal events (e.g. pathological fractures) was specified. Follow-up visits after end of treatment: Follow-up visits 30, 36, 42, 48, 54 and 60 months after end of treatment were added. Wording was added to clarify that after implementation of amendment 3, not only symptomatic skeletal events but also non-pathological fractures and bone associated events are collected for all enrolled patients in the follow-up visits after end of treatment. Any BHA treatment needs to be documented. Wording for documentation of non-pathological fractures and bone associated events (e.g. osteoporosis) and Symptomatic skeletal events (e.g. pathological fractures) was specified. End of Observation: Timing of documentation of End of Observation was adapted to the prolonged follow-up period and wording was added to clarify that the prolonged follow-up period applies only to patients who consented to the prolonged follow-up period.
9.3 Variables	Crossreference to the CRF which is mentioned in Annex 1 was updated. Table 2: Wording was adapted in the first row (First changesd to 1st, Scond changed to 2nd). Dokumentaion of any BHA treatment added to Variables. Dokumentation of Adverse Events specified (Any Adverse Events). Dokumentation of Averse Events at Basline Visit is not planned, therefore the respective marking was deleted. Dokumentation of non-pathological fractures, bone associated events and pathological fractures during follow-up period specified. Adaption of footnote ** to also document any BHA treatment. Adaption of footnote # to specify that non-pathological fractures , pathological fractures and bone-associated events need to be documented during the follow-up period.
9.3.2	“Incidence of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment and 5 year follow-up period.” added as outcome variable .
9.5 Study size	Text was adapted to reflect the change of the originally planned sample size of 500 patients (original protocol) to a planned sample size of 250 patients (Amendment 02) and 75 patients (Amendment 03). Text was added to provide the expected number of deaths and the expected 95% CI for median OS with regard to a sample size of 75 patients and the adapted study timelines.
9.6 Data management	Crossreference to the DMP which is mentioned in Annex 1 was updated.
9.7.1 Statistical Considerations	Text was added to clarify that the statistical analysis plan (SAP) will incorporate the protocol amendments. Text was deleted with regard to stratified analysis (e.g. according to baseline

	characteristics) "All enrolled patients having received concomitant abiraterone plus prednisone/prednisolone remain in the study and will be analyzed, both within the complete study population analysis set as well as a separate subgroup." was added. Text regarding the previously planned interim analyses was deleted.
9.7.2 Analysis of demography, disease details, prior and concomitant medication and other baseline data	"Use of the anti-hormonal agents abiraterone plus predinisone/prednisolone or enzalutamide and other anti-androgens will be tabulated according to timing of use relative to Radium-223 dichloride, to include sequential use, concurrent use and layered use." was added.
9.7.5 Analysis of secondary outcome(s)	"Incidence proportions and incidence rates of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment (reported as adverse events) and 5 year follow-up period will be presented. Fractures reported as adverse events will be identified by the MedDRA High Level Group Term of 'Fractures'. In addition, all fractures and bone associated events will be listed, along with information regarding use of the anti-hormonal agents abiraterone plus prednisone/prednisolone, enzalutamide, or use of other anti-androgens, and timing with respect to radium-223 use." was added.
9.7.7 Analysis of other data	"Covariate-adjusted Cox proportional-hazards regression will be used to estimate the association of clinical covariates with the time to event variables (i.e. OS, SSE-FS). Each covariate will be assessed as a univariate covariate in the model, and a multivariate model may be explored in addition. Parameters collected during retrospective visits may also be used to perform an explorative analysis on OS and SSE-FS. Further details will be given in the SAP." changed to "Not applicable".
9.7.8 Bias, confounding and effect-modifying factors	"Primary and secondary outcome variables and safety data will be analyzed with regard to different baseline factors. However, unknown and unmeasured risk factors for the outcome variables will exist and might lead to confounding when comparing results in different subgroups and when comparing study results with historical results from clinical studies. Therefore, no formal comparisons of groups will be performed, and caution should be applied when making any informal comparisons, including comparisons of subgroups within the study, and comparisons with historical results from clinical studies." changed to"Unknown and unmeasured risk factors for the outcome variables may exist and might lead to confounding when comparing results with results from other clinical studies. Therefore, caution should be applied when making any informal comparisons with results from other clinical studies."
9.9 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 explored and disseminated in a timely manner. However this study is a single arm cohort study without an active comparison group. Therefore, caution should be applied when making any comparisons, including comparisons of subgroups within the study, and comparisons with historical results from clinical studies. Due to the non-controlled design with one cohort only, any observed effects in this study may not be attributed to treatment with Radium 223 alone, but will also reflect the natural course of disease. Differentiation of treatment effect and natural course of disease is not possible with this design." changed to "This prospective observational cohort study provides an opportunity to collect data of real-life safety and effectiveness information that can be explored and disseminated in a timely manner. However, a limitation of the study is related to the reduced sample size of

	75 patients, which results in less precise estimates, as compared to the earlier sample sized of 250 and 500 patients. Therefore, interpretation of results should proceed with caution, taking into consideration the reduced precision of estimates. Since this study is a single arm cohort study without an active comparison group, caution should be applied when making any comparisons, including comparisons of subgroups within the study, and comparisons with historical results from clinical studies. This caution applies in particular to the collection of pathological and non-pathological fractures and bone associated events with special attention to those occurring under concomitant treatment with abiraterone plus prednisone/prednisolone (until amendment 3 came into force). Due to the non-controlled design with one cohort only, any observed effects in this study may not be attributed to treatment with Radium-223 alone, but will also reflect the natural course of disease. Differentiation of treatment effect and natural course of disease is not possible with this design."
10.3 Regulatory authority approvals/authorizations	"Since the study qualifies as a PASS, GVP module VIII will be followed [33]." added.
10.5 Patient information and informed consent	"Patients who are currently participating in the study when Amendment 03 becomes active will be informed about prolongation and adaption of the follow-up period and will be asked to provide written informed consent to prolonged study participation." added.
11.2 Collection	Timelines of SAE reporting changed from "within 24 hours" to "one business day" of awareness. "The documentation of any AE / SAE ends with the last treatment of the patient with Radium-223 dichloride including 30 days after the last administration of Radium-223 dichloride." changed to "With the exception of pathological fractures (as part of symptomatic skeletal events), non-pathological fractures and bone-associated events, the documentation of any AE/SAE ends 30 days after the last administration of Radium-223. All pathological fractures (as part of symptomatic skeletal events), non-pathological fractures and bone associated events have to be documented as (S)AE throughout the whole follow-up period up to 5 years.".
11.3 Management and Reporting	"Any SAE or pregnancy entered into the CRF / EDC system will be forwarded immediately (within 24 hours of awareness) to the pharmacovigilance country person being responsible for SAE processing." changed to "Any SAE or pregnancy entered into the CRF / EDC system will be forwarded immediately (within one business day of awareness) to the pharmacovigilance country person being responsible for SAE processing."
12 Plans for disseminating and communicating study results	"and in the EU PAS register at "http://www.encepp.eu/encepp_studies/indexRegister.shtml"." added.
13 List of References	Reference 33 added
Annex 1List of stand-alone documents	Version and date of CRF updated. Version and Date of DMP uptated.
Annex 2 ENCePP checklist for study protocols	ENCePP Checklist for Study Protocols added.
Annex 4 Description of	Detailed description of Amendments added for Amendment 01 (23 February

Amendments	2017), Amendment 02 (14 August 2017), Amendment 03 (30 April 2018)
Annex 5 Signature pages	Changed protocol version, date of protocol and study type. Information on EU PAS register number changed from “Study not registered” to Study not yet registered”. Tense changed to Past Tense in information on Bayer Pharma AG of the respective signature pages. Academic title added for Study safety lead Changed Study medical expert from Jörg Pinkert to Juliane Brendel Changed Study conduct responsible from Markus Langen to Thomas Neußer Affiliation of Study statistician changed from Bayer Health Care Pharmaceuticals Inc. to Bayer U.S. LLC Function of Study data manager changed from Study Data Manager to Principle Data Manager, Information on building deleted Academic Title and Title of Study epidemiologist changed from PHD to MD, MPH and Head TA OPT/HEM to Head TA ONC2, respectively Qualified Person responsible Pharmacovigilance (QPPV) added Country Medical Director (Germany) added

Annex 5: Signature pages

Signature Page - Study Safety Lead

Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Protocol version identifier	4.0
Date of last version of protocol	30 April 2018
IMPACT study number	18043
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03), Radium-223 dichloride
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Function	Study safety lead
Name	Ilona Schlegel, MD
Title	Local Pharmacovigilance Manager
Address	Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

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

Date, Signature: _____, _____

Signature Page - Study Medical Expert

Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Protocol version identifier	4.0
Date of last version of protocol	30 April 2018
IMPACT study number	18043
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03), Radium-223 dichloride
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Function	Study medical Expert
Name	Dr. Juliane Brendel
Title	Senior Medical Advisor Oncology
Address	Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

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

Date, Signature: _____, _____

Signature Page - Study Conduct Responsible

Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Protocol version identifier	4.0
Date of last version of protocol	30 April 2018
IMPACT study number	18043
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03), Radium-223 dichloride
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Function	Study conduct responsible
Name	Thomas Neußer, Ph.D.
Title	Project Leader Non-interventional studies
Address	Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

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

Date, Signature: _____, _____

Signature Page - Study Statistician

Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Protocol version identifier	4.0
Date of last version of protocol	30 April 2018
IMPACT study number	18043
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03), Radium-223 dichloride
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Function	Study Statistician
Name	Alice Benson
Title	Global Integrated Analysis Project Lead
Address	Bayer U.S. LLC, Whippany, NJ, USA

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

Date, Signature: _____, _____

Signature Page - Study Data Manager

Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Protocol version identifier	4.0
Date of last version of protocol	30 April 2018
IMPACT study number	18043
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03), Radium-223 dichloride
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Function	Principle Data Manager
Name	Christian de Vries
Title	Global Clinical Data Manager Non-Interventional Studies
Address	Bayer AG, 13342 Berlin, Germany

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

Date, Signature: _____, _____

Signature Page - Study Epidemiologist

Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Protocol version identifier	4.0
Date of last version of protocol	30 April 2018
IMPACT study number	18043
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	Radiopharmaceuticals (V10XX03), Radium-223 dichloride
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Function	Study Epidemiologist
Name	Zdravko Vassilev, MD, MPH
Title	Head TA ONC2
Address	Bayer U.S. Pharmaceuticals Division, Global Epidemiology, 100 Bayer Blvd, Whippany, NJ 07981, USA

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

Date, Signature: _____, _____

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

Responsible

Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Protocol version identifier	4.0
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Active substance (medicinal product)	Radiopharmaceuticals (V10XX03), Radium-223 dichloride
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Function	Study health economics and outcomes research (HEOR) responsible
Name	Michael Meinhardt
Title	Market Access Manager
Address	Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

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

Date, Signature: _____, _____

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Protocol version identifier	4.0
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Function	Qualified person responsible for pharmacovigilance (QPPV)
Name	Michael Kayser
Title	European Qualified Person for Pharmacovigilance (QPPV)
Address	Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany

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

Date, Signature: _____, _____

Signature Page - Country Medical Director (Germany)

Title	URANIS –Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Protocol version identifier	4.0
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Function	Country Medical Director
Name	Dr. Konstanze Diefenbach
Title	Medical Director Germany
Address	Bayer Vital GmbH, K56, 51366 Leverkusen, Germany

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

Date, Signature: _____, _____