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Official Title:	A Phase 4 long-term follow-up study to define the safety profile of radium-223 dichloride
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16996

Cover page of the integrated clinical study protocol

A Phase 4 long-term follow-up study to define the safety profile of radium-223 dichloride

For this study, the protocol and subsequent protocol amendments were released as follows:

- **Original protocol,** Version 1.0, dated 03 SEP 2014
- **Amendment 1** (global amendment described in Section 13.1) forming integrated protocol Version 2.0, dated 13 SEP 2016
- **Amendment 2** (global amendment described in Section 13.2) forming integrated protocol Version 3.0, dated 11 APR 2018

This document integrates the original protocol and all global amendments.

Title page

A Phase 4 long-term follow-up study to define the safety profile of radium-223 dichloride

Radium-223 dichloride long-term follow-up program

Test drug:	BAY 88-8223 / Radium-223 dichloride / Xofigo®		
Study purpose:	Safety		
Clinical study phase:	4	Date:	11 APR 2018
Registration:	EudraCT: 2014-002407-25	Version no.:	3.0
Sponsor's study no.:	16996		
Sponsor:	Bayer AG, D-51368 Leverkusen, Germany Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, USA *Sponsor name modified by Amendment 1.*		

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Sponsor Medical Expert name modified by Amendments 1 and 2.

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

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Signatory name modified by Amendments 1 and 2.

Name: PPD PPD Role: PPD (PPD

Date: PPD

Signature: PPD

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: _____ Signature: _____

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's Investigator Site File.

Synopsis

Title	A Phase 4 long-term follow-up study to define the safety profile of radium-223 dichloride
Short title	Radium-223 dichloride long-term follow-up program
Clinical study phase	4
Study objective(s)	The primary objectives are to define the long-term safety profile of radium-223 dichloride (for up to 7 years after the last dose of radium-223 dichloride); to assess the incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy; to assess the incidence of bone fractures and bone associated events (e.g., osteoporosis); and, in subjects who receive cytotoxic chemotherapy, to assess the incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice. *Section modified by Amendments 1 and 2.*
Test drug(s)	No study treatment will be provided in this long-term follow-up study. Each feeder trial investigated BAY 88-8223 (radium-223 dichloride).
Name of active ingredient	Not applicable to this follow-up study.
Dose(s)	Not applicable to this follow-up study.
Route of administration	Not applicable to this follow-up study.
Duration of treatment	Not applicable to this follow-up study.
Reference drug(s)	Not applicable to this follow-up study.
Name of active ingredient	Not applicable to this follow-up study.
Dose(s)	Not applicable to this follow-up study.
Route of administration	Not applicable to this follow-up study.
Duration of treatment	Not applicable to this follow-up study.
Indication	As defined in the feeder trial protocols.
Diagnosis and main criteria for inclusion /exclusion	Subject was previously enrolled in a selected company-sponsored feeder trial, and has received at least 1 dose of radium-223 dichloride or placebo in the feeder trial. Written informed consent. There are no exclusion criteria for this study.
Study design	Interventional single-arm Phase 4 study

Methodology	Subjects enrolled into the study will be transferred from the selected company-sponsored feeder trials with radium-223 dichloride. Subjects, their treating health care professional, or caregiver will be contacted by telephone (face-to-face data collection is possible and will replace the telephone contact if the subject is on-site within the time window of the planned telephone contact) every 6 months (± 28 days) for 7 years (or as defined in the feeder trial protocols) following the last dose of radium-223 dichloride or placebo in the feeder trial, or until death, to determine the following: • All radium-223 dichloride-/placebo-related adverse events (AEs) and serious adverse events (SAEs) • All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy • All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. • Cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics) • In subjects who receive cytotoxic chemotherapy: all occurrences of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter • Survival status. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data. *Section modified by Amendments 1 and 2.*
Type of control	Not applicable
Number of subjects	With the currently active feeder trials, approximately 800 subjects are expected to be enrolled into this long-term safety follow-up study, but the number of subjects may increase if additional trials feed into this study.
Primary / secondary variable(s)	The primary variables are all safety-related and include: • Incidence and severity of radium-223 dichloride-/placebo-related AEs • Incidence of radium-223 dichloride-/placebo-related SAEs • Incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy • Incidence of bone fractures and bone associated events (e.g., osteoporosis), regardless of investigator assessment of causality; • In subjects who receive cytotoxic chemotherapy: incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice

Time point/frame of measurement for primary variable(s)	Up to 7 years after the last dose of radium-223 dichloride or placebo in the feeder trials, or as defined in the feeder trial protocols. *Section modified by Amendments 1 and 2.*
Plan for statistical analysis	This is primarily a descriptive safety study. All subjects enrolled in this study will have received at least 1 dose of radium-223 dichloride or placebo in a selected feeder trial and will be included in the safety evaluation. The incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy; the incidence of bone fractures and bone associated events (e.g., osteoporosis); and in subjects who receive cytotoxic chemotherapy, the incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter, will be summarized using measures that will depend upon whether the study includes a comparator group or is a single-cohort study. Other considerations include the length of follow-up time and time-to-event methods. The safety data from feeder trials and 16996 will be combined within each study for all AE summaries. For pooled analyses, all data across the selected feeder trials and 16996 will be combined by treatment groups and by treatment doses, as appropriate. Additional statistical analysis will be performed as described in the 16996 statistical analysis plan (SAP), feeder trial SAPs, and /or as previously communicated to Health Authorities. *Section modified by Amendments 1 and 2.*

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List of abbreviations

Section modified by Amendment 2 (Section 13.2.1.11).

AE	Adverse event
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer
BHA	Bone health agent
CRO	Clinical research organization
CRPC	Castration-resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events; Version 4.03
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European Union
FDA	United States Food and Drug Administration
GCL	Global Clinical Leader
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IRB	Institutional review board
NCI	National Cancer Institute
OS	Overall survival
QoL	Quality of life
RANKL	Receptor activator for nuclear factor κB ligand
SAE	Serious adverse event
SAP	Statistical analysis plan
SRE	Skeletal-related event
SSE	symptomatic skeletal event
SSE-FS	symptomatic skeletal event–free survival
SUSAR	Suspected, unexpected, serious adverse reaction
US	United States

Definitions of terms

Radium-223 dichloride	The investigational product, a bone-targeting alpha particle-emitting radiopharmaceutical, is a ready-to-use solution for intravenous injection containing the drug substance radium-223 dichloride. The active moiety is the alpha particle-emitting nuclide radium-223, present as a divalent cation.

1. Introduction

1.1 Background

Section modified by Amendment 2 (Section 13.2.1.1).

Bone metastases are common in many solid tumors, notably those arising from the prostate, breast, and lung, as well as multiple myeloma, and may cause major morbidity including fractures, severe pain, nerve compression, and hypercalcaemia.

Regardless of the nature and location of bone metastases, the use of bone targeted treatments, including potent bone health agents (BHAs, e.g. bisphosphonates or denosumab) and bone radionuclide therapy can decrease bone pain, can decrease risk of pathologic fractures, and can improve quality of life (QoL).

Alpha particle-emitting radiopharmaceuticals represent a new class of cancer therapy for the treatment of patients with bone metastases.(1, 2) Unlike beta-emitting radiopharmaceuticals, alpha particle-emitting radiopharmaceuticals have a more localized action (3) (a range of 2 to 10 cell diameters) and are much more potent, causing double-strand deoxyribonucleic acid (DNA) breaks leading to cell death.(4) Radium-223 dichloride (Xofigo, formerly Alpharadin) is a calcium mimetic, alpha-emitting nuclide, which selectively targets areas of increased bone turnover in bone metastases.(5) The half-life of radium-223 is 11.4 days,(3) allowing sufficient time for its preparation, distribution, and administration to subjects. The high-energy alpha particle radiation (4) results in a potent and highly localized cytotoxic effect in the target areas containing metastatic cancer cells, thereby potentially reducing exposure of surrounding normal tissues, particularly bone marrow.(5)

Prostate cancer

Prostate cancer has become an increasingly important health issue globally. Prostate cancer is the fifth most common tumor type worldwide, with 679,060 men diagnosed each year,(6) and is one of the leading causes of cancer-related morbidity and death.(7)

Prostate cancer is hormone-sensitive at the time of initial diagnosis. Although most patients with advanced metastatic disease initially respond to conventional androgen deprivation therapy with medical (8) or surgical (9) castration, the median duration of disease control has been 13 to 22 months and overall survival (OS) has been 28 to 36 months.(10) After progression to castration-resistant disease, approximately 90% of men already have bone metastases, with all their related undesirable effects, such as pain and deterioration of health-related QoL.(11) Patients with metastatic castration-resistant prostate cancer (CRPC) have a very limited life expectancy and most often die of their prostate cancer.(12)

Because more than 90% of patients with CRPC are at risk for bone metastases, an agent that specifically targets this major complication of disease and provides a survival benefit represents a relevant treatment option and major therapeutic advance. Radium-223 dichloride is approved in the United States (US) and the European Union (EU; as of 2013) for the treatment of CRPC patients with symptomatic bone metastases and no known visceral metastases. Approval was based on results of the randomized Phase 3 trial Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA), in which radium-223 prolonged OS and time

to first symptomatic skeletal event (SSE), versus placebo, among CRPC subjects with symptomatic bone metastases, and was generally well tolerated with low myelosuppression rates and manageable gastrointestinal adverse events (AEs).(2)

Breast cancer

Breast cancer is the most common cancer among women worldwide, with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers).(13)

Despite recent progress in diagnostic and therapeutic approaches of early breast cancer, a significant proportion of patients relapse following adjuvant treatment and approximately 5% of women present with metastatic disease at the time of their initial diagnosis.(14)

The clinical presentation in the metastatic setting may range from an aggressive clinical course in patients with multiple and/or extensive organ involvement to a rather indolent clinical course in those with a solitary or only few metastatic lesions (oligometastatic disease).

Bone is a frequent site of metastatic spread, with approximately 65% to 75% of patients with metastatic breast cancer having skeletal involvement.(15) The skeleton is the first site of distant spread in 46% to 47% of patients with breast cancer. Bone-only metastases have been reported to occur in 17% to 37% of women with metastatic breast cancer.(16,17,18)

Due to the disrupted bone remodeling process, patients with metastatic bone lesions are at risk of increased morbidity including skeletal complications typically referred to as skeletal-related events (SREs): pathological fracture, the need for radiotherapy to bone, the need for surgery to bone, spinal cord compression, and hypercalcemia.

These events will ultimately impair the patient's QoL and functional independence.

A multidisciplinary therapeutic approach is generally recommended in patients presenting with bone metastases. Current therapeutic options include systemic therapies such as endocrine therapies, chemotherapy, and BHAs (e.g., bisphosphonates, denosumab). Local therapies such as external beam radiotherapy as well as other supportive interventions (i.e., orthopedic interventions for prevention or correction of pathological fractures) are also an important part of the therapeutic management for symptom palliation.

Patients with multiple, mainly osteoblastic lesions and pain syndrome may also benefit from treatment with radionuclide therapy. Bone-seeking radionuclides have been developed for palliation of bone pain from metastases.(19) Metastron (strontium-89) and Quadramet (samarium-153 ethylene diamine tetramethylene phosphonate) have been approved in several countries for symptom palliation in patients with bone metastases.(20) The bone-seeking nature of these agents results in direct delivery of beta radiation to the sites of disease. Due to the long range of the beta particles from these radioisotopes, the major dose-limiting factor with this treatment modality is toxicity to the bone marrow cells, limiting the use of these agents to pain palliation only as they have not demonstrated an OS benefit. This toxicity has seriously limited their clinical use.

Multiple myeloma

Multiple myeloma is the 3rd most prevalent blood cancer after non-Hodgkin's lymphoma and leukemia, and represents approximately 1.8% of all cancers and 2.1% of all cancer deaths.(21)

Multiple myeloma is a cancer of plasma cells, differentiated B-cell lymphocytes normally responsible for producing antibodies. In multiple myeloma, collections of abnormal plasma cells accumulate in the bone marrow, interfering with the production of normal blood cells. Most cases of multiple myeloma also feature the production of a paraprotein, an abnormal immunoglobulin fragment, such as an immunoglobulin light chain, that can cause kidney problems. Bone lesions and hypercalcemia are also often encountered.

Multiple myeloma bone lesions are due to increased osteoclast activity and reduced osteoblast function, resulting from the overexpression of RANKL (receptor activator for nuclear factor-κB ligand) by bone marrow stroma (22). RANKL activates osteoclasts, which reabsorbs bone. The resultant bone lesions are lytic in nature and are best seen in plain radiographs, which may show "punched-out" reabsorptive lesions (including the "pepper pot" appearance of the skull on radiography). Bone pain affects more than 70% of subjects and is the most common symptom. Myeloma bone pain usually involves the spine and ribs, and worsens with physical activity. Persistent localized pain may indicate a pathological bone fracture. Involvement of the vertebrae may lead to spinal cord compression. The breakdown of bone also leads to release of calcium into the blood, leading to hypercalcemia and its associated symptoms.

The infiltration of the bone marrow with differentiated plasma cells that cause lytic lesions in large bones and vertebrae, leading to SREs, is a characteristic of relapsed multiple myeloma. The investigation of radium-223 dichloride in an *in vivo* multiple myeloma model has shown promising bone-targeting effects as monotherapy and in combination with bortezomib.(23)

All indications

Further details on radium-223 dichloride can be found in the latest version of the Investigator's Brochure (IB), which contains comprehensive information on the study drug.

Until now, no cases of myelodysplastic syndrome or bone sarcoma have been reported from clinical studies involving radium-223 dichloride. One case of acute promyelocytic leukemia was reported from study 16544 (biopsy confirmed) which was confounded by prior exposure to docetaxel. Two cases in ALSYMPCA were reported as aplastic anemia, one in the treatment arm (biopsy confirmed), confounded by prior exposure to samarium, docetaxel, and external radiation therapy, and 1 case in the placebo arm (without confirmed biopsy). In ALSYMPCA, 12 cases of new primary malignancies were observed, 7 in the radium-223 dichloride arm (N=600) and 5 in the placebo arm (N=301).(2) No cases of radium-223 dichloride-induced cancer have been reported in completed clinical studies in follow-up of up to 3 years.

1.2 Study rationale

Section modified by Amendment 2 (Section 13.2.1.1).

This study will be conducted to define the safety profile of radium-223 dichloride to meet a US Food and Drug Administration (FDA)-mandated post-marketing requirement and a request from the German Federal Office for Radiation Protection. The key attribute of radium-223 dichloride is its specific targeting of bone with limited radiation exposure beyond the intended target. However, the proximity of the bone marrow space to site of action of radium-223 dichloride means that there is potential for radiation-induced bone marrow abnormalities. These abnormalities, including bone marrow dysplasia or new primary malignancies, may not become evident until years after the initial exposure to radium-223 dichloride; therefore, long-term follow-up is required to detect them. For this reason, the long-term safety of radium-223 dichloride will be assessed in this study, with the follow-up period extending to up to 7 years after the last dose of radium-223 dichloride or placebo.

This study originally was intended to collect long-term follow-up data from prostate cancer studies only; however, radium-223 dichloride is also being studied for other indications. In order to collect comprehensive safety information across all clinical trials with radium-223 dichloride and to allow collection of long-term safety data across indications, subjects with breast cancer and multiple myeloma will also be allowed to enter the long-term follow-up study.

1.3 Benefit-risk assessment

In this study, the only study evaluation is capturing of safety and survival information every 6 months (face-to-face data collection is possible and will replace the telephone contact if the subject is on-site within the time window of the planned telephone contact). As such, there is no medical risk associated with participating in this trial. The benefit of study participation is longer follow-up of the subject and thereby potentially improved detection and treatment of possible side effects related to prior treatments or signs and symptoms of the disease itself.

2. Study objectives

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2.1.2).

The primary objectives are to define the long-term safety profile of radium-223 dichloride (for up to 7 years after the last dose of radium-223 dichloride); to assess the incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy; to assess the incidence of bone fractures and bone associated events (e.g., osteoporosis); and, in subjects who receive cytotoxic chemotherapy, to assess the incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice.

3. Study design

3.1 Design overview

Section modified by Amendments 1 (Section 13.1) and 2 (Sections 13.2.1.1, 13.2.1.2, and 13.2.1.9).

When eligible, subjects will enter this follow-up study and they, their health care professional, or caregiver will be contacted via telephone (face-to-face data collection is possible and will replace the telephone contact if the subject is on-site within the time window of the planned telephone contact) at 6-month intervals (± 28 days) to record:

- Investigator-reported radium-223 dichloride-/placebo-related AEs and related serious adverse events (SAEs);
- All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy;
- All bone fractures and bone associated events (e.g., osteoporosis), regardless of investigator assessment of causality
- Cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics);
- In subjects who receive cytotoxic chemotherapy, all occurrences of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter;
- Survival status.

Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data. The current study will be terminated at the time the last remaining subject in this study has completed the 7-year follow-up assessment period (or follow-up as defined in the feeder trial protocols) or died.

This study originally was intended to collect long-term follow-up data from prostate cancer studies only; however, radium-223 dichloride is also being studied for other indications. In order to collect comprehensive safety information across all clinical trials with radium-223 dichloride and to allow collection of long-term safety data across indications, subjects with breast cancer and multiple myeloma will also be allowed to enter the long-term follow-up study.

With the currently active feeder trials, approximately 800 subjects are expected to be accrued into this long-term safety follow-up study, but the number of subjects may increase if additional trials feed into this study.

3.2 Primary and secondary variables

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2.1.2).

This long-term follow-up study will enroll subjects who will be transferred from selected company-sponsored trials with radium-223 dichloride (feeder trials).

The primary variables are all safety-related and include:

- Incidence of and severity of radium-223 dichloride-/placebo-related AEs
- Incidence of radium-223 dichloride-/placebo-related SAEs
- Incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy
- Incidence of bone fractures and bone associated events (e.g., osteoporosis), regardless of investigator assessment of causality
- In subjects who receive cytotoxic chemotherapy: incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice

3.3 Justification of the design

This is primarily a descriptive safety study. All subjects enrolled in this study will have received at least 1 dose of radium-223 dichloride or placebo in the selected feeder trials and will be included in the safety evaluation. The subject population will include subjects treated with placebo and will therefore allow the comparison of the long-term safety profile with and without treatment with radium-223 dichloride.

The procedures chosen for the evaluation of long-term safety in this study population are consistent with the ethical standards used in studies of oncology drugs, and are appropriate for the long-term safety evaluation of subjects from the feeder trials.

3.4 End of study

The end of the study as a whole will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (EU and non-EU).

3.5 Primary completion

The primary completion event for this study is the last visit within the 7-year follow-up (or follow-up as defined in the feeder trial protocols) after last dose of radium-223 dichloride or placebo for the last remaining subject in this study for all centers in the respective country.

The primary completion date for this study according to the FDA Amendment Act is specified in a separate document (not part of this study protocol).

4. Study population

4.1 Inclusion criteria

Eligible subjects must meet the inclusion criteria listed below:

1. Subject was previously enrolled in a selected company-sponsored feeder trial, and has received at least 1 dose of radium-223 dichloride or placebo in the feeder trial.
2. Written informed consent.

4.2 Exclusion criteria

Not applicable to this follow-up study.

4.3 Justification of selection criteria

The selection criteria in this study are consistent with the ethical standards used in studies of oncology drugs, and are appropriate for the long-term safety evaluation of subjects from the feeder trials.

4.4 Withdrawal of subjects from study

4.4.1 Withdrawal

Section modified by Amendment 1 (Section 13.1).

Withdrawal criteria

Subjects *may* be withdrawn from study if the following reason occurs:

- At the specific request of the sponsor and in liaison with the investigator (e.g., obvious non-compliance, inability to provide medical information).

Subjects *will* be withdrawn from the study for the following reasons:

- Withdrawal of consent: At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a subject may withdraw consent and decline to participate further in the study. The subject will not suffer any disadvantage as a result. The subject will continue to be followed up until they complete the procedure for withdrawal of consent specified in this section.
- Lost to follow-up (i.e., the subject is not able to be contacted for 2 consecutive 6-month interval calls / visits): every attempt will be made to contact the subject
- Death

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 10 (Premature termination of the study).

For subjects who withdraw from the study prior to the End of Long-term Follow-up visit, the End of Long-term Follow-up visit assessments shall be completed.

In all cases, the reason for withdrawal from the study must be recorded in the electronic case report form (eCRF) and in the source documentation.

Drop-out

Drop-out is defined as a subject who discontinues study participation prematurely for any reason.

General procedures

The subject may object to the generation and processing of post-withdrawal data as specified in Section 11.4.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Process for withdrawal of consent

In order to ensure complete study data, it is specified in the informed consent form (ICF) that the subject agrees to complete follow-up assessments for 7 years in the study (or follow-up as defined in the feeder trial protocols). Only subjects who sign permission to collect this follow-up data should be included in the study.

The subject or his legally acceptable representative can withdraw this initial permission for study participation. In this case, the subject has to expressively inform the investigator (study staff is not sufficient).

4.4.2 Replacement

Withdrawn subjects will not be replaced.

4.5 Subject identification

Each subject will be assigned a new subject number (a unique identification number) for participation in this follow-up study.

The subject number is a 9 digit number consisting of:

Digits 1 to 2 = Country code
Digits 3 to 5 = Center number within the country
(Digits 1 to 5 = Trial unit)
Digits 6 to 9 = Current subject number within the center

The subject was previously enrolled in a selected radium-223 dichloride feeder trial; the site will enter the previous study number and the previous subject number on the Demography page of the eCRF.

5. Treatments

5.1 Treatments to be administered

No study treatment will be provided in this long-term follow-up study. Subjects received at least 1 dose of radium-223 dichloride or placebo in the selected company-sponsored feeder trials.

5.2 Identity of study treatment

Not applicable to this follow-up study.

5.3 Treatment assignment

Not applicable to this follow-up study.

5.4 Dosage and administration

Not applicable to this follow-up study.

5.5 Blinding

Not applicable to this follow-up study.

5.6 Drug logistics and accountability

Not applicable to this follow-up study.

5.7 Treatment compliance

Not applicable to this follow-up study.

6. Non-study therapy

6.1 Prior and concomitant therapy

Section modified by Amendments 1 (Section 13.1) and 2 (Sections 13.2.1.3, 13.2.1.4, 13.2.1.5, and 13.2.1.7).

Continuation or start of any background therapy and concomitant treatment including as part of a clinical trial is allowed in this follow-up study; however, continuation of feeder trial study drug is not allowed. Radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone.

All cancer treatments or medications (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics) received during this follow-up study will be recorded. The generic or trade name, indication, dosage, and start and stop dates must be recorded.

Based on the available data on radium-223 dichloride, the option of starting a BHA should be considered, taking into consideration applicable guidelines. Any BHA treatment taken during the study period must be recorded.

6.2 Post-study therapy

Not applicable to this follow-up study.

7. Procedures and variables

7.1 Tabular schedule of evaluations

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2.1.2, 13.2.1.4, and 13.2.1.9).

A summary of the schedule of assessments is provided in Table 7–1.

Table 7–1 Schedule of assessments

Timing:	Study Enrollment Prior to enrollment	Long-term Follow-up	
		Long-term Follow-up	End of Long-term Follow-up
		Every 6 mos until death[a]	
Window (days):		± 28	
Eligibility confirmation (check inclusion criteria)	X		
Signing of informed consent form	X		
Radium-223 dichloride-/placebo-related AEs; related SAEs; and occurrence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy.		X[b]	X[b]
All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.		X[b]	X[b]
Subjects who receive cytotoxic chemotherapy will be followed up for the occurrence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice		X[b]	X[b]
Cancer treatment[c]		X[b]	X[b]
BHA use[d]		X[b]	X[b]
Survival status		X[b]	X[b]

Abbreviations: AE = adverse event; BHA = bone health agent; eCRF = electronic case report form; mos = months; SAE = serious adverse event

a Telephone follow-up every 6 months (± 28 days) for 7 years (or follow-up as defined in the feeder trial protocols) post the last dose of radium-223 dichloride or placebo in the feeder trial or until death. Face-to-face data collection is possible and will replace the telephone contact if the subject is on-site within the time window of the planned telephone contact.

b It is the clinical site's responsibility to obtain and make available the source documentation for the information collected and to document it in the eCRF.

c Record any cancer treatments or medications (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics).

d Initiation of BHAs, including bisphosphonates or denosumab, should be considered taking into consideration applicable guidelines. Any BHA treatment taken during the study period must be recorded.

7.2 Visit description

7.2.1 Study enrollment

The subject must sign the ICF prior to any study-specific assessments (enrollment in the study is defined as the signing of the ICF). Confirmation of eligibility criteria must occur at the time of signing the ICF.

7.2.2 Long-term follow-up

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2.1.2, 13.2.1.4, and 13.2.1.9).

Subjects, their treating health care professional, or caregiver will be contacted by telephone (face-to-face data collection is possible and will replace the telephone contact if the subject is on-site within the time window of the planned telephone contact) every 6 months (± 28 days) for 7 years (or follow-up as defined in the feeder trial protocols) following the last radium-223 dichloride or placebo treatment in the feeder trial or until death, to determine the following:

- All radium-223 dichloride-/placebo-related AEs and related SAEs occurring during this period have to be documented and reported. Concomitant treatment associated with these events will not be collected unless it is cancer medication / treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics) or new BHA treatment. If a subject is unable to provide required details for events of interest, this information will need to be obtained from the primary provider.
- All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer, or any other new primary malignancy must be reported as SAEs at any time and regardless of the investigator's causality assessment.
- All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- Cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics).
- Any BHA treatment taken during the study period must be recorded.
- In subjects who receive cytotoxic chemotherapy, all occurrences of febrile neutropenia or hemorrhage during chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice.
- Survival status.

Training for conducting the follow-up contacts will be provided to clinical site personnel including, but not limited to, use of a telephone script. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

It is the clinical site's responsibility to obtain and make available the source documentation for the information collected from the subject and document it in the eCRF.

7.2.3 End of long-term follow-up

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2.1.2, 13.2.1.4, and 13.2.1.9).

The end of study assessments for subjects who are in this follow-up study will include the following:

- All radium-223 dichloride-/placebo-related AEs and related SAEs have to be documented and reported. Concomitant treatment associated with these events will not be collected unless it is cancer medication / treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics). If a subject is unable to provide required details for events of interest, this information will need to be obtained from the primary provider.
- All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer, or any other new primary malignancy must be reported as SAEs at any time and regardless of the investigator's causality assessment.
- All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- Cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics).
- Any BHA treatment taken during the study period must be recorded.
- In subjects who receive cytotoxic chemotherapy, all occurrences of febrile neutropenia or hemorrhage during chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice.
- Survival status.

Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

It is the clinical site's responsibility to obtain and make available the source documentation for the information collected from the subject and document it in the eCRF.

7.3 Population characteristics

This study will enroll subjects from selected company-sponsored feeder trials who received at least 1 dose of study drug (radium-223 dichloride or placebo).

7.3.1 Demographic

Demographic information will be carried over from the selected feeder trials.

7.3.2 Medical history

Section modified by Amendment 1 (Section 13.1).

All medical history will be carried over from the selected feeder trials.

7.4 Pharmacokinetics / pharmacodynamics

Section modified by Amendments 1 (Section 13.1).

No pharmacokinetic or pharmacodynamics assessments will be performed for this study.

7.5 Safety

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2.1.2 and 13.2.1.9).

The investigator(s) and the sponsor's representative will review the safety data throughout the course of the study. The following safety variables will be evaluated:

- Adverse events: radium-223 dichloride-/placebo-related AEs and related SAEs will be collected and recorded on an ongoing basis throughout the study as described in Section 7.5.1.
- All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer, or any other new primary malignancy.
- All bone fractures and bone associated events (e.g., osteoporosis), regardless of investigator assessment of causality
- In subjects who receive cytotoxic chemotherapy, all occurrences of febrile neutropenia or hemorrhage during chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice.
- Deaths

7.5.1 Adverse events

7.5.1.1 Definitions

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2.1.2).

Definition of AE

In a clinical study, an AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In this study, for an event to be classified as an AE, it must be considered to be related to radium-223 dichloride/placebo by the investigator, and ongoing at or occurring from the time of the signing of the ICF and the end of the study. Also classified as AEs (regardless of the investigator's causality assessment) are all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer, or any other new primary malignancy; all bone fractures and bone associated events (e.g., osteoporosis) regardless of the investigator's

causality assessment; and, in subjects who receive cytotoxic chemotherapy, all occurrences of febrile neutropenia or hemorrhage.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following definitions of AEs from the feeder trials, the term "condition" may include abnormal symptoms and diseases.

- Conditions considered to be related to radium-223 dichloride/placebo by the investigator that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent will be carried over from the feeder trial and documented as AEs.
- Conditions considered to be related to radium-223 dichloride/placebo by the investigator that started or deteriorated after signing of informed consent will be documented as AEs. This includes intercurrent illnesses considered to be related to radium-223 dichloride/placebo by the investigator.

Definition of serious adverse event

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a - g):

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   – The admission results in a hospital stay of less than 12 hours

   – The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 7.2).

   – The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care)

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

d. Results in persistent or significant disability / incapacity

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

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

g. Is an occurrence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy (regardless of the investigator's causality assessment)

If disease progression leads to signs and symptoms that meet the criteria for seriousness (e.g., hospitalization), the associated signs and symptoms should be reported as SAEs, not the underlying cause (i.e., "progressive disease" should not be recorded as an SAE). In this case disease progression should be mentioned on the SAE form as an "alternative explanation."

An isolated laboratory abnormality that meets the criteria for National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard International Conference of Harmonisation criteria for an SAE. All laboratory abnormalities, including CTCAE Grade 4 abnormalities, will be documented on the laboratory eCRF (including values reported from central laboratories).

7.5.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

7.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.5.1.1.

7.5.1.2.2 Intensity

In this follow-up study, the intensity of an AE is classified according to the NCI-CTCAE grading (Version 4.03) as defined in each of the feeder trials.

7.5.1.2.3 Causal relationship

Section modified by Amendment 2 (Section 13.2.1.2 and 13.2.1.9).

Only radium-223 dichloride-/placebo-related AEs and related SAEs will be collected and recorded in this study. All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs at any time, and regardless of the investigator's causality assessment. All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

The assessment of the causal relationship between an AE and the radium-223 dichloride/placebo treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the eCRF.

The assessment is based on the question whether there was a "reasonable causal relationship" to radium-223 dichloride/placebo.

Possible answers are "yes" or "no"

An assessment of "no" would include:

1. The existence of a highly likely alternative explanation, e.g., mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g., the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that the AE is reasonably associated with the use of radium-223 dichloride/placebo.

Important factors to be considered in assessing the relationship of the AE to radium-223 dichloride/placebo include:

- The temporal sequence from drug administration during the feeder trial:
  The event should occur after the drug was given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: clinical / preclinical
- Exposure to physical and / or mental stresses:
  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of radium-223 dichloride/placebo, coupled with the individual subject's pharmacodynamics should be considered.
- The assessment is not possible

7.5.1.2.4 Action taken with study treatment

Not applicable to this follow-up study.

7.5.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy

- Other

7.5.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered / resolved
- Recovering / resolving
- Recovered / resolved with sequelae
- Not recovered / not resolved
- Fatal
- Unknown

7.5.1.3 Assessments and documentation of adverse events

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2.1.2).

The investigator has to record on the respective eCRF pages all radium-223 dichloride-/ placebo-related AEs ongoing at or occurring from the time of the signing of the ICF and the end of the study. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 7.5.1.2.

Each event should be described in detail along with start and stop dates (onset and resolution of event), intensity, temporal and causal relationship to feeder trial-related investigational product and / or protocol-related procedures, possible alternative factors (co-morbidities, co-medications), therapeutic action taken, result of therapeutic action, and ultimate outcome of the AE. The investigator's assessment of AEs with grades and causality assessments must be documented and retained in the source documentation.

If more than one radium 223-dichloride- or placebo-related AE occurs, each event should be recorded separately. All AEs and SAEs are to be followed until resolved or as clinically required.

All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs at any time, and regardless of the investigator's causality assessment. All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. If a subject is unable to provide required details for events of interest, this information will need to be obtained from the primary provider.

Adverse events may be reported spontaneously by the subject, the subject's health care professional, or the subject's caregiver, or elicited through questioning during each follow-up telephone call and / or visit during the study. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data. As far as possible, all radium-223 dichloride-/placebo-related AEs must be described by their duration (start and stop date), severity (graded according to the NCI-CTCAE, Version 4.03), relationship to treatment, and according to the need of other specific therapy. All information will be recorded in the source documentation and AE eCRF.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to radium-223 dichloride/placebo.

7.5.1.4 Reporting of serious adverse events

Section modified by Amendment 2 (Section 13.2.1.2).

The definition of SAEs is given in Section 7.5.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

If disease progression leads to signs and symptoms that meet the criteria for seriousness (e.g., hospitalization), the associated signs and symptoms should be reported as SAEs, not the underlying cause (i.e., "progressive disease" should not be recorded as an SAE). In this case, disease progression should be mentioned on the SAE form as an "alternative explanation."

Reporting of additional malignancies

All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs at any time, regardless of the investigator's causality assessment.

Reporting of bone fractures and bone associated events

All bone fractures and bone associated events (e.g., osteoporosis) should be collected as SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the Investigator Site File. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs considered to be related to radium-223 dichloride/placebo; all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy; and bone fractures and bone associated events (e.g., osteoporosis; (if the criteria of SAE were met, regardless of the investigator's causality assessment) occurring during the observation period defined in Section 7.5.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the eCRF as well as the complementary pages provided in the Investigator File must be completed for each SAE.

Any SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Any CTCAE Grade 4 screening laboratory abnormality that is part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the

protocol inclusion / exclusion criteria. If an investigator is in doubt about the applicable reporting obligations, he / she should consult with the study monitor for the sponsor.

Notification of the Independent Ethics Committees / Institutional Review Boards

Notification of the Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) about all relevant events (e.g., SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and / or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g., SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g., SUSARs) according to all applicable regulations.

7.5.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the IB / summary of product characteristics.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

7.5.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a female study subject during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For a pregnancy in the partner of a male study subject, all efforts will be made to obtain information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

7.6 Other procedures and variables

Not applicable to this follow-up study.

7.7 Appropriateness of procedures / measurements

The procedures chosen for the evaluation of long-term safety in this study population are consistent with the appropriate ethical standards used in studies of oncology drugs.

8. Statistical methods and determination of sample size

8.1 General considerations

Statistical analysis will be performed using Statistical Analysis Software; the version used will be specified in the statistical analysis plan (SAP).

8.2 Analysis sets

Section modified by Amendment 1 (Section 13.1).

Safety: All subjects who have received at least 1 dose of radium-223 dichloride or placebo in the feeder trials. This safety population will be used in the analysis of all safety endpoints. Subjects will be included in the analyses according to the treatment they received.

8.3 Variables and planned statistical analyses

8.3.1 Primary and secondary variables

The primary and secondary variables are as defined in Section 3.2.

8.3.2 Statistical and analytical plans

Section modified by Amendment 1 (Section 13.1).

Studies of all clinical phases with different designs and different endpoints will be included in the evaluation. There will be separate analyses of the individual feeder trials, and pooled analysis of the final data across studies, as appropriate.

All statistical analyses will be descriptive in nature. In general, summary statistics (n, mean, standard deviation, median, minimum, maximum, and 95% confidence intervals for continuous variables, and number of subjects and percentage in each category for categorical variables) will be provided.

No formal statistical testing is planned for the overall analysis. Source data for summaries will be presented as subject data listings.

The details for analyses will be specified in the SAP.

8.3.2.1 Safety analysis

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2.1.2).

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities and grouped by system organ class and preferred term. Events will be summarized by frequency and proportion of total subjects, system organ class, and preferred term.

The safety data from feeder trials and 16996 will be combined within each study for all AE summaries. For pooled analyses, all data across the selected feeder trials and 16996 will be combined by treatment groups and by treatment doses, as appropriate. Separate summaries will be given for: all events related to study drug, all events by NCI-CTCAE grade, SAEs, and AEs leading to death.

Deaths and SAEs will be summarized and listed.

The incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy; the incidence of bone fractures and bone associated events (e.g., osteoporosis); and for subjects who receive cytotoxic chemotherapy, the incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter, will be summarized using statistical measures that will depend upon whether the study includes a comparator group or is a single-cohort study. Other considerations include the length of follow-up time and time-to-event methods.

Statistical measures that can be used include incidence proportion, incidence rate, and cumulative incidence (or competing risk approach). Definitions of each measure will be described in detail in the SAP.

8.3.3 Missing data / drop outs

Missing data will not be imputed for statistical analysis. However, when appropriate, rules for handling missing or partial information will be implemented so as not to exclude data from subjects for analyses due to missing or partially complete data. The details for the handling of missing data will be specified in the SAP.

8.4 Determination of sample size

Sample size calculation is not applicable for this follow-up study. All subjects from the feeder trials may participate in this study on a voluntary basis.

8.5 Planned interim analyses

Section modified by Amendment 1 (Section 13.1).

There are no planned interim analyses.

9. Data handling and quality assurance

9.1 Data recording

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet-based electronic data capture (EDC) software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking

access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made, and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

It is the expectation of the sponsor that key data entered into the eCRF have source documentation available at the site.

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

9.2 Monitoring

In accordance with applicable regulations, Good Clinical Practice (GCP), and sponsor's / clinical research organization's (CRO's) procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor / designee will monitor (remotely or on-site) the site activity to verify that the:

- Data are authentic, accurate and complete. Supporting data may be requested
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol
- Any other study agreements, GCP, and all applicable regulatory requirements are met

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.3 Data processing

Data will be collected as described in Section 9.1. Clinical data management will be performed in accordance with applicable sponsor's / CRO's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources.

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

9.4 Missing data

As specified in Section 8.3.3, the details for the handling of missing data will be specified in the SAP.

9.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator / institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s) / IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator / institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his / her time and the time of his / her staff to the auditor / inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

9.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator / institution will notify the sponsor if the archival arrangements change (e.g., relocation or transfer of ownership).

The Investigator Site File is not to be destroyed without the sponsor's approval.

The contract with the investigator / institution will contain all regulations relevant for the study center.

10. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g., treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,

  - Safety findings from this study (e.g., SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g., recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame

The investigator has the right to close his / her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g., IEC[s] / IRB[s]; competent authority[ies]; study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing subjects, including those in post-study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 4.4.1.

11. Ethical and legal aspects

11.1 Investigator(s) and other study personnel

Section modified by Amendment 2 (Section 13.2.1.8, 13.2.1.9, and 13.2.1.10).

The sponsor's Medical Expert for this study is:

Name: PPD PPD

Address: PPD

SBU Oncology – Development Operations

Bayer S.p.A. – socio unico

Medical & Data Management

Viale Certosa, 210

20156 Milano, Italy

Telephone No: PPD

The coordinating principal investigator, planned as the final clinical study report signatory, will be identified in the future.

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's Investigator Site File.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained, and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g., health authority, ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

External data evaluation bodies (e.g., Independent Data Monitoring Committee [IDMC])

There will be no IDMC in the study, as it is not applicable to this follow-up study.

11.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and / or any sub-investigator) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

11.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s) / IRBs will be obtained for all participating centers / countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment, or renewal of the IEC / IRB approval must be obtained and also forwarded to the sponsor. The responsible unit

(e.g., IEC / IRB, head of the study center / medical institution) 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 GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC / IRB / sponsor approval or favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC / IRB / head of medical institution / sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 10.

11.4 Subject information and consent

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2.1.6 and 13.2.1.11).

All relevant information on the study will be summarized in an integrated subject information sheet and ICF provided by the sponsor or the study center. A sample subject information and ICF is provided as a document separate to this protocol. Subjects will not be compensated for taking part in this study.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject / legal representative or proxy consenter (if the subject is under legal protection), prior to his / her entry into the study (i.e., before any procedures associated with the selection for the study are performed or any study-specific data are recorded on study-specific forms).

The investigator will also mention that written approval of the IRB / IEC has been obtained.

Each subject / legal representative or proxy consenter will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the SAP.

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the ICF and has done so, may he / she enter the study. Additionally, the investigator will personally

sign and date the form. The subject / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the Investigator Site File or, if locally required, in the patient's note / file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The ICF and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written ICF. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his / her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC's / IRB's approval / favorable opinion in advance of use.

11.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his / her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

Non-study-related use of data, samples or images

Not applicable to this follow-up study.

11.6 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

11.7 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and / or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g., pathologist report), 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. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC / IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

12. Reference list

Section modified by Amendment 2 (Section 13.2.1.1).

1. Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol. 2007;8(7):587-94.
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13. Protocol amendments

13.1 Amendment 1

Amendment 1 (dated 13 SEP 2016) is an amendment to the original protocol dated 03 SEP 2014. Changes to the protocol include:

- Updated the protocol to reflect the recent Bayer AG legal entity name change
- Updated the study GCL name
- Clarified that all cytotoxic chemotherapy and radiotherapy received by subjects is to be recorded for this study
- Clarified the secondary variable, the safety analyses, and removed secondary objective and reference to an interim analysis
- Added an option for the study site to obtain information directly from the subject's primary health care professional or caregiver
- Removed references to collection of medical history
- Removed protocol language not applicable to this study

13.1.1 Overview of changes

Modification 1

Updated the protocol to reflect the recent Bayer AG legal entity name change.

Rationale: Bayer HealthCare AG merged with Bayer AG, an affiliated company within the Bayer Group, effective as of 1st July 2016. Thereby, Bayer Healthcare AG ceased to exist and Bayer AG became its legal successor and automatically took over all of the Bayer HealthCare AG's rights, obligations, and liabilities by law. As a result of the above mentioned merger, Bayer AG assumes the role of the sponsor for these trials. Bayer HealthCare Pharmaceuticals Inc. is and has at any time been the sponsor for the US territory for this trial as set forth in FDA IND form 1571.

Sections affected include:

- Headers
- Title Page

Modification 2

Updated the study GCL name.

Rationale: Change reflects the current protocol signatory.

Sections affected include:

- Signature of the sponsor's medically responsible person

Modification 3

Clarified that all cytotoxic chemotherapy and radiotherapy received by subjects is to be recorded for this study.

Rationale: To clarify for study sites that all chemotherapies and radiotherapies are to be reported for subjects in this study; reporting of chemotherapies and radiotherapies is not restricted to prostate cancer treatment.

Sections affected include:

- Synopsis – Methodology
- 3.1 – Design overview
- 6.1 – Prior and concomitant therapy
- 7.1 – Tabular schedule of evaluations: footnote 'c'
- 7.2.2 – Long-term follow-up
- 7.2.3 – End of long-term follow-up

Modification 4

Clarified the secondary variable, the safety analyses, and removed secondary objective and reference to an interim analysis

Rationale: This is a safety follow-up study and analysis of OS will be performed within the feeder studies. Therefore, the secondary objective related to OS and references to efficacy analyses (of OS) were removed. References to interim analyses were removed as no interim analysis is currently planned.

Sections affected include:

- Synopsis – Study objective(s)
- Synopsis – Primary/secondary variables
- Synopsis – Plan for statistical analysis
- 2 – Study objectives
- 3.2 – Primary and secondary variables
- 7.4 – Efficacy
- 7.5 – Safety
- 8.2 – Analysis sets
- 8.3.2 Statistical and analytical plans
- 8.3.2.1 – Efficacy analysis
- 8.3.2.1 – Safety analysis
- 8.5 – Planned interim analyses

Modification 5

Added an option for the study site to obtain information directly from the subject's primary health care provider.

Rationale: Provides the option for sites to collect study data directly from subject's health care professionals or caregiver in case the subject or his/her care provider is unable to provide information or to obtain cleaner data.

Sections affected include:

- Synopsis - Methodology
- 3.1 – Design overview
- 7.2.2 – Long-term follow-up
- 7.6.1.3 (now 7.5.1.3) – Assessments and documentation of adverse events

Modification 6

Removed references to collection of medical history.

Rationale: Medical history is not being collected by the study sites for this study, it is being rolled over directly from the feeder study databases. Therefore, reference to recording medical history has been removed to improve clarity.

Sections affected include:

- 7.3.2 – Medical history
- 7.6.1.1. – Definitions

Modification 7

Removed protocol language not applicable to this study.

Rationale: Standard protocol language had been carried over to this protocol that was not applicable to the procedures for this safety follow-up study. This language has been removed.

Sections affected include:

- 4.4.1 – Withdrawal (Process for withdrawal of consent)
- 7.6.1.3 (now 7.5.1.3) – Assessments and documentation of adverse events
- 11.4 – Subject information and consent

13.1.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text". Corrections of typing errors or omissions are not highlighted in this amendment.

Page Headers

This section was changed as a result of Modification 1.

Old text:

New text:

Title page: Sponsor

This section was changed as a result of Modification 1.

Old text:

~~**Bayer HealthCare AG, D-51368 Leverkusen, Germany**~~

New text:

a) (Non-US): Bayer AG, D-51368 Leverkusen, Germany

b) (US territory): Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, USA

Signature of sponsor's medically responsible person

This section was changed as a result of Modification 2.

Old text:

PPD

New text:

PPD

Synopsis: Study objective(s); 2: Study objectives

This section was changed as a result of Modification 4.

Deleted text:

~~The secondary objective is to evaluate overall survival (OS).~~

Synopsis: Methodology; 7.2.2: Long-term follow-up

This section was changed as a result of Modification 5.

Added text:

Subjects, their treating health care professional, or caregiver will be contacted by telephone (face-to-face data collection is possible and will replace the telephone contact if the subject is on-site within the time window of the planned telephone contact) every 6 months (± 28 days) for 7 years (or as defined in the feeder trial protocols) following the last dose of radium-223 dichloride or placebo in the feeder trial, or until death, to determine the following:

Synopsis: Methodology, 3.1: Design overview, 7.2.2: Long-term follow-up, 7.2.3: End of long-term follow-up

This section was changed as a result of Modification 3.

Old text:

Cancer treatment (including androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics)

New text:

Cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics)

Synopsis: Primary/secondary variables, 3.2: Primary and secondary variables

This section was changed as a result of Modification 4.

Deleted text:

~~The secondary variable is OS, defined as the time in days from the applicable feeder trial start date to the date of death due to any cause~~.

Synopsis: Plan for statistical analysis

This section was changed as a result of Modification 4.

Old text:

~~All subjects who received at least 1 dose of radium-223 dichloride or placebo in the selected feeder trials and who have post-baseline survival data available will be used for the determination of OS and will be grouped according to the treatment to which they are randomized / assigned in the feeder trial.~~

~~Adverse events, as defined in this study protocol, for the subjects from the selected feeder trials will be combined by treatment groups and by treatment doses, as appropriate. Overall analysis will include all radium-223 dichloride-treated subjects from the feeder trials combined in 1 group. The combined safety data will be used for all AE summaries, including subgroup analyses to reflect the patient population that entered this study.~~

~~An informal interim analysis is planned for combined data as well as individual data from the feeder trials.~~ Additional statistical analysis will be performed as described in the 16996 statistical analysis plan (SAP), feeder trial SAPs, and /or as previously communicated to Health Authorities.

New text:

The safety data from feeder trials and 16996 will be combined within each study for all AE summaries. For pooled analyses, all data across the selected feeder trials and 16996 will be combined by treatment groups and by treatment doses, as appropriate.

Additional statistical analysis will be performed as described in the 16996 statistical analysis plan (SAP), feeder trial SAPs, and /or as previously communicated to Health Authorities.

Section 3.1: Design overview

This section was changed as a result of Modification 5.

Added text:

When eligible, subjects will enter this follow-up study and they, their health care professional, or caregiver will be contacted via telephone (face-to-face data collection is possible and will replace the telephone contact if the subject is on-site within the time window of the planned telephone contact) at 6-month intervals (± 28 days) to record:

Section 4.4.1: Withdrawal

This section was changed as a result of Modification 7.

Deleted text:

In this case, the subject has to expressively inform the investigator (study staff is not sufficient) ~~and has to sign the Declaration of Objection to the Collection of Study Data after Withdrawal of Consent. The objection is also valid, if the declaration is not in place for any reason, but the investigator documented the objection in the source documentation~~.

Section 6.1: Prior and concomitant therapy

This section was changed as a result of Modification 3.

Old text:

All cancer treatments or medications (including androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics) received during this follow-up study will be recorded. The generic or trade name, indication, dosage, and start and stop dates must be recorded.

New text:

All cancer treatments or medications (including any systemic cytotoxic chemotherapy and radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics) received during this follow-up study will be recorded. The generic or trade name, indication, dosage, and start and stop dates must be recorded.

Section 7.1: Tabular schedule of evaluations; footnote 'c'

This section was changed as a result of Modification 3.

Old text:

c Record any cancer treatments or medications (including androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics).

New text:

c Record any cancer treatments or medications (including any systemic cytotoxic chemotherapy and radiotherapy for any malignancy; androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics).

Section 7.2.2: Long-term follow-up, 7.2.3: End of long-term follow-up

This section was changed as a result of Modification 3.

Old text:

All radium-223 dichloride-/placebo-related AEs and SAEs occurring during this period have to be documented and reported. Concomitant treatment associated with these events will not be collected unless it is cancer medication / treatment (including androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics). If a subject is unable to provide required details for events of interest, this information will need to be obtained from the primary provider.

New text:

All radium-223 dichloride-/placebo-related AEs and SAEs occurring during this period have to be documented and reported. Concomitant treatment associated with these events will not be collected unless it is cancer medication / treatment (including <u>any systemic cytotoxic chemotherapy and radiotherapy for any malignancy;</u> androgen synthesis inhibitors / androgen-receptor antagonists and radiation treatment; excluding analgesics). If a subject is unable to provide required details for events of interest, this information will need to be obtained from the primary provider.

Section 7.3.2: Medical history

This section was changed as a result of Modification 6.

Old text:

~~Relevant~~ medical history will be carried over from the selected feeder trials.

~~Detailed instructions on the differentiation between (i) medical history and (ii) AEs can be found in Section 7.6.1.1.~~

New text:

<u>All</u> medical history will be carried over from the selected feeder trials.

Section 7.4: Efficacy

This section was changed as a result of Modification 4.

Section deleted in its entirety.

Was Section 7.6, now Section 7.5: Safety

This section was changed as a result of Modification 4.

New bullet:

- <u>Deaths</u>

Was Section 7.6.1.1, now Section 7.5.1.1: Definitions

This section was changed as a result of Modification 6.

Old text:

In the following ~~differentiation between medical history and AEs~~, the term "condition" may include abnormal symptoms and diseases.

- ~~Conditions not considered to be related to radium-223 dichloride/placebo by the investigator that started before signing of informed consent and for which no symptoms or treatment are present after signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).~~
- ~~Conditions not considered to be related to radium-223 dichloride/placebo by the investigator that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g., allergic pollinosis).~~

New text:

In the following definitions of AEs from the feeder trials, the term "condition" may include abnormal symptoms and diseases.

Section 7.6.1.3 (now 7.5.1.3): Assessments and documentation of adverse events

This section was changed as a result of Modifications 5 and 7.

Old text:

Adverse events may be reported spontaneously by the subject or elicited through ~~open (non-leading)~~ questioning during each follow-up telephone call and / or visit during the study.

New text:

Adverse events may be reported spontaneously by the subject, the subject's health care professional, or the subject's caregiver, or elicited through questioning during each follow-up telephone call and / or visit during the study.

Section 8.2: Analysis sets

This section was changed as a result of Modification 4.

Deleted text:

~~The following 2 populations will be defined:~~

~~**Intent-to-treat:** All subjects who have received at least 1 dose of radium-223 dichloride or placebo in the feeder trials and who have post-baseline (of applicable feeder trial) survival data available will be used for the determination of OS. Subjects will be included in this analysis according to the treatment to which they were randomized / assigned in the feeder trial.~~

Section 8.3.2: Statistical and analytical plans

This section was changed as a result of Modification 4.

Old text:

There will be separate analyses ~~at the interim cut~~ of the individual feeder trials, pooled analysis of the ~~interim cut,~~ final ~~analysis of the individual feeder trials, and pooled analysis of the final~~ data

New text:

There will be separate analyses of the individual feeder trials, and pooled analysis of the final data across studies, as appropriate

Section 8.3.2.1: Efficacy analysis

This section was changed as a result of Modification 4.

Section deleted in its entirety.

Was Section 8.3.2.2, now Section 8.3.2.1: Safety analysis

This section was changed as a result of Modification 4.

Old text:

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities and grouped by system organ class and preferred term. Events will be summarized by frequency and proportion of total subjects, system organ class, and preferred term.

~~Adverse events for the subjects from the feeder trials will be combined by treatment groups and by treatment doses, as appropriate. Overall analysis will include all radium-223 dichloride treated subjects from the feeder trials combined in 1 group. The combined safety data will be used for all AE summaries, including subgroup analyses to reflect the patient population that entered this study.~~

~~Separate summaries will be given for: all events, all events by NCI-CTCAE grade, SAEs, AEs leading to death, and AEs leading to discontinuation.~~

Deaths~~,~~ SAEs~~, and AEs leading to discontinuation~~ will be summarized and listed.

The incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy; and for subjects who receive cytotoxic chemotherapy, the incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter, will be summarized using statistical measures that will depend upon whether the study includes a comparator group or is a single-cohort study. Other considerations include the length of follow-up time and time-to-event methods.

Statistical measures that can be used include incidence proportion, incidence rate, ~~KM rate (or 1 minus the KM rate),~~ and cumulative incidence (or competing risk approach). Definitions of each measure will be described in detail in the SAP.

New text:

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities and grouped by system organ class and preferred term. Events will be summarized by frequency and proportion of total subjects, system organ class, and preferred term.

The safety data from feeder trials and 16996 will be combined within each study for all AE summaries. For pooled analyses, all data across the selected feeder trials and 16996 will be combined by treatment groups and by treatment doses, as appropriate. Separate summaries will be given for: all events related to study drug, all events by NCI-CTCAE grade, SAEs, and AEs leading to death.

Deaths and SAEs will be summarized and listed.

The incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy; and for subjects who receive cytotoxic chemotherapy, the incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter, will be summarized using statistical measures that will depend upon whether the study includes a comparator group or is a single-cohort study. Other considerations include the length of follow-up time and time-to-event methods.

Statistical measures that can be used include incidence proportion, incidence rate, and cumulative incidence (or competing risk approach). Definitions of each measure will be described in detail in the SAP.

Section 8.5: Planned interim analyses

This section was changed as a result of Modification 4.

Old text:

~~One informal interim analysis is planned for combined data from all feeder trials prior to the completion of the last feeder trial. In addition, interim analysis is planned for the individual feeder trials, including subgroup analyses with regard to population, doses, comparative treatment, and combination treatment groups, as appropriate. Additional statistical analysis will be performed as described in the 16996 SAP, feeder trial SAPs, and / or as previously communicated to Health Authorities.~~

New text:

There are no planned interim analyses.

Section 11.4: Subject information and consent

This section was changed as a result of Modification 7.

Deleted text:

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject / legal representative or proxy consenter (if the subject is under legal protection), prior to his / her entry into the study (i.e., before ~~any examinations and~~ procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB / IEC has been obtained.

Each subject / legal representative or proxy consenter will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- ~~The subject's consent covers end-of-study examinations as specified in the visit description described in Section 7.2 to be conducted after withdrawal of consent.~~
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the SAP.

~~Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the SAP. The subject has the right to object to the generation and processing of this post-withdrawal data. For this, he needs to sign a corresponding declaration of objection; alternatively, the subject's oral objection may be documented in the subject's source data.~~

13.2 Amendment 2

Amendment 2 (dated 11 APR 2018) is an amendment to the integrated protocol version 2.0 dated 13 SEP 2016. Changes to the protocol include:

- Updated indications to include breast cancer and multiple myeloma.
- New request that bone fractures and bone associated events (e.g., osteoporosis) need to be reported as (S)AEs, including during long-term follow-up, regardless of investigator's causality assessment.
- Addition that radium-223 dichloride should not be given with abiraterone plus prednisone/prednisolone.
- Based on the available data on radium-223 dichloride, initiation of BHAs, including bisphosphonates or denosumab, should be considered taking into consideration applicable guidelines. Any BHA treatment taken during the study period must be recorded.
- Deletion of guidance related to recording of contrast media.
- Clarification that subjects will not be compensated for taking part in this study.
- Clarification that subjects are permitted to take concomitant medications as part of a clinical trial while participating in the current study.
- Clarification that there will be no independent data monitoring committee.
- Clarification of reporting of related SAEs.
- Updated the study Global Clinical Leader and Study Medical Expert names.
- Minor clarifications

13.2.1 Overview of changes

13.2.1.1 Modification 1

Updated indications to include breast cancer and multiple myeloma.

Sections affected include:

- 1 Introduction
- 3 Study design
- 12 Reference list

Rationale: This study is being conducted to define the safety profile of radium-223 dichloride to meet a US FDA mandated post marketing requirement and a request from the German Federal Office for Radiation Protection. Potential radiation-induced bone marrow abnormalities may not become evident until years after initial exposure to radium-223 dichloride; therefore, long-term follow-up is required to detect them. This study originally was intended to collect long-term follow-up data from prostate cancer studies only; however, radium-223 dichloride is also being studied for other indications. To collect comprehensive safety information across all clinical trials with radium-223 dichloride and to allow collection of long-term safety data across indications, subjects with breast cancer and multiple myeloma will also be allowed to enter this long-term follow-up study.

13.2.1.2 Modification 2

All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

Sections affected include:

- Synopsis –Study Objective(s), Methodology, Primary / Secondary Variables; Plan for Statistical Analysis
- 2 Study objectives
- 3.1 Design overview
- 3.2 Primary and secondary variables
- 7.1 Tabular schedule of evaluations
- 7.2.2 Long-term follow-up
- 7.2.3 End of long-term follow-up
- 7.5 Safety
- 7.5.1.1 Definitions
- 7.5.1.2.3 Causal relationship
- 7.5.1.3 Assessments and documentation of adverse events
- 7.5.1.4 Reporting of serious adverse events
- 8.3.2.1 Safety analysis

Rationale: 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 IDMC recommendation following an ad hoc independent analysis where more treatment emergent fractures, symptomatic skeletal event–free survival (SSE-FS), and total deaths events were observed in the active treatment arm compared with the placebo arm. The IDMC also recommended that all bone fractures and bone associated events (e.g., osteoporosis) occurring in follow-up period are to be documented regardless of investigator's causality assessment. In order to collect comprehensive safety information across all clinical trials with radium-223 dichloride, documentation of fractures (pathological and non-pathological) regardless of relationship, is also implemented in the present trial. The incidence of bone fractures and bone associated events will be summarized as part of the statistical analysis.

13.2.1.3 Modification 3

Addition that radium-223 dichloride should not be given with abiraterone plus prednisone/prednisolone.

Sections affected include:

- 6.1 Prior and concomitant therapy

Rationale: 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.

13.2.1.4 Modification 4

The option of starting a BHA including bisphosphonates or denosumab during the follow-up periods, should be considered taking into consideration applicable guidelines. Any BHA treatment taken during the study period must be recorded.

Sections affected include:

- 6.1 Prior and concomitant therapy

Rationale: 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 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 on radium-223 dichloride, the option of starting a BHA, including bisphosphonates or denosumab, should be considered, taking into consideration applicable guidelines. Treatment with a BHA should be captured in the eCRF.

13.2.1.5 Modification 5

Deletion of guidance text related to recording of contrast media. The statement "Contrast media will not be captured as concomitant medication unless there is an AE or SAE related to administration of contrast media." was removed from the text.

Sections affected include:

- 6.1 Prior and concomitant therapy

Rationale: Guidance is not applicable to this long-term follow-up study as radiologic examinations are not mandated by protocol, but conducted per local standard of care. Only AEs and SAEs considered to be related to administration of radium-223 /placebo are to be collected in this study.

13.2.1.6 Modification 6

Clarification that subjects will not be compensated for taking part in this study.

Sections affected:

- 11.4 Subject information and consent

Rationale: Upon review by a French Ethics Committee, a request was made to clarify in the protocol, in addition to the existing notice in the ICF, that study subjects receive no payment for participation in the study.

13.2.1.7 Modification 7

Continuation or start of any background therapy and concomitant treatment including as part of a clinical trial is allowed in this follow-up study; however, continuation of feeder trial study drug is not allowed.

Sections affected:

- 6.1 Prior and concomitant therapy

Rationale: As there are no study specific procedures in the follow-up study and the purpose of the study is limited to collection of safety data, patients may receive investigational treatment as part of another clinical trial while participating in the present study.

13.2.1.8 Modification 8

Clarification that there will be no independent data monitoring committee.

Sections affected include:

- 11.1 Investigator(s) and other study personnel

Rationale: The purpose of the study is to collect long term safety data and patient will not receive any study specific treatment during the study. Based on this, an IDMC is not deemed necessary.

13.2.1.9 Modification 9

Clarification of reporting of related SAEs.

Sections affected include:

- Synopsis (Primary / secondary variable(s)
- 3.1 Design overview
- 7.1 Tabular schedule of evaluations
- 7.2.2 Long-term follow-up
- 7.2.3 End of long-term follow-up
- 7.5 Safety

Rationale: Only radium-223 dichloride-/placebo-related AEs and related SAEs will be collected and recorded in this study. This wording was made consistent throughout the text.

13.2.1.10 Modification 10

Updated the study GCL and the Study Medical Expert names.

Sections affected include:

- Title page
- Signature of the sponsor's medically responsible person
- 11.1 Investigator(s) and other study personnel

Rationale: Change reflects the current medical expert and protocol signatory.

13.2.1.11 Minor clarifications

- Added the definition for several abbreviations in the list of abbreviations and in the text where appropriate.
- Corrected the heading numbering in the previous overview of changes for Amendment 1.
- Minor grammatical revisions such as number agreement and including both male and female subjects, and correction of typographical errors.
- For Word-related technical reasons, numbered footnotes have been replaced with a summary of changes at the start of each amended section.

13.2.2 Changes to the protocol text

Changes to the protocol text are provided in a separate tracked changes document.

14. Appendices

14.1 National Cancer Institute - Common Terminology Criteria for Adverse Events, Version 4.03

US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Version 4.03 published 14 JUN 2010. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.