Document Type:	Study Protocol
Official Title:	A three arm randomized, open-label Phase II study of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) versus 80 kBq/kg (88 kBq/kg after implementation of new NIST update and versus 50 kBq/kg (55 kBq/kg after implementation of NIST update) in an extended dosing schedule in subjects with castration-resistant prostate cancer metastatic to the bone
NCT Number:	NCT02023697
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Cover page for the integrated clinical study protocol

A three arm randomized, open-label Phase II study of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) versus 80 kBq/kg (88 kBq/kg after implementation of NIST update), and versus 50 kBq/kg (55 kBq/kg after implementation of NIST update) in an extended dosing schedule in subjects with castration-resistant prostate cancer metastatic to the bone

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

- Original protocol, Version 1.0, dated 09 AUG 2013
- Amendment 1 (global amendment described in Section 13.1) forming integrated protocol Version 2.0, dated 19 NOV 2013
- Amendment 2 (global amendment described in Section 13.2) forming integrated protocol Version 3.0, dated 13 AUG 2015
- Amendment 3 (global amendment described in Section 13.3) forming integrated protocol Version 4.0, dated 16 MAY 2017
- Amendment 4 (global amendment described in Section 13.4) forming integrated protocol Version 5.0, dated 28 MAR 2018

This document integrates the original protocol and all global amendments.

Title page

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), 3 (Section 13.3), and 4 (Section 13.4.1.4).

A three arm randomized, open-label Phase II study of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) versus 80 kBq/kg (88 kBq/kg after implementation of NIST update), and versus 50 kBq/kg (55 kBq/kg after implementation of NIST update) in an extended dosing schedule in subjects with castration-resistant prostate cancer metastatic to the bone

Standard dose versus high dose and versus extended standard dose radium-223 dichloride in castration-resistant prostate cancer metastatic to the bone

Test drug:	BAY 88-8223 / Radium-223 dichloride		
Study purpose:	Efficacy, dose finding		
Clinical study phase:	II	Date:	28 MAR 2018
EudraCT no.:	2013-003118-42	Version no.:	5.0
Study no.:	16507		
Sponsor:	**(Non US): Bayer AG, D-51368 Leverkusen, Germany (US territory): Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, USA**		
Sponsor's medical expert:	PPD PPD Rua Cancioneiro de Evora, 255 Building E1, 1st floor 04708-010 São Paulo – SP Brazil Phone: PPD		

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 responsible person changed by Amendments 2, 3 and 4.

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

Name: PPD Role: Global Clinical Leader, PPD

Date: 12 April 2018 Signature: PPD

Signature of principal investigator

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

Name:

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 three arm randomized, open-label Phase II study of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) versus 80 kBq/kg (88 kBq/kg after implementation of new NIST update and versus 50 kBq/kg (55 kBq/kg after implementation of NIST update) in an extended dosing schedule in subjects with castration-resistant prostate cancer metastatic to the bone *Title modified by Amendments 1 and 2.*
Short title	Standard dose versus high dose and versus extended standard dose radium-223 dichloride in castration-resistant prostate cancer metastatic to the bone
Clinical study phase	Phase II
Study objectives	The following objectives will be used to compare radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses with radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses in radium-223 dichloride-naïve subjects; and in subjects receiving radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST standard implementation update) every 28 days up to 6 doses, to compare a regimen of up to a further 6 doses of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days with no further radium-223 dichloride treatment. Co-primary objectives: • To evaluate efficacy as measured by symptomatic skeletal event-free survival (SSE-FS) of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses compared to radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses in subjects with castration-resistant prostate cancer (CRPC) metastatic to the bone not previously receiving radium-223 dichloride; and • To evaluate efficacy as measured by SSE-FS of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days for up to 6 additional doses compared to no further radium-223 dichloride treatment in subjects with CRPC metastatic to the bone who previously received radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses, and survived SSE free and are eligible for further radium-223 dichloride treatment Symptomatic skeletal events (SSEs) are defined as: o The use of external beam radiotherapy (EBRT) to relieve skeletal symptoms o New symptomatic pathological bone fractures (vertebral and non-vertebral) o Tumor-related orthopedic surgical intervention o Spinal cord compression

	Secondary objectives: • To evaluate safety and tolerability • To evaluate overall survival (OS) • To evaluate pain improvement rate • To evaluate time to pain progression • To evaluate time to first SSE • To evaluate time to radiological progression • To evaluate radiological progression-free survival (rPFS) Exploratory objectives: • To evaluate quantitated whole body technetium-99 bone scan tumor burden area and index, and determine bone tumor response • To explore the impact of subject body size on the efficacy and safety of radium-223 dichloride • Time to increase in physical symptoms of disease based on the National Comprehensive Cancer Network (NCCN) FACT-P Symptom Index-17 (NCCN-FACT FPSI-17) physical disease related symptoms subscale score measured up to Week 48 after the start of treatment • To evaluate laboratory indicators of efficacy, including: o Prostate specific antigen (PSA) response o Time to PSA progression o Alkaline phosphatase (ALP) response o Time to ALP progression o Percentage change in ALP from baseline • To evaluate change in analgesic use as measured by the Analgesic Quantification Algorithm (AQA) *Study objectives modified by Amendments 1, 2, and 3.*
Test drug	BAY 88-8223
Name of active ingredient	Radium-223 dichloride
Doses	50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses (Treatment Arm A), 80 kBq/kg (88 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses (Treatment Arm B), or 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days for up to 12 doses (Treatment Arm C) *Doses modified by Amendment 2.*
Route of administration	Intravenous (IV) injection (slow bolus)
Duration of treatment	Maximum of 6 doses at 28-day intervals (24 weeks) in Treatment Arms A and B; maximum of 12 doses at 28-day intervals (48 weeks) in Treatment Arm C

Background treatment / concomitant medications / prohibited therapies	Concomitant best standard of care (BSoC) is permitted according to local clinical practice. Allowed concomitant treatments for prostate cancer include: luteinizing-hormone-releasing hormone (LHRH) analogs, surgery, radiation therapy, flutamide, bicalutamide, nilutamide, cyproterone acetate, ketoconazole, corticosteroids, estrogens, and enzalutamide. Radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone. Subjects who have not undergone bilateral orchiectomy are to receive LHRH agonists or antagonists or polyestradiol phosphate throughout the study. Subjects receiving bone health agents (BHA), such as bisphosphonates or denosumab, prior to receiving study drug treatment may be maintained on these therapies throughout all or part of the treatment period. Subjects in the treatment period can also initiate these therapies at any time. Based on the available data on radium-223 dichloride, the option of starting a BHA during the follow-up periods should be considered taking into consideration applicable guidelines. Treatment with bisphosphonates or denosumab may be stopped at the discretion of the investigator. Cytotoxic chemotherapy, including taxanes, estramustine, and mitoxantrone, for prostate cancer, other systemic radioisotopes, concomitant hemibody EBRT, or other investigational drugs may not be used during the treatment period. If prohibited therapy is considered appropriate BSoC for a subject during the treatment period, further radium-223 dichloride administrations must be discontinued, and if possible, prohibited treatment should not be given until following the end of treatment (EOT) visit, defined as 30 days after the last injection of radium-223 dichloride. *Background treatment, concomitant medications, and prohibited therapies modified by Amendments 2 and 4.*
Indication	For the treatment of subjects with CRPC who have bone metastases
Diagnosis and main criteria for inclusion	Eligible subjects must meet all of the inclusion criteria and none of the exclusion criteria listed below. The main criteria for inclusion are: • Histologically or cytologically confirmed adenocarcinoma of the prostate • Castration-resistant disease defined as: a. Serum testosterone level: ≤ 50 ng/dL (1.7 nmol/L) b. Bilateral orchiectomy or maintenance on androgen ablation therapy with LHRH agonist or antagonist,* or polyestradiol phosphate c. Serum PSA progression defined as 2 subsequent increases in PSA over a previous reference value, with a PSA value of ≥ 2 ng/mL at the time of the second increase **OR** Radiographic evidence of disease progression in bone (according to Prostate Cancer Clinical Trials Working Group 2 [PCWG2] criteria) with or without PSA progression *In subjects who were treated with combined androgen blockade (a

growth-hormone-releasing hormone analog or orchiectomy in combination with continuous anti-androgen) as initial therapy for a prolonged period of time, or who have responded to adding a peripheral anti-androgen as second line therapy, progressive disease should be documented after discontinuing anti-androgen treatment (for at least 6 weeks for bicalutamide and at least 4 weeks for flutamide and others) to exclude an anti-androgen withdrawal response.

- Subjects must be ≥ 18 years of age.
- Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2. In case of ECOG PS 2, the PS must be due to metastatic prostate cancer to the bone.
- Life expectancy ≥ 6 months
- Two or more skeletal metastases (≥ 2 hot spots) on bone scintigraphy within 8 weeks of randomization
- Laboratory requirements:
    a. Absolute neutrophil count ≥ 1.5 x 10^9/L
    b. Platelet count ≥ 100 x 10^9/L
    c. Hemoglobin ≥ 9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin support within 4 weeks prior to screening
    d. Total bilirubin level ≤ 1.5 x institutional upper limit of normal (ULN) (< 3 x ULN for subjects with documented Gilbert's syndrome)
    e. Aspartate transaminase and alanine transaminase ≤ 2.5 x ULN
    f. Creatinine ≤ 1.5 x ULN
    g. Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2 according to either the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation or the Modification of Diet in Renal Disease abbreviated formula
    h. Albumin > 25 g/L
- Written, signed informed consent. Subject must be able to understand and be willing to sign the written informed consent form (ICF). A signed ICF must be appropriately obtained prior to the conduct of any study-specific procedure.
- Sexually active males agree to use condoms and/or their female partners of reproductive potential to use a method of effective birth control during treatment and for 6 months following the completion of treatment with radium-223 dichloride.

The main criteria for exclusion are:

- History of visceral metastasis, or visceral metastases as assessed by computed tomography (CT) / magnetic resonance imaging (MRI) of the abdomen and pelvis and / or chest X-ray (in the presence of

suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]) within the previous 8 weeks of randomization

- Lymphadenopathy with lymph nodes exceeding 3 cm in short axis diameter
- Current central nervous system (CNS) metastases. Subjects with neurological symptoms suggestive of CNS metastasis must undergo contrast CT scan or MRI of the CNS within 30 days of the start of treatment to exclude CNS metastasis. Imaging of the CNS is otherwise not required.
- Chronic conditions associated with non-malignant abnormal bone growth (e.g., confirmed Paget's disease of bone)
- Blood transfusions or use of erythropoietin within 4 weeks prior to screening, during screening, or prior to the start of treatment
- Treatment with an investigational drug within the 4 weeks prior to randomization
- Treatment with cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, within the previous 4 weeks prior to randomization, or planned treatment with these prohibited cytotoxic chemotherapy agents for prostate cancer during the treatment period or follow-up
- Prior treatment with radium-223 dichloride
- Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186, or rhenium-188
- Prior hemibody EBRT
- Use of biologic response modifiers, such as granulocyte macrophage colony-stimulating factor or granulocyte colony-stimulating factor, within 4 weeks prior to screening
- Other malignancy treated within the last 3 years (except treated non-melanoma skin cancer or low-grade superficial bladder cancer)
- Imminent or established untreated spinal cord compression based on clinical findings and / or MRI. Following treatment of spinal cord compression, the subject may be eligible if all other eligibility criteria are fulfilled.
- Any other serious illness or medical condition such as, but not limited to:
    a. Any uncontrolled infection
    b. Cardiac failure New York Heart Association Class III or IV
    c. Crohn's disease or ulcerative colitis
    d. Bone marrow dysplasia
    e. Unmanageable fecal incontinence
- Previous assignment to treatment in this study

Main criteria for inclusion modified by Amendments 1 and 2.

	Main criteria for exclusion modified by Amendments 1 and 2.
Study design	International, multicenter, randomized, open-label Phase II study
Methodology	Subjects enrolled into the study will be randomized to one of the 3 treatment arms in 1:1:1 fashion: radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) IV every 28 days for up to 6 doses (Treatment Arm A) or radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) IV every 28 days for up to 6 doses (Treatment Arm B) or radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) IV every 28 days for up to 12 doses (Treatment Arm C). The randomization will be permuted-block, stratified by use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total ALP (< 220 U/L versus ≥ 220 U/L), and by average worst pain score (WPS) of the Brief Pain Inventory Short Form (BPI-SF) (WPS ≤ 4 versus WPS > 4). The treatment period for efficacy purposes begins at the time of randomization. During the treatment period, study medication is administered every 28 days (± 7 days) from Dose 1 and may be delivered in an outpatient setting. At each visit, prior to receiving radium-223 dichloride, the subject will be evaluated for adverse events (AEs) and laboratory abnormalities to determine whether it is safe to continue treatment. Symptomatic skeletal events will be assessed every 28 days through the latter of Week 24 or the EOT visit (Week 24 for Treatment Arms A and B, and Week 48 for Treatment Arm C) and every 12 weeks thereafter, until an SSE is experienced. Subjects in Treatment Arms A and B who have not experienced an SSE will be contacted by telephone at Weeks 28, 32, 40, and 44, evaluated for SSE risk, and encouraged to come to the clinic if a risk is identified. Radiological assessment, including whole body technetium-99 bone scan, MRI / CT scan of the abdomen and pelvis, and chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), will be performed at Week 8, Week 16, Week 24, then every 12 weeks for 2 years after the subject's last dose of radium-223 dichloride or until radiologic progression. If progression is detected by bone scan, a confirmatory bone scan is required at least 6 weeks later. Radiological assessments will continue until disease progression is experienced in bone according to the PCWG2 criteria or in soft tissue according to Response Evaluation Criteria in Solid Tumors 1.1 guidelines. Radiographic imaging will be evaluated by blinded central review. Pain endpoints will be based on subject-reported outcome data. Pain data will be collected every 4 weeks through Week 48 in all treatment arms using a handheld device. Pain will be assessed by means of selected questions from the BPI-SF daily for 4 days immediately prior to randomization, in order to stratify subjects by WPS ≤ 4 or > 4, and then as follows: • for Treatment Arms A and B, daily for 7 days prior to each scheduled dosing visit from Dose 1, Day 1 through Week 24. During the Active Follow-up, pain data will be collected for the 7 days prior to Week 36 and 48 visits, and for 7 days prior to each telephone contact at

Weeks 28, 32, 40 and 44.

- for Treatment Arm C, daily for 7 days prior to each scheduled dosing visit from Dose 1, Day 1 through Week 48.

Pain will also be assessed by means of the BPI-SF questionnaire every clinic visit or telephone contact from Dose 1, Day 1 visit until the Week 48 visit. In treatment Arms A and B only, the BPI-SF questionnaire will also be completed on the day of each telephone contact at Weeks 28, 32, 40, and 44.

The NCCN-FACT FPSI-17 questionnaire will be completed by the subject in all treatment arms every clinic visit starting on Dose 1, Day 1 up to Week 48 visit. In treatment Arms A and B only the NCCN-FACT FPSI-17 questionnaire will also be completed on the day of each telephone contact at Weeks 28, 32, 40, and 44.

Both the pain assessment using the BPI-SF questionnaire and the NCCN-FACT FPSI-17 questionnaire will be self-administered by the subject using a handheld device.

Analgesic use will be collected throughout the study. In addition analgesic use over the 24-hour period prior to the day of the visit will be collected by the study investigator at each visit for all treatment arms from Dose 1, Day 1 until the Week 48 visit, and analgesic use over the 24-hour period prior to each telephone contact (in Arms A or B) will be collected by the study investigator at the telephone contact at Weeks 28, 32, 40, and 44.

The AQA score will be calculated programmatically from the assessments of analgesic use in the last 24 hours.

A Joint Safety Review Committee will conduct safety reviews at regular intervals. There is no formal interim analysis planned. The main objective of these safety reviews is to ensure subject safety and to identify whether any protocol modifications are needed.

Following the EOT visit, subjects will enter the active follow-up period and will come to the clinic for selected safety and efficacy evaluations every 12 weeks for at least 2 years following last study treatment. Subjects not experiencing an SSE by 2 years following last study treatment will continue active follow-up until the subject experiences an SSE or the primary endpoint matures, whichever occurs first. During active follow-up, every effort will be made to follow subjects through clinic visits; however, phone contacts will be undertaken for subjects unable to come to the clinic.

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and serious AEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic therapies for prostate cancer, including androgen synthesis inhibitors

	/ androgen-receptor antagonists, systemic radioisotopes, 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data. Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject. Until the transition to the long term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up). *Methodology modified by Amendment 1, 2, 3, and 4.*
Type of control	Active treatment control with standard dose radium-223 dichloride
Number of subjects	Approximately 360 subjects
Primary / Secondary variables	The primary efficacy variable will be SSE-FS. The safety variables include: • Incidence and severity of treatment-emergent AEs (TEAEs) and laboratory abnormalities graded by National Cancer Institute-Common Terminology Criteria Adverse Events version 4.03 and coded by Medical Dictionary for Regulatory Activities • Incidence of serious TEAEs • Incidence of drug-related AEs in the follow-up period The secondary efficacy variables include: • OS • Time to first SSE • rPFS • Time to radiological progression • Pain improvement rate

	• Time to pain progression *Secondary efficacy variables modified by Amendments 1 and 2.*
Plan for statistical analysis	Subjects will be randomized 1:1:1 to: Treatment Arm A: radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) intravenously every 28 days up to 6 doses ("standard dose") Treatment Arm B: radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) intravenously every 28 days up to 6 doses ("high dose") Treatment Arm C: radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) intravenously every 28 days up to 12 doses ("extended dosing") The primary efficacy endpoint, SSE-FS, will be analyzed separately in 2 respective comparisons, as described below. Both comparisons will be performed at the time of final analysis, after the latest of (1) approximately 135 SSE-FS events in subjects included in Comparison 1 as defined below; (2) approximately 75 SSE-FS events following the 6th dose in subjects included in Comparison 2 as defined below, and (3) the last subject has been followed for 30 days from last treatment. In the event the applicable number of events is not reached, the primary endpoint analysis will mature 7 years after the last subject has received last treatment. No alpha adjustment for multiple comparisons will be performed in this Phase II study. **Comparison 1: Standard dose versus high dose: SSE-FS from randomization in radium-223 dichloride-naïve subjects** Comparison 1 will test the following hypotheses: The Null Hypothesis (H0)1: In a population of radium-223 dichloride-naïve subjects with CRPC metastatic to the bone, population SSE-FS in subjects treated with a regimen of up to 6 doses of 80 kBq/kg (88 kBq/kg after implementation of NIST update) (high dose) radium-223 dichloride is equal to population SSE-FS in subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride, versus The Alternative Hypothesis (HA)1: In a population of radium-223 dichloride-naïve subjects with CRPC metastatic to the bone, population SSE-FS in subjects treated with a regimen of up to 6 doses of 80 kBq/kg (88 kBq/kg after implementation of NIST update) (high dose) radium-223 dichloride is greater than population SSE-FS in subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride. Comparison 1 will analyze SSE-FS with the randomization date as the start

	date. Comparison 1 will pool SSE-FS in subjects in Treatment Arm A, with SSE-FS truncated at 24 weeks in subjects in Treatment Arm C, and compare this pooled value with SSE-FS in Treatment Arm B. Only intent-to-treat (ITT) subjects will be included in this ITT analysis. In this study, extended dosing subjects (Treatment Arm C) will receive the same treatment regimen as standard dose subjects (Treatment Arm A) for the first 6 doses, with Dose 7 scheduled to start after 24 weeks. Accordingly, data from Treatment Arm C subjects arising during the first 24 weeks is relevant to this comparison and including it increases the analysis' power under the study assumptions. It will be performed using a log-rank test with a 1-sided alpha of 0.1 stratified by the randomization factors (previous chemotherapy [≤ 1 regimen versus > 1 regimen], and total ALP [< 220 U/L versus ≥ 220 U/L]). The high-dose regimen will be declared superior to the standard-dosing regimen if the 1-sided p-value from the stratified log rank test is less than 0.1. The hazard ratio (high dose / standard dose) will be computed together with 2-sided 80% and 95% confidence intervals using a stratified Cox regression model with treatment as a factor and previous chemotherapy [≤ 1 regimen versus > 1 regimen] and total ALP [< 220 U/L versus ≥ 220 U/L] as strata in the model for the ITT analysis set. Kaplan-Meier survival distribution tables and plots will also be produced for both Treatment Arms A and B. Additional details will be provided in the statistical analysis plan.
	Comparison 2: No further radium-223 dichloride treatment versus extended dosing: SSE-FS analysis from the 6th dose in subjects receiving standard-dose regimen Comparison 2 will test the following hypotheses: H02: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond the 6th dose in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (extended dose) radium-223 dichloride is equal to population SSE-FS beyond the 6th dose in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen, versus HA2: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond the 6th dose in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (extended dose) radium-223 dichloride is greater than population SSE-FS beyond the 6th dose in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen. Comparison 2 will be an analysis of SSE-FS from the 6th dose in subjects surviving SSE-free to the 6th dose. It will compare subjects in Treatment Arm

	A with subjects in Treatment Arm C. Comparison 2 will be performed using a log-rank test with a 1-sided alpha of 0.1 stratified by the randomization factors (previous chemotherapy [≤ 1 regimen versus > 1 regimen] and total ALP [< 220 U/L versus ≥ 220 U/L]). The extended dosing regimen will be declared superior to the standard dosing regimen if the 1-sided p-value from the stratified log rank test is less than 0.1. The following secondary efficacy time-to-event endpoints will have hypothesis testing performed with comparisons analogous to those for the primary endpoint: OS, time to first SSE, time to radiological progression, and rPFS. Other endpoints, including safety and tolerability variables, will be analyzed descriptively for each treatment group. *Plan for statistical analysis modified by Amendments 1, 2, and 3.*

Table of contents

Table of tables

List of abbreviations

Section modified by Amendment 1 (Section 13.1), 2 (Section 13.2), and 4 (Section 13.4.1.5).

AE	Adverse event
ALP	Alkaline phosphatase
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AQA	Analgesic Quantification Algorithm
BHA	Bone health agent
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory Short Form
BSLA	Bone scan lesion area
BSoC	Best standard of care
CBC	Complete blood count
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRO	Clinical research organization
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DK	Decay correction factor
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
EOT	End of treatment
ePRO	Electronic patient-reported outcome
EU	European Union
FPSI-DRS-P	FACT-P Symptom Index-17 physical disease related symptoms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GM-CSF	Granulocyte macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
HA	The Alternative Hypothesis
H0	The Null Hypothesis
IB	Investigator's Brochure

ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IDMS	Isotope Dilution Mass Spectrometry
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
IVRS / IWRS	Interactive voice / web response system
JSRC	Joint Safety Review Committee
kBq	KiloBecquerel; SI unit of radioactivity
LDH	Lactate dehydrogenase
LHRH	Luteinizing-hormone-releasing hormone
MBq	Megabecquerel, SI unit of radioactivity
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
mCi	milli-curie
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCCN-FACT FPSI-17	NCCN-FACT-P Symptom Index-17
NCI	National Cancer Institute
NE	Not evaluable
NIST	National Institute of Standards and Technology
OME	Oral morphine equivalent
OS	Overall survival
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PD	Progressive disease
PR	Partial response
PRD	Patient ready dose
PRO	Patient-reported outcome
PS	Performance status
PSA	Prostate specific antigen
q6	Every 6
q12	Every 12
QoL	Quality of life
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiological progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SI	International System of Units
SRE	Skeletal-related event
SSE	Symptomatic skeletal event

SSE-FS	Symptomatic skeletal event-free survival
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
U/L	Units/liter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization
wk	Week
WPS	Worst pain score

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.
Dose	Doses are given as kBq per kilogram body weight. The term “dose” is used to describe the quantity of radioactivity from radium-223 administered.
PCWG2 guidance	The Prostate Cancer Clinical Trials Working Group 2 guidance should be followed, as described in Section 14.2 (1)

1. Introduction

1.1 Background

Section modified by Amendment 1 (Section 13.1).

According to the American Cancer Society estimates for 2013, the number of new prostate cancer cases will be 238,590 and the number of deaths from prostate cancer is expected to be 29,720 in the United States (US).(2) A recent review of tumor registry-derived data estimated the number of prostate cancers cases in Europe to be 417,000, with 92,000 deaths.(3)

Bone metastases are the main cause of disability and death in subjects with castration-resistant prostate cancer (CRPC),(4,5) and approximately 90% of men with CRPC have radiological evidence of bone metastasis.(4) Although treatment with docetaxel chemotherapy is well-established in this population and has been shown to achieve disease responses and improve overall survival (OS), the magnitude of the OS benefit is modest.(6) It is estimated that approximately 50% of men diagnosed with CRPC are either judged unfit to tolerate docetaxel or elect not to receive it. Consequently, recent drug development efforts have attempted to improve on options for patients with CRPC and metastases using multiple strategies, including cytotoxic chemotherapy, hormonal therapy, and immunotherapy.

In the context of CRPC with bone metastasis, the bisphosphonate zoledronic acid,(7) has been available for more than 10 years for the treatment of prostate cancer with bone metastasis. More recently, denosumab, the monoclonal antibody that targets receptor activator of nuclear factor κB ligand, was approved by the Food and Drug Administration (FDA) in November 2010 for the prevention of skeletal-related events (SREs) and as an alternative to zoledronic acid.(8) Importantly, while these 2 drugs are able to modify the course of patients with metastatic CRPC and bone metastasis, neither agent has been found to improve OS in this group of patients.

Over the past 3 years, a variety of new drugs have been approved for the treatment of CRPC, including the vaccine Sipuleucel-T in 2010 for asymptomatic or minimally symptomatic patients, cabazitaxel also in 2010, abiraterone acetate plus prednisone in 2011, and enzalutamide in 2012. These drugs demonstrated improved OS, and are tolerable, but they were approved without respect to the specific clinical manifestations of CRPC.(9,10,11)

Given the reality that more than 90% of patients with CRPC develop bone metastases, and the well-known subsequent impact on quality of life (QoL) as well as survival, an agent that specifically targets the major complications of bone metastasis, provides a survival benefit, and has a good safety profile would represent a relevant treatment option and a major therapeutic advance.

Alpha particle-emitting radiopharmaceuticals represent a new class of cancer therapy for the treatment of men with CRPC with bone metastases.(12) Unlike beta emitting

radiopharmaceuticals, alpha particle-emitting radiopharmaceuticals have a more localized action(13) (a range of 2 to 10 cell diameters) and are much more potent, causing double-strand deoxyribonucleic acid (DNA) breaks leading to cell death.(14)

Radium-223 is a calcium mimetic, alpha particle emitting nuclide, which selectively targets areas of increased bone turnover.(15) The half-life of radium-223 is 11.4 days, allowing sufficient time for its preparation, distribution, and administration to subjects.(16) Unlike beta particle-emitting radionuclides, which cause single strand DNA breaks, which can be repaired, alpha particle-emitting radium-223 causes difficult to repair double-strand DNA breaks,(16) resulting in a highly cytotoxic effect in target areas containing bone metastatic cancer cells.(15) Since radium-223 is targeted to bone, its distribution to soft tissue is limited.(15)

The results of nonclinical pharmacology studies indicate that radium-223 dichloride delivers potent radiation targeted to bone in areas of high metabolic activity and increased bone turnover, such as skeletal metastases. No effects on central nervous system (CNS), respiratory, or cardiovascular function were observed in safety pharmacology or toxicology studies conducted in rats and dogs.(16) Radium-223 dichloride is rapidly eliminated from blood and distributed to bone. In mice and dogs, excretion occurred by both feces and urine. No histological changes were observed in organs involved in the excretion of radium-223 dichloride.(17) In humans, clinical data show that excretion occurs mainly via the feces, with minimal urinary excretion and no entero-hepatic recirculation.(18)

In preclinical studies, in single and repeated dose toxicity studies in rats administered radium-223 dichloride, the main findings were reduced body weight gain, hematological changes, reduced serum alkaline phosphatase (ALP), and microscopic findings in the bone marrow (depletion of hematopoietic cells, fibrosis), spleen (secondary extra-medullary hematopoiesis), and bone (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption / disorganization of the physis / growth line). With the exception of body weight decrease, these findings were related to radiation-induced impairment of hematopoiesis and a reduction of osteogenesis, and occurred in the dose range of 20 to 80 kBq (0.000541 to 0.00216 mCi) per kilogram body weight.(17)

Dose-limiting myelotoxicity was seen in dogs after single administration of 450 kBq (0.0122 mCi) radium-223 dichloride per kilogram body weight (9 times the clinically recommended standard dose).(17)

Osteosarcomas occurred in rats at extended times (7 to 12 months) after treatment with single doses of ≥ 325 kBq/kg and repeated doses of ≥ 25 kBq/kg (12 doses) or ≥ 325 kBq/kg (4 doses). However, the relevance of these animal data needs to be interpreted with caution. The appearance of osteosarcomas was anticipated based on literature references identifying sarcomas in animals treated with ionizing radiation or bone-seeking radionuclides, particularly in skeletally immature and growing animals. Further details on the toxicology studies can be found in the Investigator's Brochure (IB).(16)

Nine clinical studies with radium-223 dichloride have been conducted in over 1,300 subjects with prostate or breast cancer with bone metastases.(16)

The safety and tolerability of radium-223 dichloride was first investigated in a single injection dose ranging study in 31 subjects diagnosed with prostate (n = 21) or breast cancer (n = 10).(18) Thirty-one subjects with breast or prostate cancer received escalating single or multiple doses of radium-223 dichloride (single doses of 46, 93, 163, 213, or 250 kBq/kg body weight; multiple doses of 5 x 50 kBq/kg at 3-week intervals or 2 x 125 kBq/kg at 6-week intervals), and subjects were followed for 8 weeks. Mild and reversible myelosuppression with a nadir 2 to 4 weeks after the injection was observed. Preliminary evidence of efficacy was seen with reduction in total serum ALP concentrations and improved pain control across all dose levels.

Radium-223 dichloride was subsequently evaluated in a double-blind, placebo-controlled, randomized Phase II study. Subjects diagnosed with CRPC and bone pain needing external beam radiotherapy (EBRT) received up to 4 doses of 50 kBq/kg body weight intravenous (IV) radium-223 dichloride administered every 4 weeks in the active arm.(16,19) The relative change in bone ALP from baseline to 4 weeks post-last treatment was -66% (range: -92% to 125%) for the 33 subjects who received treatment compared with 9% (range: -77% to 384%) for the 31 subjects who received placebo. The results obtained with biochemical markers for bone turnover (type I collagen cross-linked C-telopeptide, procollagen I N propeptide) and tumor load (prostate specific antigen [PSA]) support the presence of a treatment effect during the treatment period and for 1 to 2 months after the end of treatment (EOT).

A Phase II double-blind, randomized, dose-ranging study was performed to assess the palliative effect of 4 single dose levels (5, 25, 50, and 100 kBq/kg body weight radium-223 dichloride) in 100 hormone refractory prostate cancer subjects. The target population was subjects suffering from bone pain (with at least a score 2 on the Brief Pain Inventory [BPI] average pain) due to multiple bone metastases secondary to prostate cancer. The aims of the study were to assess the effect of one injection of radium-223 dichloride on painful bony metastases, and to assess tolerability and safety. A significant dose response for pain index was seen at Week 2 (P = 0.035). At Week 8, there were 40%, 63%, 56%, and 71% pain responders (reduced pain and stable analgesic consumption) in the 5, 25, 50, and 100 kBq/kg groups, respectively. There was also a significant improvement in the pain and functional indexes of the Brief Pain Inventory Short Form (BPI-SF) for all dose groups (P = 0.04, 0.01, 0.002, and 0.02; Wilcoxon signed rank test). Furthermore, a decrease in bone ALP in the highest dose group was demonstrated (P = 0.0067). All doses were safe and well tolerated.

A Phase III study was conducted to evaluate the efficacy and safety of radium-223 dichloride. ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) was a multinational, randomized, double-blind, placebo-controlled study in subjects with symptomatic CRPC with bone metastases.(20,21,22) A total of 922 subjects were randomized 2:1 to receive 6 IV doses of either 50 kBq/kg radium-223 dichloride or placebo every 4 weeks. Subjects were followed until 3 years from the first dose of study drug. The ALSYMPCA study was terminated by the Independent Data Monitoring Committee (DMC) based on the results of a

pre-planned interim analysis that evaluated OS. Overall survival was statistically significantly longer with radium-223 dichloride (hazard ratio = 0.695, 95% confidence interval [0.552% to 0.875%]; 2-sided P = 0.00185) compared to placebo. Median OS was prolonged to 14.0 months with radium-223 dichloride treatment compared to 11.2 months with placebo. Time to first SRE was statistically significantly longer in the radium-223 dichloride group compared to placebo (median 13.5 months for radium-223 dichloride versus 8.4 months for placebo; P = 0.00046). Overall, treatment-emergent serious adverse events (SAEs) were experienced by fewer subjects (43.2%, 220 / 509) in the radium-223 dichloride group than subjects in the placebo group (54.9%, 139 / 253).

A randomized, double-blind, dose-finding, multicenter Phase II study evaluated 122 randomized CPRC subjects who received 3 injections of radium-223 dichloride at 6-week intervals.(23) The doses were 25 kBq/kg (n = 41), 50 kBq/kg (n = 39), and 80 kBq/kg (n = 42). Efficacy was evaluated using blood samples to measure PSA and other tumor markers, and SREs and pain assessments were recorded. Safety was evaluated using adverse events (AEs), physical examinations, and clinical laboratory tests. The study met its primary endpoint with a statistically significant dose-response relationship in confirmed (≥ 50%) PSA declines for no subjects in the 25 kBq/kg dose group, 2 subjects (6%) in the 50 kBq/kg dose group, and 5 subjects (13%) in the 80 kBq/kg dose group (P = 0.0297). A greater than 50% decrease in bone ALP levels was identified in 6 subjects (16%), 24 subjects (67%), and 25 subjects (66%) in the 25, 50, and 80 kBq/kg dose groups, respectively (P < 0.0001). The most common treatment-related AEs occurring up to Week 24 across all dose groups were diarrhea (21%), nausea (16%), and anemia (14%). No difference in incidence of hematologic events was seen among the dose groups. These data suggested that treatment with 80 kBq/kg radium-223 dichloride may result in better efficacy as compared with 50 kBq/kg in patients with CRPC without a significant increase in toxicity.(23)

Further details of the efficacy and safety of radium-223 dichloride can be found in the IB,(16) which contains comprehensive information on the study drug.

1.2 Study rationale

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Clinical experience with radium-223 dichloride, as described above, demonstrates that treatment with 6 administrations of radium-223 dichloride at 50 kBq/kg (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) every 4 weeks is associated with important clinical benefits, including a significant improvement in median OS as compared to placebo in subjects with CRPC and bone metastases, and with a favorable safety profile. Side effects are mild and predominantly gastrointestinal (diarrhea and vomiting). Myelosuppression is minimal with a low incidence of Grade ≥ 3 neutropenia and thrombocytopenia, and no evidence of cumulative bone marrow toxicity. These observations suggest that treatment beyond 6 doses is plausible.

The dose-response relationships that were observed in the Phase II studies suggest that further clinical benefit, in terms of disease control and pain relief, may be achieved with higher doses of radium-223 dichloride without a worse safety profile.

The tolerability of radium-223 dichloride and preliminary evidence of a dose-response relationship suggest possible strategies for enhancing the efficacy of radium-223 by increasing exposure to radium-223 dichloride. Two potential strategies to increase total dose are: 1) to increase the total number of treatments with the standard 50 kBq/kg (55 kBq/kg after implementation of NIST update) dose or 2) to increase the total dose given for each treatment, while retaining the 6-dose regimen.

This 3-arm randomized study was designed to explore both treatment strategies by comparing the standard dose regimen of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 4 weeks for up to 6 doses to the high dose regimen of 80 kBq/kg (88 kBq/kg after implementation of NIST update) and, in subjects receiving the standard dose regimen, to compare an extended regimen of up to 6 additional doses of radium-223 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 4 weeks with no further radium-223 dichloride treatment. Efficacy will be evaluated in terms of symptomatic skeletal event-free survival (SSE-FS). Radiological progression-free survival and time to progression will be evaluated as secondary objectives. Additional secondary objectives include pain improvement rate and time to progression based on subjects' self-assessment of pain, change in analgesic use based on subjects' analgesic use in the last 24 hours as evaluated by the Analgesic Quantification Algorithm (AQA).

This study will be conducted to provide data regarding the optimal use of radium-223 dichloride and long-term safety CCI [redacted].

Long-term safety assessment

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, both acute and 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.

2. Study objectives

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), and 3 (Section 13.3).

The following objectives will be used to compare radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses with radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) every 28

days for up to 6 doses in radium-223 dichloride-naïve subjects; and, in subjects receiving radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days up to 6 doses, to compare a regimen of up to a further 6 doses of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days with no further radium-223 dichloride treatment.

Co-primary objectives:

- To evaluate efficacy as measured by SSE-FS of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses compared to radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses in subjects with CRPC metastatic to the bone not previously receiving radium-223 dichloride; and

- To evaluate efficacy as measured by SSE-FS of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days for up to 6 additional doses compared to no further radium-223 dichloride treatment in subjects with CRPC metastatic to the bone who previously received radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days for up to 6 doses, and survived SSE free and are eligible for further radium-223 dichloride treatment.

Symptomatic skeletal events (SSEs) are defined as:

  - The use of external beam radiotherapy (EBRT) to relieve skeletal symptoms
  - New symptomatic pathological bone fractures (vertebral and non-vertebral)
  - Tumor-related orthopedic surgical intervention
  - Spinal cord compression

Secondary objectives:

- To evaluate safety and tolerability
- To evaluate overall survival (OS)
- To evaluate pain improvement rate
- To evaluate time to pain progression
- To evaluate time to first SSE
- To evaluate time to radiological progression
- To evaluate radiological progression-free survival (rPFS)

Exploratory objectives:

- To evaluate quantitated whole body technetium-99 bone scan tumor burden area and index, and determine bone tumor response
- To explore the impact of subject body size on the efficacy and safety of radium-223 dichloride
- Time to increase in physical symptoms of disease based on the National Comprehensive Cancer Network (NCCN) FACT-P Symptom Index-17 (NCCN-FACT FPSI-17) physical disease related symptoms (FPSI-DRS-P) subscale score measured up to Week 48 after the start of treatment
- To evaluate laboratory indicators of efficacy, including:
  - PSA response
  - Time to PSA progression
  - ALP response
  - Time to ALP progression
  - Percentage change in ALP from baseline
- To evaluate change in analgesic use as measured by the AQA.

3. Investigators and other study personnel

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), 3 (Section (13.3), and 4 (13.4.1.4).

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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 sheet before subject recruitment may start at the respective center. Likewise, all protocol amendments / integrated protocols must be signed and dated by the principal investigator 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 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.

Joint Safety Review Committee

A Joint Safety Review Committee (JSRC), which may contain sponsor, investigator, and/or independent members, will conduct safety reviews at regular intervals. There is no formal interim analysis planned. The objective of these safety reviews is to ensure subject safety and

to identify whether any protocol modifications are needed. The JSRC will not evaluate efficacy. Details on the JSRC and its safety review monitoring will be described in a separate JSRC charter.

4. Study design

4.1 Design overview

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), 3 (Section 13.3), and 4 (13.4.1.2).

Subjects enrolled into the study will be randomized to one of the 3 treatment arms in a 1:1:1 fashion: radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) IV every 28 days for up to 6 doses (Treatment Arm A), or radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) IV every 28 days for up to 6 doses (Treatment Arm B), or radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) IV every 28 days for up to 12 doses (Treatment Arm C).

The randomization will be permuted-block, stratified by use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total ALP (< 220 U/L versus ≥ 220 U/L), and by average worst pain score (WPS) of the BPI-SF (WPS ≤4 versus WPS > 4).

The treatment period for efficacy purposes begins at the time of randomization. During the treatment period, study medication is administered every 28 days (± 7 days) from Dose 1 and may be delivered in an outpatient setting. At each visit, prior to receiving radium-223 dichloride, the subject will be evaluated for AEs and laboratory abnormalities to determine whether it is safe to continue treatment.

Symptomatic skeletal events will be assessed every 28 days through the latter of Week 24 or the EOT visit (Week 24 for Treatment Arms A and B, and Week 48 for Treatment Arm C) and every 12 weeks thereafter, until an SSE is experienced. Subjects in Treatment Arms A and B who have not experienced an SSE will be contacted by telephone at Weeks 28, 32, 40, and 44, evaluated for SSE risk, and encouraged to come to the clinic if a risk is identified.

Symptomatic skeletal events are defined as:

- The use of EBRT to relieve skeletal symptoms
- New symptomatic pathological bone fractures (vertebral and non-vertebral)
- Tumor-related orthopedic surgical intervention
- Spinal cord compression

Radiological assessment, including whole body technetium-99 bone scan, magnetic resonance imaging (MRI) / computed tomography (CT) scan of the abdomen and pelvis, and

chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), will be performed at Week 8, Week 16, Week 24, then every 12 weeks for 2 years after the subject's last dose of radium-223 dichloride or until radiologic progression. If progression is detected by bone scan, a confirmatory bone scan is required at least 6 weeks later. Radiological assessments will continue until disease progression is experienced in bone according to the Prostate Cancer Clinical Trials Working Group 2 [PCWG2] criteria or in soft tissue according to Response Evaluation Criteria in Solid Tumors 1.1 [RECIST 1.1] guidelines, see Section 14.1 and Section 14.2). Radiographic imaging will be evaluated by blinded central review.

Pain endpoints will be based on subject-reported outcome data. Pain will be assessed by means of selected questions from the BPI-SF daily for 4 days immediately prior to randomization, in order to stratify subjects by WPS ≤ 4 or > 4, and then daily for 6 days prior to Cycle 1, Day 1 or subsequent visits including telephone contacts, as applicable, plus the day of the visit or telephone contact, until Week 48. Pain will also be assessed by means of the BPI-SF questionnaire for all treatment arms at each clinic visit or telephone contact from Dose 1, Day 1 until the Week 48 visit and for treatment Arms A and B on the day of each telephone contact at Weeks 28, 32, 40, and 44.

The NCCN-FACT FPSI-17 questionnaire will be completed by the subject in all treatment arms every clinic visit starting on Dose 1, Day 1 up to Week 48 visit and for treatment Arms A and B on the day of each telephone contact at Weeks 28, 32, 40, and 44 (see Section 14.8).

Both the pain assessment using the BPI-SF questionnaire and the NCCN-FACT FPSI-17 questionnaire will be self-administered by the subject using a handheld device.

Analgesic use will be collected throughout the study. In addition analgesic use over the 24-hour period prior to the day of the visit will be collected by the study investigator at each visit for all treatment arms from Dose 1, Day 1 until the Week 48 visit, and analgesic use over the 24-hour period prior to each telephone contact (in Arms A and B) will be collected by the study investigator at the telephone contact at Week 28, 32, 40, and 44.

The AQA score will be calculated programmatically from the assessments of analgesic use in the last 24 hours (see Section 14.9).

Following the EOT visit, subjects will enter the active follow-up period and will come to the clinic for selected safety and efficacy evaluations every 12 weeks for at least 2 years following last study treatment. Subjects not experiencing an SSE by 2 years following last study treatment will continue active follow-up until the subject experiences an SSE or the primary endpoint matures, whichever occurs first. During active follow-up, every effort will be made to follow subjects through clinic visits; however, phone contacts will be undertaken for subjects unable to come to the clinic.

Active follow-up period *with* clinic visits:

Subjects who discontinue study treatment and who did not have an SSE will enter an active follow-up period with clinic visits. These subjects will be evaluated every 12 weeks

(± 7 days) for pain endpoints, radiological progression, SSEs, survival, treatment-related AEs and serious adverse events (SAEs), and the initiation of other anti-cancer therapies for prostate cancer, and cytotoxic chemotherapy and radiotherapy for any new malignancy. In addition, subjects who receive cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice. During this period, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs, regardless of the investigator's causality assessment. In addition, all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

The active follow-up period with clinic visits extends from the discontinuation of the treatment period until the subject experiences an SSE, can no longer travel to the clinic, receives further treatment with cytotoxic chemotherapy for prostate cancer, other systemic radioisotopes, hemibody EBRT, or other investigational drugs, dies, is lost to follow-up, or withdraws informed consent and actively objects to collection of further data.

Active follow-up period *without* clinic visits:

Subjects from the treatment period or the active follow-up period with clinic visits who can no longer travel to the clinical site will be followed for survival, treatment-related AEs and SAEs, SSEs, pain endpoints, and the initiation of other anti-cancer therapies (for prostate cancer, and cytotoxic chemotherapy and radiotherapy for any new malignancy) with a phone call every 12 weeks (± 7 days). In addition, subjects who receive cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice. During this period, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs, regardless of the investigator's causality assessment. In addition, all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

The active follow-up period **without** clinic visits extends from the end of treatment (EOT) period or the end of active follow-up with clinic visits until the subject experiences an SSE, dies, is lost to follow-up, or withdraws informed consent and actively objects to collection of further data.

The maximum duration of the active follow-up is 7 years from the last dose of radium-223 dichloride received by the subject.

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported radium-223 dichloride-related AEs and SAEs, all occurrences of

leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic anti-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject.

Until the transition to the long-term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up).

4.2 Primary and secondary variables

Section modified by Amendment 1 (13.1).

The primary efficacy variable will be SSE-FS.

Safety and tolerability variables will be the incidence and severity of treatment-emergent AEs (TEAEs) including serious TEAEs, and laboratory abnormalities plus drug-related AEs during the follow-up period. The severity of AEs will be graded by the National Cancer Institute Common Terminology Criteria Adverse Events (NCI-CTCAE), version 4.03 and coded by Medical Dictionary for Regulatory Activities (MedDRA).

Secondary efficacy variables will be OS, time to first SSE, rPFS, time to radiological progression, pain improvement rate, time to pain progression, and change in analgesic use.

4.3 Interim Analyses and Joint Safety Review Committee

Section modified by Amendment 1 (13.1).

No formal interim analysis is planned. A JSRC, which may contain sponsor, investigator, and/or independent members, will conduct safety reviews at regular intervals. The objective

of these safety reviews is to ensure subject safety and to identify whether any protocol modifications are needed. The JSRC will not evaluate efficacy. Details on the JSRC and its safety review monitoring will be described in a separate JSRC charter.

4.4 End of study

Section modified by Amendments 1 (13.1), and 3 (Section 13.3).

The final analysis of this study will take place after the primary endpoint cut-off is reached.

The primary endpoint cut-off will be reached at the later of 1) 135 SSE-FS events in subjects included in Comparison 1 as defined in Section 8.4 below, and 2) 75 SSE-FS events following the 6th dose in subjects included in Comparison 2 as defined in Section 8.4 below, and 3) the last subject has been followed for 30 days from last treatment. In the event the applicable number of events is not reached, the primary endpoint analysis will mature 7 years after the last subject has received last treatment.

Subjects alive at the time of the final analysis will continue to be followed for up to 7 years after the last dose of radium-223 dichloride or death for an updated analysis of long-term survival and long-term radiation-related safety.

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject for all centers in the respective country has occurred.

However, as the primary endpoint of this study is event-based, the end of the study as a whole will only be reached when this endpoint has been achieved in subjects in all participating centers (EU and non-EU).

5. Study population

5.1 Eligibility

Section modified by Amendment 2 (13.2).

Eligibility should be confirmed within 14 (± 7) days prior to randomization. At Dose 1, Day 1, the hematology values need to be confirmed to be within the treatment ranges (absolute neutrophil count [ANC] ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 9.0 g/dL) prior to dosing.

Rescreening of screen failed subjects is only allowed once after prior approval from the Bayer-designated medical representative. Sponsor approval of rescreening for a screen failed subject will be provided by written confirmation to the site. For these subjects who underwent screening procedures (i.e., scans and laboratory work) and cannot meet eligibility within the screening period (14 ± 7 days) due to logistical circumstances, screening

procedures may need to be repeated. At the time of rescreening, all expired procedures must be repeated and be within 14 ± 7 days prior to randomization. The maximum period allowed for screening will be 35 days (14 days screening + 7 day window + 14 days for rescreening).

Rescreening is also permitted where the subject's eligibility for the study depends upon the completion of washout periods as per protocol (e.g., 4 weeks from treatment with an investigational drug).

Rescreening is not permitted in cases in which the initial safety laboratory test results do not support eligibility.

5.1.1 Inclusion criteria

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Eligible subjects must meet all of the inclusion criteria listed below:

- Histologically or cytologically confirmed adenocarcinoma of the prostate
- Castration-resistant disease defined as:
    a. Serum testosterone level: ≤ 50 ng/dL (1.7 nmol/L)
    b. Bilateral orchiectomy or maintenance on androgen ablation therapy with luteinizing-hormone-releasing hormone (LHRH) agonist or antagonist,* or polyestradiol phosphate
    c. Serum PSA progression defined as 2 subsequent increases in PSA over a previous reference value, with a PSA value of ≥ 2 ng/mL at the time of the second increase **OR**

       Radiographic evidence of disease progression in bone (according to PCWG2 criteria) with or without PSA progression

  *In subjects who were treated with combined androgen blockade (a growth-hormone-releasing hormone analog or orchiectomy in combination with continuous anti-androgen) as initial therapy for a prolonged period of time, or who have responded to adding a peripheral anti-androgen as second line therapy, progressive disease (PD) should be documented after discontinuing anti-androgen treatment (for at least 6 weeks for bicalutamide and at least 4 weeks for flutamide and others) to exclude an anti-androgen withdrawal response.
- Subjects must be ≥ 18 years of age.
- Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2. In case of ECOG PS 2, the PS must be due to metastatic prostate cancer to the bone.

- Life expectancy ≥ 6 months.
- Two or more skeletal metastases (≥ 2 hot spots) on bone scintigraphy within 8 weeks of randomization.
- Laboratory requirements:
    a. ANC ≥ 1.5 x 10^9/L
    b. Platelet count ≥ 100 x 10^9/L
    c. Hemoglobin ≥ 9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin support within 4 weeks prior to screening
    d. Total bilirubin level ≤ 1.5 x institutional upper limit of normal (ULN) (< 3 x ULN for subjects with documented Gilbert's syndrome)
    e. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x ULN
    f. Creatinine ≤ 1.5 x ULN
    g. Estimated glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 according to either the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation or the Modification of Diet in Renal Disease (MDRD) abbreviated formula (see Section 14.6) (24, 25)
    h. Albumin > 25 g/L
- Written, signed informed consent. Subject must be able to understand and be willing to sign the written informed consent form (ICF). A signed ICF must be appropriately obtained prior to the conduct of any study-specific procedure.
- Sexually active males agree to use condoms and/or their female partners of reproductive potential to use a method of effective birth control during treatment and for 6 months following the completion of treatment with radium-223 dichloride.

5.1.2 Exclusion criteria

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

- History of visceral metastasis, or visceral metastases as assessed by CT / MRI of the abdomen and pelvis and / or chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]) within the previous 8 weeks of randomization
- Lymphadenopathy with lymph nodes exceeding 3 cm in short axis diameter

- Current CNS metastases. Subjects with neurological symptoms suggestive of CNS metastasis must undergo contrast CT scan or MRI of the CNS within 30 days of the start of treatment to exclude CNS metastasis. Imaging of the CNS is otherwise not required.

- Chronic conditions associated with non-malignant abnormal bone growth (e.g., confirmed Paget's disease of bone)

- Blood transfusions or use of erythropoietin within 4 weeks prior to screening, during the screening period, or prior to the start of treatment

- Treatment with an investigational drug within the 4 weeks prior to randomization

- Treatment with cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, within the previous 4 weeks prior to randomization, or planned treatment with these prohibited cytotoxic chemotherapy agents for prostate cancer during the treatment period or follow-up

- Prior treatment with radium-223 dichloride

- Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186 or rhenium-188

- Prior hemibody EBRT

- Use of biologic response modifiers, such as granulocyte macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF), within 4 weeks prior to screening

- Other malignancy treated within the last 3 years (except treated non-melanoma skin cancer or low-grade superficial bladder cancer)

- Imminent or established untreated spinal cord compression based on clinical findings and / or MRI. Following treatment of spinal cord compression, the subject may be eligible if all other eligibility criteria are fulfilled.

- Any other serious illness or medical condition such as, but not limited to:

    - Any uncontrolled infection

    - Cardiac failure New York Heart Association Class III or IV

    - Crohn's disease or ulcerative colitis

    - Bone marrow dysplasia

    - Unmanageable fecal incontinence

- Previous assignment to treatment in this study

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), and 3 (Section 13.3).

Subjects *will* be discontinued from study treatment for the following reasons:

- 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 decline further study treatment. The subject will not suffer any disadvantage as a result. The subject will continue to be followed up for safety and survival unless he completes the procedure for withdrawal of consent specified in Section 5.2.1.2.

- If, in the investigator's opinion, continuation of the study treatment would be harmful to the subject's well-being

- A dose delay of more than 4 weeks (maximum of 8 weeks between 2 injections)

- If cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, or other systemic radioisotopes are given during the treatment period

- If the subject experiences any non-hematological CTCAE Grade 4 adverse event lasting > 1 week despite adequate treatment regardless of causality.

- If the subject experiences Grade 3 neutropenia or Grades 3 or 4 thrombocytopenia lasting > 2 weeks or Grade 4 neutropenia lasting > 1 week despite adequate treatment regardless of causality. Blood transfusions and biologic response modifiers, such as GM-CSF or G-CSF can be used for the treatment of hematological abnormalities during the treatment period.

Subjects *may* be discontinued from study treatment for the following reason:

- At the specific request of the sponsor and in liaison with the investigator (e.g., obvious non-compliance, safety concerns)

For any subject who prematurely discontinues study treatment, the EOT assessments must be completed. The subject will remain in the study throughout the follow-up period. Any subject who withdraws from the study procedures but does not withdraw consent should enter active follow-up without clinic visits for survival assessment (see Section 7.1.2.8.2). In all cases, the reason for discontinuation from study treatment must be recorded in the electronic case report form (eCRF) and in the source documentation.

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

- Withdrawal of consent
  At any time during the study and without giving reasons, a subject or his legally acceptable representative may withdraw consent and decline to participate further in the study. The subject will not suffer any disadvantage as a result.

- Lost to follow-up

- Death

Details for the premature termination of the study as a whole (or components thereof [e.g., centers, treatment arms, dose steps]) are provided in Section 10 (Premature termination of the study).

For subjects who withdraw from the study prior to the EOT visit, it is recommended that the EOT assessments be completed.

5.2.1.1 Definitions

Screening failures are defined as follows:

- A subject who fails to satisfy the selection criteria at any time prior to randomization. The reason will be documented in the source documentation and the eCRF and the subject will discontinue participation in study with no further follow-up required.

- A subject who terminates the study at any time prior to randomization. The process for withdrawal of consent from the study must be followed (see Section 5.2.1.2).

Premature discontinuation of study treatment is defined as a subject who discontinues study treatment prematurely for any reason, if the subject has been administered at least one dose of study drug.

Drop-out is defined as a subject who discontinues study participation prematurely for any reason if the subject has already been randomized.

Subjects who pass screening but discontinue from the study prior to Dose 1 will be followed. Due diligence must be performed to follow-up for efficacy parameters.

5.2.1.2 Process for withdrawal of consent

In order to ensure complete study data, it is specified in the ICF that the subject agrees to complete all procedures and assessments in the treatment and follow-up periods. Only subjects who sign permission to collect follow-up data should be included in this study. This includes data on any follow-up examinations or analyses of images not analyzed at the time the subject completes the study.

The subject or his legally acceptable representative can withdraw this initial permission for study procedures and / or follow-up. 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.

5.2.2 Replacement

Withdrawn subjects will not be replaced.

5.3 Subject identification

A subject number (a unique identification number) will be assigned via an interactive voice / web response system (IVRS / IWRS) when a subject signs the ICF and is evaluated for inclusion into the study. When the subject is determined eligible for the study treatment, this number must be entered into the IVRS / IWRS. During the IVRS / IWRS update, the subject will be randomized to the treatment arm and the shipment for the initial radium-223 dichloride dose will be automatically processed.

6. Treatments

6.1 Treatments to be administered

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Subjects enrolled into the study will be randomized to one of the 3 treatment arms in a 1:1:1 fashion:

- Treatment Arm A: radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) IV every 28 days up to 6 doses (IV bolus)
- Treatment Arm B: radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) IV every 28 days up to 6 doses (IV bolus)
- Treatment Arm C: radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) IV every 28 days up to 12 doses (IV bolus)

The randomization will be permuted-block, stratified by use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total ALP (< 220 U/L versus ≥ 220 U/L) and by average WPS of the BPI-SF (WPS ≤ 4 versus WPS > 4).

6.2 Identity of study treatment

Section modified by Amendment 2 (Section 13.2).

The alpha particle-emitting radiopharmaceutical, radium-223 dichloride, is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of radium-223 dichloride for IV administration. Radium-223 is an alpha particle emitter with a physical half-life of 11.4 days. The product is isotonic and has a pH of 6.0 to 8.0. The radioactive concentration at the reference date is 1,000 kBq/mL (1,100 kBq/ mL after implementation of NIST update). The product has a pre-calibration of 14 days. When administered on a day other than the reference day, the volume should be corrected according to the physical decay table.

The product is manufactured by Institute for Energy Technology (IFE), Isotope laboratories Instituttveien 18, NO-2007, Kjeller, Norway on behalf of Bayer AS, Kjelsäsveien 172 A, N0-0884 Oslo, Norway. The product is produced according to Good Manufacturing Practice (GMP). The product will be delivered in a glass vial, ready-to-use with a certified activity. Radium-223 dichloride is shipped in a lead container and Type A radioactive package according to international transportation guidelines for radioactive materials.

The volume per vial is 6 mL, corresponding to 6 MBq (6.6 MBq after implementation of NIST update) at the reference day. Radium-223 dichloride has a shelf life of 28 days from production day, when stored at ambient temperature. The shelf life has been demonstrated for temperatures from cold storage (2ºC to 8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing. For the US, study drug may be forwarded to the country depot in vials, where it will be prepared as a patient ready dose ([PRD], in a syringe) before being delivered to the site.

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective bulkware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor study file.

6.3 Treatment assignment

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

This study is a randomized, 3-arm open-label Phase II study.

A subject number (a unique identification number) will be assigned via IVRS / IWRS when a subject is evaluated for inclusion into the study. The subjects will then undergo screening procedures and will enter the study after successful screening. Subjects will be randomized 1:1:1 to receive one of:

- Treatment Arm A: Radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) intravenously every 28 days for up to 6 doses ("standard dose")

- Treatment Arm B: Radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) intravenously every 28 days for up to 6 doses ("high dose")

- Treatment Arm C: Radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) intravenously every 28 days for up to 12 doses ("extended dose")

The randomization will be permuted-block, stratified by use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total ALP (< 220 U/L versus ≥ 220 U/L), and by average WPS of the BPI-SF (WPS ≤4 versus WPS > 4).

6.4 Dosage and administration

Written information about radium-223 dichloride and instruction about handling and injection of radioactive material will be provided to study personnel.

In general, the administration of radioactive drugs involves a potential risk for third parties, due to radiation from the subject and due to possible contamination by spilling urine or feces. When radium-223 dichloride has been injected intravenously into a subject, the risk for external radiation exposure to third parties is extremely low, due to the short range of the alpha particles (< 100 µm) and the low proportion of beta and gamma radiation emitted. For these reasons, the product can be administered in an outpatient setting. To minimize the risk of contamination, the subject and his caregivers will receive instructions regarding hygiene precautions to abide by after receiving the radioactive drug according to the investigational site radiation protection guidelines. After each dose, the subject should be given the subject information card to carry with him until the next dosing visit.

6.4.1 Dose calibration

Section modified by Amendment 2 (Section 13.2).

Radium-223 dichloride can be measured in a normal dose calibrator instrument. When written approvals for the use of radium-223 dichloride from the Radiation Protection Agency for the specific center have been received by the sponsor, a vial of radium-223 for technical use will be sent to the study center.

Different clinical study centers possess dose calibrators from various suppliers; thus, the isotope calibration factor may differ from center to center. Consequently, each center must perform the radium-223 dial setting on their relevant dose calibrator(s). For dial setting, the clinical study center will receive a sealed vial containing a radium-223 solution for calibration only. The vial is identical to the vials used for study treatment. The amount of

radium-223 in the vial will be stated on the label. Instructions for the dial setting, including the calibration log form, will be enclosed with the dispatch of the calibration sample. If calibration was previously performed and documented at a given site, that documentation needs to be provided to the sponsor (i.e., recalibration for those sites may not be necessary). A similar dose calibration and approval process will be implemented with the country PRD depot, as applicable.

As of Amendment 2, NIST has established an updated standardization for radium-223 dichloride, which indicates that an approximate 10% difference existed between activity values obtained using the current standard and the updated standardization. The current NIST standard for radium-223 dichloride (NIST 2010 [31]) will remain in effect for this protocol until all Health Authorities for which Bayer holds a marketing application for radium-223 dichloride have approved the regulatory variations for Xofigo®, anticipated Q 2 2016. All sites will be notified by Bayer when regulatory approvals are in place and the updated NIST standardization is to be implemented. Upon notification, and prior to the implementation, all sites will need to add a new dial-setting to their dose calibrators for the new NIST standardization for radium-223 dichloride (NIST update [32]), which should be documented on the appropriate study forms. This step will be performed so that all sites will have the new dial setting (NIST update [32]) in place at the time of implementation. The current dial setting (NIST 2010) will be used until the worldwide global implementation date anticipated for Q 2 2016.

The change in the NIST radium-223 standard has no impact on subjects; subjects are receiving, and will continue to receive, the same actual dose and volume that was studied in ALSYMPCA and is associated with the proven safety and efficacy of radium-223 dichloride, though the stated nominal radiation dose received is being updated to reflect the new standard. Subjects who are on-treatment at the time the new NIST reference standard goes into effect will be notified of this change and will be required to sign a Patient Information Sheet to acknowledge that they have received information on the updated NIST standard calibration. All patients randomized after the new reference standard is in effect will sign a revised ICF that contains the updated NIST standardization.

The formula for the calculation of the volume to be administered has to be changed respectively. See Section 6.4.3.

6.4.2 Dose handling

Ordering of study drug will be done by notifying the IVRS / IWRS from the study site at pre-defined lead times before each planned administration. The next dose may be requested in the IVRS / IWRS upon registration of the current dose through the pre-defined lead time (maximum number of days in transit for the given country plus a 2-day buffer) prior to the next planned dose date.

The radium-223 dichloride vials must be stored inside their lead container in a secure facility. The study drug should be used within 28 days of production.

Radium-223 dichloride is an alpha particle-emitting radiopharmaceutical and should be handled by individuals who are qualified by training and experience in the safe handling of radionuclides. One dedicated person and a back-up designee will have responsibility as assigned from the principal investigator for handling and storage of radium-223 dichloride.

Control measurements of both the radium-223 dichloride vial (before and after dispensing) and syringes (before and after administration) are performed as part of the clinical study documentation. For the US sites which have PRDs prepared at the country depot, the measurements of the vial activity before and after dose preparation should be checked and recorded by the depot staff and a copy of the documentation should be provided to the site for each PRD. All administrations of radium-223 dichloride will be based on the certified activity of radium-223 at the reference date.

6.4.3 Dose calculation

Section modified by Amendment 2 (Section 13.2).

The dosage of radium-223 dichloride is 50 kBq/kg (55 kBq/kg after implementation of NIST update) body weight (Treatment Arms A and C) or 80 kBq/kg (88 kBq/kg after implementation of NIST update) body weight (Treatment Arm B). The total activity to be injected will be calculated volumetrically using the subject's body weight, the 50 (55 kBq/kg after implementation of NIST update) or 80 kBq/kg body (88 kBq/kg after implementation of NIST update) weight dosage level, and the decay correction factor (DK) to correct for physical decay of radium-223. A table with DKs according to physical decay of the study medication will be provided with each vial of radium-223 dichloride. The total amount (volume to be drawn into the syringe) to be administered to a subject should be calculated as follows:

$$\frac{\text{Body Weight (kg)} \times 50\ \text{kBq/kg}^{a}}{\text{DK} \times 1{,}000\ \text{kBq/mL}^{b}} = \text{volume to be injected (mL)}$$

[a] 55 kBq/kg after implementation of NIST update

[b] 1,100 kBq/mL after implementation of NIST update

For high dose treatment arm:

$$\frac{\text{Body Weight (kg)} \times 80\ \text{kBq/kg}^{c}}{\text{DK} \times 1{,}000\ \text{kBq/mL}^{b}} = \text{volume to be injected (mL)}$$

[c] 88 kBq/kg after implementation of NIST update

[b] 1,100 kBq/mL after implementation of NIST update

Data regarding activity, calculations, and volume to be injected must be recorded in the source documentation and on the appropriate eCRF page. This applies to both doses that are prepared at the site and doses that are prepared by an off-site vendor.

For the US sites which have PRDs prepared at the country depot:

- The subject's weight measured at the dosing visit will be obtained at the site approximately 3 to 5 days prior to the planned dosing date.
- This weight will be communicated to the country PRD depot for preparation of the current dose; a record of this information transfer will be retained at the site.
- Documentation by the central PRD depot of the required activity, calculations, and volume in the syringe will be retained at the depot with a copy provided to the site.

6.4.4 Dose preparation

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Personnel should use appropriate protective clothing and equipment during syringe filling and application to prevent contamination with the radioactive solution (lab coats, medical gloves / protective glasses). Staff should adhere to all relevant radiation safety regulations as prescribed by local authorities administering their site radiation license, including as low as reasonably achievable principles.

A radio pharmacy will prepare a subject ready dose for dispensing to the subject. In the US, Cardinal Health is the radio pharmacy that will dispense the subject ready dose.

Filling of the syringe should take place in a safety bench or similar cabinet in the Radiopharmacy / Nuclear Medicine department. The individual responsible for study drug preparation will draw the correct volume of study drug into a syringe. The size of the syringe should be chosen according to the applied volume to reach the required dosing accuracy.

Radium-223 dichloride should not be diluted or mixed with any solutions. If the vials have been stored in a refrigerator, they should be left at room temperature for 1 hour prior to use, since cold material should not be injected in a subject.

6.4.5 Dose administration

The subject should be encouraged to arrive at the clinic well-hydrated on each dosing day. Subjects should avoid drinking or eating within 1 hour before and after administration of the study drug. After administration of study drug, the subject should be encouraged to be well-hydrated and to drink ad libitum.

Aseptic technique should be used in the administration of radium-223 dichloride. The syringe should be handed over to the individual who will perform the injection. The study medication will be administered as a slow bolus IV injection. The actual radioactivity administered must be within the tolerance limits of ± 10% of the calculated radioactivity. After administration, the equipment used in connection with the preparation and administration of drug is to be treated as radioactive waste and should be disposed of in

accordance with hospital procedure for the handling of radioactive material. For central PRD depots, the same principles apply to dose preparation and handling of radioactive material.

6.4.6 Dose adjustments

Every effort will be made to administer the full dosing regimen of radium-223 dichloride. Adjustment of dose level is not permitted.

6.4.7 Dose delays

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Study visits during the treatment period should occur at 28-day intervals (within a window of ± 7 days). Delays up to 4 weeks are allowed when the subject is recovering from toxicity. Adverse events will be followed as clinically indicated (see Section 7.5.1.3).

Dosing delays may be instituted under the following circumstances:

Disease progression:

In this subject population, disease progression is expected. Bone pain is a prominent symptom; other symptoms may include fatigue, nausea, anorexia, depression, constipation (also secondary to opioids), bowel and bladder symptoms, lymphedema, or neurological and hematological complications, as well as metastases to other organs, such as liver and lung.

The investigator should delay treatment with cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, other systemic radioisotopes, hemibody EBRT, or other investigational drug, if possible, until the follow-up period. If the investigator determines that such treatments must be given while the subject is receiving study drug, further study drug administration must be discontinued. Subjects who are discontinued from study drug will be classified as "withdrawn from treatment" and will enter the active follow-up period. If the subject is not treated with any of the prohibited anti-cancer therapies, the administration of study drug may be continued until completion of 6/12 cycles if, in the investigator's opinion, the subject will continue to receive clinical benefit from remaining on study treatment.

Myelosuppression:

Treatment-related changes in hematology parameters may occur. Hematology values will be graded according to the NCI-CTCAE, version 4.03 (14 JUN 2010).

- If a subject experiences NCI-CTCAE Grades 3 or 4 neutropenia or thrombocytopenia (see Table 6–1), the study drug administration should be delayed until recovery to Grade 2 (minimum 1.0 x 10^9/L) or better.

- If a subject experiences sustained CTCAE Grade 3 neutropenia or sustained CTCAE Grades 3 or 4 thrombocytopenia (see Table 6–1) lasting > 2 weeks despite adequate treatment and regardless of causality, the subject must be discontinued from treatment with radium-223 dichloride.

- If a subject experiences sustained CTCAE Grade 4 neutropenia (see Table 6–1) lasting > 1 week despite adequate treatment and regardless of causality, the subject must be discontinued from treatment with radium-223 dichloride.

- Blood transfusions are acceptable during the treatment period, but erythropoietin is not allowed. Use of biologic response modifiers, such as GM-CSF or G-CSF, is allowed in the management of acute toxicity during the treatment period. Such drugs (and transfusions) cannot be used for 4 weeks prior to screening and during the screening period, or prior to the start of treatment.

Table 6–1 National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) Grade 3 and 4 values for neutropenia and thrombocytopenia

Adverse Event	Grade 3	Grade 4
Neutropenia (neutrophil count decreased)	< 1,000 to 500/mm^3; < 1.0 to 0.5 x 10^9/L	< 500/mm^3; < 0.5 x 10^9/L
Thrombocytopenia (platelet count decreased)	< 50,000 to 25,000/mm^3; < 50.0 to 25.0 x 10^9/L	< 25,000/mm^3; < 25.0 x 10^9/L

Gastrointestinal events:

Diarrhea: Diarrhea should be treated as per local practice. A further dose of study medication should not be given before diarrhea has recovered to CTCAE (version 4.03) Grade 2 or lower.

Nausea / vomiting: Nausea or vomiting should be treated as per local practice. A further dose of study medication should not be given before nausea or vomiting has recovered to CTCAE (version 4.03) Grade 2 or lower.

Spinal cord compression:

If the subject experiences spinal cord compression during the treatment period, the subject should be treated for the event, and may receive further study drug administration if adequately recovered. A dose delay of up to 4 weeks is permitted.

External beam radiotherapy:

No dose delay is needed for EBRT.

Surgical intervention:

If surgery is required, the subject should continue with study treatment, if this is considered safe in the treating investigator's opinion. The surgeon needs to be notified that the subject

has been given radioactive drug and needs to follow the guidelines for radioactive protection. The subject should continue with study treatment if it is considered safe in the treating investigator's opinion.

Non-pathological fractures:

For traumatic fractures in weight-bearing bones during the treatment phase, the study drug administration should be delayed for 2 to 4 weeks from the time of fracture.

Pathological fractures:

Pathological fractures may occur as the result of either progressive disease or increased physical activity associated with significant pain palliation. Pathologic fractures are to be treated in a manner that attempts to maintain the best functional status and QoL. Study treatment may continue as planned.

Any other adverse event:

If a subject experiences any non-hematological CTCAE (version 4.03) Grade 4 adverse event regardless of causality lasting more than 7 days despite adequate treatment, further study drug administration must be discontinued.

Logistical difficulties:

Screening to Dose 1: An additional 14 days will be permitted for the 14-day screening window for 'failed' quality of investigational product that requires replacement or extraordinary logistical issues. Prior written approval by the sponsor designee is required and screening assessments may need to be repeated to be within the 14 (± 7)-day window prior to randomization. The maximum period allowed for screening will be 35 days (14 days screening + 7 day window + 14 days for rescreening).

Doses 2 to 6 (or Doses 2 to 12 for Treatment Arm C): An additional 28 days will be permitted for Doses 2 to 6 (or Doses 2 to 12 for Treatment Arm C) for 'failed' quality of investigational product that requires replacement or extraordinary logistical issues. Prior written approval by the sponsor designee is required.

A dose delay of more than 4 weeks (maximum of 8 weeks between 2 injections) will lead to study drug discontinuation.

Note: efficacy assessments should be performed as scheduled despite delays in dosing.

6.5 Blinding

This study is an open-label study.

6.6 Drug logistics and accountability

All study drugs at the investigational site will be stored in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate / clinical research organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor study file; the site-relevant elements of this information will be available in the investigator site file. Records of the study drug received at the site (and at the country PRD depot, when used in the US) will be retained as required. The responsible site personnel will confirm receipt of study drug via the IVRS / IWRS and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, and destruction of the study drug must be properly documented according to the sponsor's agreed and specified procedures. The monitor will review overall drug accountability and destruction per the site documentation only. The remains of radioactivity and contaminated material (i.e., vials, syringes, containers) should be disposed of in accordance with the local regulations and the hospital procedure, respectively. A log of study medication (received, administered to subjects, and destroyed) must be maintained and signed by the dedicated person responsible for drug handling at each center. Any labels or mandatory logs provided by the sponsor are to be utilized according to instructions. A copy of study drug documentation will be collected for the sponsor file.

Written instructions on medication destruction will be made available to affected parties as applicable.

6.7 Treatment compliance

Subjects will receive treatment with radium-223 dichloride under the supervision of a physician licensed in the administration of radioisotopes. Personnel will check the administration volume and total radioactivity injected. The activity dose (total and per body kilogram) along with the volume and the radioactivity measured in the syringe before and after the injection will be recorded in the source data and the appropriate eCRF. The actual administered radioactivity must be within the tolerance limits of ± 10% of the calculated radioactivity.

6.8 Post-study therapy

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), 3 (Section 13.3), and 4 (Section 13.4.1.2).

Subjects will have an EOT visit 30 (± 7) days following the last dose of study drug, including early discontinuation of study drug, and will be followed every 12 weeks for safety and SSE evaluations. Every effort will be made to follow subjects through clinic visits; however, phone contact will be undertaken for subjects unable to come to the clinic. The active

follow-up period will continue for 2 years after the subject's last dose of radium-223 dichloride or until the primary efficacy analysis matures, whichever occurs last.

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported radium-223 dichloride-related AEs and SAEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic anti-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes, 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject.

Until the transition to the long term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up).

6.9 Prior and concomitant therapy

6.9.1 Prior therapy

Section modified by Amendment 2 (Section 13.2).

Prior hemibody EBRT or systemic radiotherapy with strontium-89, samarium-153, rhenium-186, or rhenium-188 is not allowed. Subjects are not allowed to receive an investigational drug or cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, within 4 weeks prior to randomization in this study. Blood transfusions, erythropoietin, or biologic response modifiers, such as GM-CSF or G-CSF, are

not allowed within 4 weeks of screening, during the screening period, or prior to the start of treatment.

Information about previous treatment both for primary tumor and bone metastases will be recorded in the medical record and in the appropriate eCRF.

All other prior medications, including but not limited to pain medications, antibiotics, steroids, bisphosphonates, iron therapy, or radiation therapy taken in the 30 days prior to start of study treatment will be recorded in the subject's medical record and in the appropriate eCRF. The generic or trade name, indication, dosage, and start and stop dates must be recorded.

6.9.2 Concomitant medication

Section modified by Amendments 2 (Section 13.2) and 4 (Sections 13.4.1.1, 13.4.1.3, and 13.4.1.5).

During treatment, all concomitant medications, including therapies for prostate cancer, must be recorded in the source documentation as well as the appropriate pages of the eCRFs. The generic or trade name, indication, dosage, and start and stop dates must be recorded.

Contrast media will not be captured as concomitant medication unless there is an AE or SAE related to administration of contrast media.

Allowed concomitant treatments for prostate cancer include: LHRH analogs, surgery, radiation therapy, flutamide, bicalutamide, nilutamide, cyproterone acetate, ketoconazole, corticosteroids, estrogens, and enzalutamide. Subjects who have not undergone bilateral orchiectomy are to receive LHRH agonists or antagonists or polyestradiol phosphate throughout the study.

Radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone.

Subjects receiving bone health agents (BHA), such as bisphosphonates or denosumab, prior to receiving study drug treatment may be maintained on these therapies throughout all or part of the treatment period. Subjects in the treatment period can also initiate these therapies at any time. Based on the available data on radium-223 dichloride, the option of starting a BHA during the follow up periods should be considered, taking into consideration applicable guidelines. Treatment with bisphosphonates or denosumab may be stopped at the discretion of the investigator.

Analgesic use will be followed and any medications taken for pain should be recorded in the source documentation and in the appropriate eCRF. Use of biologic response modifiers, such as G-CSF or GM-CSF, is allowed in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator.

Blood transfusions are allowed during the treatment period, but erythropoietin is not allowed.

Cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, other systemic radioisotopes, hemibody EBRT, and investigational drugs are prohibited.

If the investigator determines that a prohibited treatment is required during the treatment period, study drug administration must be discontinued. If possible, the prohibited therapy should not be initiated for at least 4 weeks after the last dose of study drug and after completion of the EOT assessments.

7. Procedures and variables

7.1 Schedule of procedures

7.1.1 Tabulated overview

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

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), 3 (Section 13.3), and 4 (Sections 13.4.1.1 and 13.4.1.2).

Table 7–1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term Follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random.[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Informed consent	X																									
Inclusion / exclusion criteria[f]	X	X[g]						X[g]																		
Demographic data	X																									
Medical and disease history	X																									
Height	X																									
Weight[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Training on daily PRO pain collection[i]	X																									
Pain assessment[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X[k]					
Randomization[l]	X																									
Review daily PRO pain input	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X[k]					
BPI-SF[m]	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X[k]					

Table 7–1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term Follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random.[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
NCCN FACT-P Symptom Index-17 Questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]					
24-hour Analgesic use collection[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]					
Vital signs[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Physical examination[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Chemistry panel and CBC[r]	X	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]				
PSA	X	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X	X	X				
Testosterone	X																									
Whole body technetium-99 bone scans[u]	X			X		X				X		X		X			X			X[u]	X	X				

Table 7–1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term Follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random.[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Documentation of bone metastases[w]	X																									
MRI / CT scan abdomen and pelvis, chest X-ray[u]	X			X		X				X		X		X			X			X[v]	X	X				
IVRS / IWRS[x]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X								
Radium-223 dichloride administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Oral hydration[y]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Subject contact card[z]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Subject and family instructions[aa]	X	X						X																		
Record SSEs	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[cc]	X[cc]				
Record concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						

Table 7–1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term Follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random.[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Record limited concomitant medication[dd]																					X	X				
Record therapy for prostate cancer other than radium-223 dichloride		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[ee]	X	X	X	X	X
Record chemotherapy for other malignancies																					X	X	X	X	X	X
Record new primary malignancies		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs and SAEs[ff]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						

Table 7–1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term Follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random.[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Record radium-223 dichloride related AEs and SAEs[gg]																					X	X	X	X	X[hh]	X[hh]
Record SSE-related AEs and SAEs[gg]																					X	X				
Survival status																							X	X	X	X

Abbreviations: AE = adverse event; BPI-SF = Brief Pain Inventory Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; IVRS / IWRS = interactive voice / web response system; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PCWG2 = Prostate Cancer Clinical Trials Working Group 2; PRO = Patient-reported outcome; PS = performance status; PSA = prostate specific antigen; q6 = every 6; q12 = every 12; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SSE = symptomatic skeletal event; US = United States; wk = week; WPS = worst pain score.

[a] Once a subject switches from active follow-up with clinical visits to active follow-up without clinical visits, the subject will not be allowed to switch back. A subject with a possible SSE may, and is encouraged to, return to the clinic at any time to assess for the presence of an SSE.

[b.] Subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. Once a separate, extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical studies, has been implemented, the study subjects surviving after the end of the 2 years of active follow-up will be transitioned to this separate, extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

[c.] The maximum period for rescreening screen failed subjects is 35 days (14 days screening + 7-day window + 14 days for rescreening) from signing the ICF to randomization. Rescreening of a subject requires prior approval of the Bayer-designated medical representative (see Section 5.1). Eligibility should be confirmed within 14 ± 7 days of randomization.

[d.] The subject should return to the clinic in advance of the scheduled dose visit such that results of the laboratory assessment are available within 72 hours prior to dosing (each dose period is 28 ± 7 days after the prior dose of radium-223 dichloride).

[e.] Subjects who can no longer travel to the clinical site or who receive further anticancer therapy will only be followed up by telephone (active follow-up without clinic visits). Symptomatic skeletal events will not be collected over the phone.

[f.] The study record or subject's clinical record must clearly show that informed consent was obtained prior to any other study procedures being performed. Eligibility should be confirmed during the screening period and reconfirmed prior to dosing at Dose 1, Day 1.

[g.] Reconfirmation of eligibility and registration in the IVRS / IWRS: hematology results obtained within 72 hours of Dose 1, Day 1 should be reviewed and it should be confirmed that the values are still within the treatment ranges (absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 9.0 g/dL).

[h.] Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. At all sites (in US and outside US), weight is to be taken only once for each dose. For non-US sites the weight should be performed within 72 hours prior to dosing. For US sites, subject weight for the dose day should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits. Please note this is applicable to all dosing visits. Body weight can be obtained at the local healthcare provider on a calibrated scale and the results sent by fax to the Principal Investigator with advanced notice and agreement from the Covance Medical Monitor for each subject. No other procedures can be done at the local healthcare provider.

[i] When a subject is determined to be eligible, the subject will be trained on daily PRO pain data collection using a handheld device. The subject will then complete the pain assessment daily for 4 days prior to randomization and then daily for one week (6 days prior to Cycle 1, Day 1 or subsequent visits, as applicable, plus the morning of the visit).

[j.] Pain will be assessed during the screening period daily for 4 days prior to randomization and daily for one week (6 days prior to Cycle 1, Day 1 or subsequent visits, as applicable, plus the day of the visit). Subjects will complete the daily pain assessment using a handheld device. The daily PRO pain input results should be reviewed at the visit to check for completeness.

[k] For Treatment Arms A and B only, pain data will be collected daily using the handheld device for one week (6 days prior to the applicable visit, plus the morning of the visit) prior to Week 36 and 48 visits, and daily for one week (6 days prior to the applicable phone call, plus the morning of the phone call) prior to each telephone contact at Weeks 28, 32, 40 and 44. For Treatment Arms A and B only the BPI-SF and the NCCN FACT-P Symptom Index-17 (NCCN-FACT FPSI-17) questionnaires will be completed on the day of the Week 36 and 48 visits and on the day of each telephone contact at Weeks 28, 32, 40 and 44. Twenty-four (24) hour analgesic use will be collected by the study investigator at Week 36 and 48 Visits and at each telephone contact (in Arms A and B) at Weeks 28 (±7 days), 32 (±7 days), 40 (±7 days), and 44 (±7 days).

[l.] The randomization will be permuted-block, stratified by the use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total alkaline phosphatase (< 220 U/L versus ≥ 220 U/L), and by average WPS of the BPI-SF (WPS ≤4 versus WPS > 4). Treatment group assignment will occur when the subject is randomized via IVRS / IWRS; this randomization step at up to 28 days prior to Dose 1. Randomization triggers an order for study drug (durations vary based on country specific ordering lead times; US depot requires additional step).

[m.] The BPI-SF questionnaire will be completed at each clinic visit from Dose 1, Day 1 until the Week 48 visit and for Treatment Arms A and B only, on the day of each telephone contact at Weeks 28, 32, 40 and 44. For further details, see Section 14.7.

[n.] Prior to randomization, the subject will use the hand-held device to complete selected questions from the BPI-SF questionnaire, Question 3, worst pain in the last 24 hours will be completed for at least 4 days during a period of no more than 1 week prior to randomization. The average of the 4 days will be used as the randomization stratification value.

o. Twenty-four (24)-hour analgesic use will be collected and it will be assessed by the study investigator until the Week 48 visit. Twenty-four (24)-hour analgesic use will also be collected by the study investigator at each telephone contact (in Arms A and B) or visit at Weeks 28, 32, 40, and 44.

p. Systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes.

q. After a complete physical examination at screening, subsequent physical examinations may be 'brief,' but should include any systems with symptoms. All physical examinations will be performed by a physician according to the standard of care.

r. Complete blood count, including hematocrit, hemoglobin, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be collected. Chemistry panel including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total alkaline phosphatase, aspartate transaminase, alanine transaminase, lactate dehydrogenase (screening only), and albumin (screening only).

s. Laboratory assessments should be performed within 72 hours of the visit and the results assessed and documented prior to dosing.

t. The PSA result for each dosing visit may be assessed post-dose.

u. Radiological / progression (according to PCWG2 criteria) will be assessed by means of whole body technetium-99 bone scan, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and MRI / CT scan of the abdomen and pelvis. Baseline tumor assessment should be performed within 14 (± 7) days of randomization. If standard of care bone scan and / or MRI / CT scan of the abdomen and pelvis and chest X-ray within 8 weeks of randomization are available, they do not need to be repeated at baseline. If they are not available, they should be performed within 14 days ± 7 days of randomization (i.e., during the screening period). Subsequent tumor assessment should be performed at Week 8, Week 16, Week 24 and every 12 weeks thereafter for up to 2 years after the subject's last dose of radium-223 dichloride or until radiological progression (according to PCWG2 criteria or RECIST guidelines), or death, whichever comes first. If progression is detected by bone scan, a confirmatory bone scan is required at least 6 weeks later. All images should be obtained with the same technique (e.g., CT or MRI) as those obtained at screening. Schedule deviations of ± 2 weeks for imaging / tumor evaluations are allowed.

v. Imaging is not required at the EOT visit if the subject discontinued due to radiological progression or the last tumor evaluation is not older than 4 weeks.

w. Bone imaging should be within 8 weeks of randomization. If no prior documentation is available, a whole body technetium-99 bone scan will be obtained at screening (within 14 ± 7 days of randomization).

x. The IVRS / IWRS will be used to register requests for eligibility / study drug doses. Once the subject eligibility is approved and registered in the IVRS / IWRS, including entry of required demographic and stratification information, the initial drug shipment may be prepared. Additional IVRS / IWRS transactions for dose orders may be required; follow the country-specific guidance in the IVRS / IWRS manual. The latest order date for the next dose is no later than the pre-defined lead time (number of days from order received to delivery to site in the country) prior to the planned dosing date. The planned date for the next dose must be specified, when the dose is requested in the IVRS / IWRS. At Doses 1 through 5, the site should order the next dose in the IVRS / IWRS, as soon as the current visit's dose is registered in the IVRS / IWRS. The latest order date for the next dose is no later than the pre-defined lead time (number of days from order received to delivery to site in the country) prior to the planned dosing date. For subject visit registrations in the IVRS / IWRS, see the IVRS / IWRS manual.

y. The subject should be encouraged to arrive at the clinic well-hydrated on each dosing day and to drink ad libitum after each dose of radium-223 dichloride. The subject should avoid drinking or eating within 1 hour before and after administration of the study drug.

z. The subject contact card is to be provided at each dosing visit for the subject to carry with him until the next visit.

aa. Subject and family instructions should be reviewed with the subject during screening through Dose 1, Day 1.

bb. Subjects identified with possible SSEs will be asked to come to the clinic for an SSE evaluation. An SSE risk questionnaire will be developed. Symptomatic skeletal events will not be identified over the telephone.

cc. If a subject has an SSE in the active follow-up period, he will continue active follow-up for 2 years following last study treatment. At Weeks 28, 32, 40, and 44, subjects in Treatment Arms A and B will receive telephone contacts assessing for possible SSE risks. Subjects exhibiting symptoms indicative of possible SSEs will be encouraged to visit the clinic early to assess SSE

status. Symptomatic skeletal events will not be determined over the phone.

[dd.] Except for complete analgesic use information recorded through Week 48, limited concomitant medication, including narcotic pain medication, will be recorded during the active follow-up with clinic visits period. Contrast agents will only be captured as concomitant medication if there is an AE or SAE related to administration of contrast media.

[ee.] Subjects who receive further anticancer therapy during the active follow-up period will have an end of active follow-up with clinic visits and will enter the active follow-up without clinic visits (telephone follow-up). Subjects who receive further anticancer therapy after 2 years from last study treatment will enter long-term follow-up. Radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone.

[ff.] All AEs and SAEs will be assessed and recorded from the time the ICF is signed until 30 days after the last dose of study medication. All AEs should be assessed and documented prior to each dose of radium-223 dichloride.

[gg.] Any AEs and SAEs occurring beyond 30 days after the last treatment must be documented and reported if considered to be related to study medication or if related to an SSE. However, 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. In addition, during follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

[hh.] Any SAEs must be documented and reported if considered to be related to study medication. However, 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. In addition, during follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

7.1.2 Timing of assessments

7.1.2.1 Screening period

Section modified by Amendments 1 (13.1) and 2 (Section 13.2).

The subject should come to the clinic for screening, preferably in the morning. The following documentation should be collected and assessments should be performed during the screening period:

Within 14 (± 7) days prior to randomization:

- Signing of the ICF prior to any study specific procedures (enrollment in the study is defined as the signing of the ICF)
- Confirmation of eligibility criteria
- Documentation of demographic data, including age, gender, race, and ethnicity
- Height and weight (Note: Body weight should be obtained without shoes, using a calibrated electronic physician [column] scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study, if possible.)
- ECOG PS
- Documentation of medical history
- Documentation of disease history, including prior and current anticancer treatments
- Laboratory assessments
    - Complete blood count (CBC), including hematocrit, hemoglobin, red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC) count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils
    - Chemistry panel, including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total ALP, AST, ALT, lactate dehydrogenase (LDH), and albumin
- PSA
- Testosterone

- Vital signs (systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes)

- Complete physical examination

- Review of subject and family instructions

- Recording of SSEs
  The investigator will assess the subject for the following disease events:

  - Use of EBRT to relieve skeletal symptoms

  - New symptomatic pathological bone fractures (vertebral and non-vertebral)

  - Tumor-related orthopedic surgical intervention

  - Spinal cord compression

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed within 14 ± 7 days prior to randomization (i.e., during the screening period). If MRI / CT scan of the abdomen and pelvis, and chest X-ray performed within 8 weeks of randomization are available, they do not need to be repeated at baseline.

- Documentation of bone metastases

  - If standard of care bone scan within 8 weeks of randomization is available, the scan does not need to be repeated at baseline. If this scan is not available, the scan should be performed within 14 ± 7 days prior to randomization (i.e., during the screening period).

- Recording of AEs from the time the subject signs the ICF

- Recording of concomitant medications

- When a subject is determined to be eligible, the subject will be trained on daily Patient-reported outcome (PRO) pain data collection using a handheld device. Eligible subjects will then complete the pain assessment daily

  - for the 4 days immediately prior to randomization. The average of the daily WPS over the 4-day period will be used for stratification (WPS $\leq$ 4 versus WPS > 4); 4 days of daily WPS data must be taken before randomization can occur.

- for 6 full days prior to the dosing visit plus the morning of the day of the dosing visit prior to Dose 1, Day 1.

- At all sites (in US and outside US), weight is to be taken only once for each dose.
  - For non-US sites, the weight should be performed within 72 hours prior to dosing.
  - For US sites using the central PRD depot ONLY, subject weight for Dose 1, Day 1 should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits.

The IVRS / IWRS will be used to register requests for eligibility / study drug doses. Once the subject eligibility is approved and registered in the IVRS / IWRS, including entry of required demographic and stratification information, the initial drug shipment may be prepared. Additional IxRS transactions for dose orders may be required; follow the country-specific guidance in the manual. The latest order date for the next dose is no later than the pre-defined lead time (number of days from order received to delivery to site in the country) prior to the planned dosing date. The planned date for the next dose must be specified, when the dose is requested in the IVRS / IWRS. At Doses 1 through 5, the site should order the next dose in the IVRS / IWRS, as soon as the current visit's dose is registered in the IVRS / IWRS. For subject visit registrations in the IVRS / IWRS, see the IVRS / IWRS manual.

7.1.2.2 Randomization

Section modified by Amendment 2 (Section 13.2).

The treatment period for efficacy purposes begins at the time of randomization. Subjects will be randomized to either: radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) IV every 28 days for up to 6 doses or radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) IV every 28 days up to 6 doses or radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) IV every 28 days up to 12 doses. The randomization will be permuted-block, stratified by the use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total ALP (< 220 U/L versus ≥ 220 U/L), and by the average of the daily WPS of the screening BPI-SF (WPS ≤4 versus WPS > 4). Treatment group assignment will occur when the subject is randomized via IVRS / IWRS; this randomization step at up to 28 days prior to Dose 1. Randomization steps triggers an order for study drug (durations vary based on country specific ordering lead times; US depot requires additional step).

7.1.2.3 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C)

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

On Day 1 of study therapy, the subject should return to the clinic, preferably in the morning and the following assessments will be performed prior to dosing, except where specified otherwise:

- Reconfirmation of eligibility: hematology results obtained within 72 hours prior to Dose 1, Day 1 should be reviewed and it should be confirmed that the values are still within the treatment ranges (absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 9.0 g/dL).

- BPI-SF questionnaire using a handheld device (should be self-administered at the beginning of the visit and should be checked for completion at the visit; see Section 14.7).

- NCCN-FACT FPSI-17 questionnaire, using a handheld device, is also self-administered at the beginning of the visit and should be checked for completion at the visit prior to treatment (see Section 14.8).

- Registration in the IVRS / IWRS

- ECOG PS

- Laboratory assessments (should be performed within 72 hours prior to the visit and the results assessed and documented prior to treatment)

    - CBC, including hematocrit, hemoglobin, RBC count, MCV, MCH, MCHC, WBC count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils

    - Chemistry panel, including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total ALP, AST, and ALT

- PSA (result may be assessed post-dose)

- At all sites (in US and outside US), weight is to be taken only once for each dose.

    - For non-US sites, the weight should be performed within 72 hours prior to dosing.

    - For US sites using the central PRD depot ONLY, subject weight for Dose 1, Day 1 should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should

be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits.

- Vital signs (systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes)
- Brief physical examination (see description in Section 7.5.3.2)
- Review of subject and family instructions (can be done at any time during the visit)
- Review of the daily pain PRO input results at the visit to check for completeness
- Analgesic use evaluation: Analgesic use will be collected and it will be assessed by the study investigator.
- Recording of SSEs
  The investigator will assess the subject for the following disease events:
  - Use of EBRT to relieve skeletal symptoms
  - New symptomatic pathological bone fractures (vertebral and non-vertebral)
  - Tumor-related orthopedic surgical intervention
  - Spinal cord compression
- Recording of AEs; all AEs should be assessed and documented prior to the radium-223 dichloride dose
- Recording of concomitant medications
- Recording of therapy for prostate cancer other than radium-223 dichloride
- Recording of new primary malignancies
- Administration of radium-223 dichloride
- Providing the subjects with the subject contact card to carry with him until the next visit (can be done at any time during the visit)
- Subjects will complete the pain assessment daily for 6 days prior to the dosing visit plus the morning of the dosing visit prior to Dose 1, Day 1.

The subject should be encouraged to arrive at the clinic well-hydrated and to drink ad libitum prior to and after the radium-223 dichloride dose. Subjects should avoid drinking or eating within 1 hour before and after administration of the study drug.

Dose 2 should be ordered as soon as Dose 1 is registered in the IVRS / IWRS. The planned date for the next dose must be specified, when the dose is requested in the IVRS / IWRS. The order date for the next dose cannot be earlier than the pre-defined country lead time, see IVRS / IWRS manual.

7.1.2.4 Doses 2 to 6 (Treatment Arms A and B)

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

The subject should return to the clinic at each dose visit during the treatment period, preferably in the morning, and the following assessments are required to be performed prior to dosing, except where specified otherwise (each dose period is 28 ± 7 days after the prior dose of radium-223 dichloride):

- BPI-SF questionnaire using a handheld device (should be self-administered at the beginning of each visit and should be checked for completion at the visit; see Section 14.7)
- NCCN-FACT FPSI-17 questionnaire, using a handheld device, is also self-administered at the beginning of the visit and should be checked for completion at the visit prior to treatment (see Section 14.8)
- ECOG PS
- Laboratory assessments (should be performed within 72 hours prior to the visit and the results assessed and documented prior to treatment at each treatment visit)
    - CBC, including hematocrit, hemoglobin, RBC count, MCV, MCH, MCHC, WBC count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils
    - Chemistry panel, including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total ALP, AST, and ALT
- PSA (result may be assessed post-dose)
- At all sites (in US and outside US), weight is to be taken only once for each dose.
    - For non-US sites, the weight should be performed within 72 hours prior to dosing.
    - For US sites using the central PRD depot ONLY, subject weight for the next dose, Day 1 should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All

efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits.

- Vital signs (systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes)
- Brief physical examination (see description in Section 7.5.3.2)
- Review of the daily PRO pain input results at the visit to check for completeness
- Analgesic use evaluation: Analgesic use will be collected and it will be assessed by the study investigator.
- Recording of SSEs
  The investigator will assess the subject for the following disease events:
  - Use of EBRT to relieve skeletal symptoms
  - New symptomatic pathological bone fractures (vertebral and non-vertebral)
  - Tumor-related orthopedic surgical intervention
  - Spinal cord compression
- Recording of AEs; all AEs should be assessed and documented prior to each dose of radium-223 dichloride
- Recording of therapy for prostate cancer other than radium-223 dichloride
- Recording of concomitant medications
- Recording of new primary malignancies
- Administration of radium-223 dichloride
- Providing the subjects with the subject contact card to carry with him until the next visit (can be done at any time during the visit)
- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed at Week 8, Week 16, Week 24, then every 12 weeks for 2 years after the subject's last dose of radium-223 dichloride or until radiologic progression.
  - Bone scans will be assessed by adapted PCWG2 criteria (30). Per adapted PCWG2 criteria, confirmation of bone progression by a 2nd scan $\geq$ 6 weeks later is required in all cases. A SPECT or MRI (with and without contrast

media) should be obtained to clarify any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression. The subject should remain on study treatment in the interim unless the investigator determines that there is immediate need to initiate cytotoxic chemotherapy.

- All images should be obtained with the same technique (e.g., MRI or CT scan) as those obtained at screening

- For radiologic progression confirmed during the treatment period and continued radium-223 dichloride therapy: If radium-223 dichloride treatment is continued beyond the date of confirmed radiologic disease progression (according to PCWG2 criteria), the MRI / CT scan of the abdomen and pelvis, chest X-ray, and whole body technetium-99 bone scan may be discontinued, but all other visit assessments should continue. See Section 7.1.2.7.2.

- For disease progression confirmed during the treatment period and premature discontinuation of radium-223 dichloride therapy: If the subject discontinues treatment prematurely for radiologically confirmed progression (according to PCWG2 criteria) or because the subject begins a new therapy with cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, other systemic radioisotopes, hemibody EBRT, or an investigational drug, the subject should have all assessments as required per the EOT visit (Section 7.1.2.6) except that the imaging requirements should follow the guidance in Table 7–2.

- Subjects will complete the pain assessment daily for 6 days prior to the dosing visit plus the morning of the dosing visit.

- The subject should be encouraged to arrive at the clinic well-hydrated on each dosing day and to drink ad libitum prior to and after each radium-223 dichloride dose. Subjects should avoid drinking or eating within 1 hour before and after administration of the study drug.

At Doses 2 through 5, subsequent doses should be ordered as soon as the current visit's dose is registered in the IVRS / IWRS. The planned date for the next dose must be specified, when the dose is requested in the IVRS / IWRS. The order date for the next dose cannot be earlier than the pre-defined country lead time.

7.1.2.5 Doses 2 to 12 (Treatment Arm C)

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

The subject should return to the clinic at each dose visit during the treatment period, preferably in the morning, and the following assessments are required to be performed prior

to dosing, except where specified otherwise (each dose period is 28 ± 7 days after the prior dose of radium-223 dichloride):

- BPI-SF questionnaire using a handheld device (should be self-administered at the beginning of each visit through Week 48 and should be checked for completion at the visit; see Section 14.7)
- NCCN-FACT FPSI-17 questionnaire, using a handheld device, is also self-administered at the beginning of the visit and should be checked for completion at the visit prior to treatment (see Section 14.8).
- ECOG PS
- Laboratory assessments (should be performed within 72 hours prior to the visit and the results assessed and documented prior to treatment at each treatment visit)
    - CBC, including hematocrit, hemoglobin, RBC count, MCV, MCH, MCHC, WBC count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils
    - Chemistry panel, including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total ALP, AST, and ALT
- PSA (result may be assessed post-dose)
- At all sites (in US and outside US), weight is to be taken only once for each dose.
    - For non-US sites, the weight should be performed within 72 hours prior to dosing.
    - For US sites using the central PRD depot ONLY, subject weight for the next dose, Day 1 should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits.
- Vital signs (systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes)
- Brief physical examination (see description in Section 7.5.3.2)
- Review of the daily PRO pain input results at the visit to check for completeness through Week 48

- Analgesic use evaluation through Week 48: Analgesic use will be collected and it will be assessed by the study investigator.

- Recording of SSEs
  The investigator will assess the subject for the following disease events:

  - Use of EBRT to relieve skeletal symptoms
  - New symptomatic pathological bone fractures (vertebral and non-vertebral)
  - Tumor-related orthopedic surgical intervention
  - Spinal cord compression

- Recording of AEs; all AEs should be assessed and documented prior to each dose of radium-223 dichloride

- Recording of therapy for prostate cancer other than radium-223 dichloride

- Recording of concomitant medications

- Recording of new primary malignancies

- Administration of radium-223 dichloride

- Providing the subjects with the subject contact card to carry with him until the next visit (can be done at any time during the visit)

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed at Week 8, Week 16, Week 24, then every 12 weeks for 2 years after the subject's last dose of radium-223 dichloride or until radiologic progression.

  - Bone scans will be assessed by adapted PCWG2 criteria (30). Per adapted PCWG2 criteria, confirmation of bone progression by a 2^{nd} scan $\geq$ 6 weeks later is required in all cases. A SPECT or MRI (with and without contrast media) should be obtained to clarify any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression. The subject should remain on study treatment in the interim unless the investigator determines that there is immediate need to initiate cytotoxic chemotherapy.

  - All images should be obtained with the same technique (e.g., MRI or CT scan) as those obtained at screening

- For radiologic progression confirmed during the treatment period and continued radium-223 dichloride therapy: If radium-223 dichloride treatment is continued beyond the date of confirmed radiologic disease progression (according to PCWG2 criteria), the MRI / CT scan of the abdomen and pelvis, chest X-ray, and whole body technetium-99 bone scan may be discontinued, but all other visit assessments should continue. See Section 7.1.2.7.2.

- For disease progression confirmed during the treatment period and premature discontinuation of radium-223 dichloride therapy: If the subject discontinues treatment prematurely for radiologically confirmed progression or because the subject begins a new therapy with cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, other systemic radioisotopes, hemibody EBRT, or investigational drugs, the subject should have all assessments as required per the EOT visit (Section 7.1.2.6) except that the imaging requirements should follow the guidance in Table 7–2.

- Subjects will complete the pain assessment daily for 6 days prior to the dosing visit plus the morning of the dosing visit.

- The subject should be encouraged to arrive at the clinic well-hydrated on each dosing day and to drink ad libitum prior to and after each radium-223 dichloride dose. Subjects should avoid drinking or eating within 1 hour before and after administration of the study drug.

At Doses 2 through 11, subsequent doses should be ordered as soon as the current visit's dose is registered in the IVRS / IWRS. The planned date for the next dose must be specified, when the dose is requested in the IVRS / IWRS. The order date for the next dose cannot be earlier than the pre-defined lead time.

7.1.2.6 End of treatment visit

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

The subject should return to the clinic 30 (± 7) days following the last study treatment or the time of premature discontinuation from study treatment, preferably in the morning, and the following assessments should be performed:

- BPI-SF questionnaire using a handheld device (should be self-administered at the beginning of the visit and should be checked for completion at the visit; see Section 14.7)

- NCCN-FACT FPSI-17 questionnaire, using a handheld device, is also self-administered at the beginning of the visit and should be checked for completion at the visit prior to treatment (see Section 14.8).

- ECOG PS

- Laboratory assessments (should be performed within 72 hours prior to the visit and the results assessed and documented on the visit date)
    - CBC, including hematocrit, hemoglobin, RBC count, MCV, MCH, MCHC, WBC count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils
    - Chemistry panel, including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total ALP, AST, and ALT
- PSA
- Weight
- Vital signs (systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes)
- Brief physical examination (see description in Section 7.5.3.2)
- Review of the daily PRO pain input results at the visit to check for completeness)
- Analgesic use evaluation: Analgesic use will be collected and it will be assessed by the study investigator
- Recording of SSEs
  The investigator will assess the subject for the following disease events:
    - Use of EBRT to relieve skeletal symptoms
    - New symptomatic pathological bone fractures (vertebral and non-vertebral)
    - Tumor-related orthopedic surgical intervention
    - Spinal cord compression
- Recording of AEs and SAEs for 30 days after the last treatment
- Recording of concomitant medications
- Recording of therapy for prostate cancer other than radium-223 dichloride
- Recording of new primary malignancies
- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and

characterize the lesion[s]), and whole body technetium-99 bone scan on the EOT visit, if the last tumor evaluation is older than 4 weeks

- Per adapted PCWG2 criteria (30), confirmation of bone progression by a 2nd scan ≥ 6 weeks later is required in all cases. A SPECT or MRI (with and without contrast media) should be obtained to clarify any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression.

- All images should be obtained with the same technique (e.g., MRI or CT scan) as those obtained at screening

- For premature discontinuation due to radiological soft tissue progression per modified RECIST 1.1 criteria, the confirmation MRI / CT scan of the abdomen and pelvis and chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]) should be completed within the window required per PCWG2 guidance. In case of unequivocal soft tissue progression, a confirmatory scan is not mandatory and it will be performed at the investigator's discretion.

- For premature discontinuation due to radiological bone progression that has been noted on imaging but not confirmed, the confirmation bone scan should be completed within the window required per PCWG2 guidance.

- For premature discontinuation after confirmed radiological progression per PCWG2 guidance, the MRI / CT scan of the abdomen and pelvis, chest X-ray, and the whole body technetium-99 bone scan do not need to be repeated.

- Subjects will complete the pain assessment daily for the 6 days prior to plus the morning of the Week 28 telephone contact (Treatment Arms A and B only).

In case the subjects cannot travel to the clinical site due to deterioration of disease, the EOT visit will be replaced by a follow-up telephone call from the clinical site. Adverse events, information on new primary malignancies, including acute myeloid leukemia, and hematological conditions, such as myelodysplastic syndrome, aplastic anemia, myelofibrosis, as well as any anticancer therapies, will be discussed and captured in the eCRFs. In these cases, the active follow-up with clinic visits will not take place and the subject will go directly into the active follow-up without clinic visits. Since this information will be collected over the telephone from the subject, 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.

7.1.2.7 Active follow-up

Section modified by Amendment 1 (Section 13.1).

The active follow-up has 2 distinct periods: the active follow-up with clinic visits and the active follow-up without clinic visits. Once a subject switches from active follow-up with clinical visits to active follow-up without clinical visits, the subject will not be allowed to switch back. However, in the event an SSE is identified at an unscheduled clinic visit in an active follow-up subject, an unscheduled-visit SSE should be recorded regardless of whether the subject is receiving clinic visits or telephone-only follow-up.

7.1.2.7.1 Active follow-up with clinic visits

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), 3 (Section 13.3), and 4 (Section 13.4.1.2).

The subject should return to the clinic every 12 weeks (± 14 days) following the EOT visit until the subject experiences a symptomatic skeletal event or until the primary efficacy analysis matures, whichever occurs first. Active follow-up will continue for 2 years in this study and not more than 7 years total including the long term follow-up study (if the subject has signed the ICF).

To the extent possible, subjects discontinuing treatment prematurely should nonetheless complete the Week 8, 16, 24, 36, and 48 clinic visits and any applicable tumor assessments scheduled with respect to treatment start. Similarly, subjects in Treatment Arms A and B should receive Week 28, 32, 40, and 44 telephone contacts at the regularly scheduled time with respect to treatment start.

In addition to the visits at Weeks 36 and 48 (from the start of treatment) the subjects in Treatment Arms A and B will receive telephone contacts at Weeks 28, 32, 40, and 44 (from the start of treatment) to assess for possible SSE risks and will continue PRO data collection. Pain data, 24-hour analgesic use, BPI and NCCN-FACT FPSI-17 questionnaires will also be collected as detailed below.

The following assessments will be performed during the clinic visits:

- BPI-SF questionnaire (should be administered at the beginning of the Week 36 and 48 visits and should be checked for completion at the visit; see Section 14.7). (Treatment Arms A and B only).
- NCCN-FACT FPSI-17 questionnaire is also administered at the beginning of the visit and should be checked for completion at the visit prior to treatment (see Section 14.8). (Treatment Arms A and B only).
- ECOG PS
- Laboratory assessments (should be performed within 72 hours prior to the visit and the results assessed and documented on the visit date)

- CBC, including hematocrit, hemoglobin, RBC count, MCV, MCH, MCHC, WBC count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils
- Chemistry panel, including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total ALP, AST, and ALT

- PSA
- Vital signs (systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes)
- Brief physical examination (see description in Section 7.5.3.2)
- Review of the daily PRO pain input results at the Week 36 and 48 visits to check for completeness (Treatment Arms A and B only)
- Analgesic use evaluation at the Week 36 and 48 visits: Analgesic use will be collected and it will be assessed by the study investigator (Treatment Arms A and B only).
- Recording of SSEs
  The investigator will assess the subject for the following disease events:
  - Use of EBRT to relieve skeletal symptoms
  - New symptomatic pathological bone fractures (vertebral and non-vertebral)
  - Tumor-related orthopedic surgical intervention
  - Spinal cord compression
- All AEs and SAEs have to be reported if considered to be related to study medication as well as any events considered to be related to an SSE. However, 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.
- In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- Recording of limited concomitant medication, including narcotic pain medication
- Recording of therapy for prostate cancer
- Recording of new primary malignancies

- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan performed every 12 weeks until the end of active follow-up period, radiological progression (according to PCWG2 criteria), or death, whichever occurs first

    - Per adapted PCWG2 criteria (30), confirmation of bone progression by a 2nd scan ≥ 6 weeks later is required in all cases. A SPECT or MRI (with and without contrast media) should be obtained to clarify any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression.

    - All images should be obtained with the same technique (e.g., MRI or CT scan) as those obtained at screening

- After the Week 36 visit, subjects will complete the pain assessment daily for the 7 days prior to the Week 40 telephone contact.

Telephone contact for SSE risks and PRO pain and analgesic use data collection at Weeks 28 (±7 days), 32 (±7 days), 40 (±7 days), and 44 (±7 days), subjects in Treatment Arms A and B only

The subjects will receive telephone contacts at Weeks 28, 32, 40, and 44 assessing for possible SSE risks. Subjects exhibiting symptoms indicative of possible SSEs will be encouraged to visit the clinic early to assess SSE status. Symptomatic skeletal events will not be determined over the phone.

In the intervals between the visits, the subjects will continue to be followed for PRO pain data collection and analgesic use data collection as follows:

- Pain will be assessed daily for 6 days prior to the visit plus the morning of each telephone contact at Weeks 28, 32, 40, and 44 and the daily PRO pain input data will be reviewed for completeness at the telephone contact.

- 24-hour analgesic use will be collected by the study investigator at each telephone contact at Weeks 28, 32, 40, and 44.

- The BPI-SF questionnaire will be completed on the day of each telephone contact (should be completed prior to the contact and should be checked for completion at the contact; see Section 14.7)

- NCCN-FACT FPSI-17 questionnaire will be completed on the day of each telephone contact (should be completed prior to the contact and should be checked for completion at the telephone contact; (see Section 14.8).

For subjects who die > 30 days after the administration of last study treatment, submission of the AE page of the eCRF is not required unless the death is considered related to radium-223 dichloride. In any case the date of death information will also be collected in the end-of-follow-up page of the eCRF.

If a subject discontinues due to an AE or another reason other than progression, every effort should be made to follow-up for tumor assessment every 12 weeks for MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan until disease progression or the start of a new anticancer treatment.

If a subject is no longer able to travel to the clinic due to deteriorating status, the subject will enter the active follow-up without visits and will be followed by telephone.

If a subject has an SSE in the active follow-up period, he will continue the active follow-up period for 2 years from last study treatment. If a subject becomes unable to travel to the clinic after 2 years after his last treatment, he will enter long-term follow-up.

7.1.2.7.2 Active follow-up without scheduled clinic visits

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), 3 (Section 13.3), and 4 (Section 13.4.1.2).

This period starts when subjects can no longer travel to the clinic or if the subject receives further treatment with any of the following anticancer therapies during the follow-up period: cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, other systemic radioisotopes (samarium-153, strontium-89, rhenium-186, or rhenium-188), hemibody EBRT, or other investigational drugs. Subjects who cannot travel to the clinic will be contacted by telephone every 12 weeks (± 14 days) for 2 years following the last study treatment to determine the following:

- Survival status
- Recording of therapy for prostate cancer
- All AEs and SAEs occurring beyond 30 days after the last treatment have to be documented and reported if considered to be related to study medication. Concomitant medication associated with these events will **not** be collected. If a subject is unable to provide required details for events of interest, this information may need to be obtained from the primary provider.
- Recording of new primary malignancies
- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy

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

- In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

Since this information will be collected over the telephone from the subject, 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.

Table 7–2 Changes to follow-up visit assessments

Subject Status	Changes to Assessments	Assessments to Continue
Active Assessment Follow-up		
Achieves radiologic progression	Discontinue MRI / CT scan abdomen and pelvis, chest X-ray, and whole body technetium-99 bone scan	All active follow-up assessments, including safety and laboratory assessments; reporting AEs / SAEs related to study medication[a] or an SSE and documenting new primary malignancies through survival
Begins new anticancer therapy for prostate cancer due to radiological disease progression	Perform end of active follow-up with clinic visits and discontinue further active follow-up with clinic visits	Change contacts to active follow-up without scheduled clinic visits (telephone follow-up) [a]
If subject starts treatment with bisphosphonates, denosumab, and other supportive therapies	Continue MRI / CT scan abdomen and pelvis, chest X-ray, and whole body technetium-99 bone scan	All active follow-up assessments, including safety and laboratory assessments; reporting AEs / SAEs related to study medication[a] or an SSE and documenting new primary malignancies through survival
Can no longer travel	Discontinue all scans and active follow-up with clinic visits	Change contacts to active follow-up without scheduled clinic visits (telephone follow-up) [a]

Abbreviations: AE = adverse event; CT = computed tomography; MRI = magnetic resonance imaging; SAE = serious adverse event; SSE = symptomatic skeletal event

a. In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

Only subjects who withdraw consent from the study will be required to follow the procedures outlined in Section 5.2.1.2 (i.e., sign the Declaration of Objection to the Collection of Study Data after Withdrawal of Consent for the active assessment follow-up period).

7.1.2.8 End of active follow-up

7.1.2.8.1 End of active follow-up with clinic visits

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), 3 (Section 13.3), and 4 (Section 13.4.1.2).

The subject should return to the clinic for the end of follow-up with clinic visits, preferably in the morning, and the following assessments will be performed:

- ECOG PS
- Laboratory assessments (should be performed within 72 hours prior to the visit and the results assessed and documented on the visit date)
    - CBC, including hematocrit, hemoglobin, RBC count, MCV, MCH, MCHC, WBC count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils
    - Chemistry panel, including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total ALP, AST, and ALT
- PSA
- Vital signs (systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes)
- Brief physical examination (see description in Section 7.5.3.2)
- Recording of SSE assessment
  The investigator will assess the subject for the following disease events:
    - Use of EBRT to relieve skeletal symptoms
    - New symptomatic pathological bone fractures (vertebral and non-vertebral)
    - Tumor-related orthopedic surgical intervention
    - Spinal cord compression
- All AEs and SAEs have to be reported if considered to be related study medication as well as any events considered to be related to an SSE. However, 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. In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported

as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

- Documentation of limited concomitant medication, including narcotic pain medication
- Documentation of therapy for prostate cancer
- Documentation of new primary malignancies
- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy
- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan
    - Per adapted PCWG2 criteria (30), confirmation of bone progression by a 2nd scan ≥ 6 weeks later is required in all cases. A SPECT or MRI (with and without contrast media) should be obtained to clarify any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression.
    - All images should be obtained with the same technique (e.g., MRI or CT scan) as those obtained at screening

For subjects who die > 30 days after the administration of last study treatment, submission of the AE page of the eCRF is not required unless the death is considered related to radium-223 dichloride. In any case the date of death information will also be collected in the end-of-follow-up page of the eCRF.

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported radium-223 dichloride-related AEs and SAEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic anti-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality

assessment. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject.

Until the transition to the long term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up).

7.1.2.8.2 End of active follow-up without scheduled clinic visits

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), 3 (Section 13.3), and 4 (Section 13.4.1.2).

The active follow-up period without clinic visits will continue for 2 years after the subject's last dose of radium-223 dichloride. The end of active follow-up procedures for subjects who are in the active follow-up period without clinic visits will include the following:

- Survival status
- Documentation of therapy for prostate cancer
- All AEs and SAEs occurring beyond 30 days after the last treatment have to be documented and reported if considered to be related to study medication. Concomitant medication associated with these events will **not** be collected. If a subject is unable to provide required details for events of interest, this information may need to be obtained from the primary provider.
- Documentation of new primary malignancies
- Documentation of cytotoxic chemotherapy and radiotherapy for any new primary malignancy
- All occurrences of hematological conditions such as myelodysplastic syndrome, aplastic anemia, myelofibrosis, and primary bone cancer or any other new primary malignancy, such as acute myeloid leukemia, must be reported as SAEs regardless of the investigator's causality assessment.

- In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

Since this information will be collected over the telephone from the subject, 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.

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported radium-223 dichloride-related AEs and SAEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic anti-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject.

Until the transition to the long term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up).

7.1.2.9 Long-term follow-up to 7 years following last dose

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), 3 (Section 13.3), and 4 (Section 13.4.1.2).

This period starts when subjects have completed the active follow-up period and ends 7 years after the last dose of radium-223 dichloride or when the subject dies. All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study

for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported radium-223 dichloride-related AEs and SAEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic anti-cancer therapy for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject.

Until the transition to the long term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up).

7.1.2.9.1 Long-term follow-up (via telephone follow-up)

Section modified by Amendments 1 (Section 13.1), 3 (Section 13.3), and 4 (Section 13.4.1.2).

Subjects, their treating health care professional, or caregiver will be contacted by telephone every 6 months (± 14 days) for 7 years following the last study treatment or until death to determine the following:

- Survival status
- Recording of prostate cancer therapies
- All radium-223 dichloride/placebo related AEs
- All SAEs occurring during this period have to be documented and reported if considered to be related to study medication. 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; all

systemic anti-cancer therapy for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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.

- Recording of new primary malignancies
- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy
- All occurrences of hematological conditions such as myelodysplastic syndrome, aplastic anemia, myelofibrosis, and primary bone cancer or any other new primary malignancy, such as acute myeloid leukemia, must be reported as SAEs at any time and regardless of the investigator's causality assessment
- In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- In subjects who receive cytotoxic chemotherapy: all occurrences of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter.

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

Since this information will be collected over the telephone from the subject, their treating health care professional, or caregiver, 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.

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.

7.1.2.9.2 End of long-term follow-up

Section modified by Amendments 1 (Section 13.1), 3 (Section 13.3) and 4 (Section 13.4.1.2).

The end of study procedures for subjects who are in the long-term follow-up period will include the following:

- Survival status
- Recording of prostate cancer therapies

- All SAEs have to be documented and reported if considered to be related to study medication. 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; all systemic anti-cancer therapy for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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.

- Recording of new primary malignancies

- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy

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

- In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

- In subjects who receive cytotoxic chemotherapy: all occurrences of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter.

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

Since this information will be collected over the telephone from the subject, their treating health care professional, or caregiver, 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 Population characteristics

7.2.1 Demographic

Demographic data to include age (reported as date of birth), gender, race, and ethnicity will be collected at the time of enrollment.

7.2.2 Medical history

Section modified by Amendment 2 (Section 13.2).

Medical history findings (i.e., previous diagnoses, diseases, or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the ICF
- Considered relevant to the study up to 6 months prior to screening: history of fractures, trauma, osteomyelitis, joint and dental infections, cellulitis, edema, arthritis, metabolic bone disease, or limitation of function; history of orthopedic (e.g., presence and location of prosthetic implants) and non-orthopedic (e.g., ileal conduit) surgery that might affect the results of bone scintigraphy; history of recent scintigraphy, especially with 131I, 67Ga, or 111In.

Detailed instructions on the differentiation between (i) medical history and (ii) AEs can be found in Section 7.5.1.1.

7.2.3 Disease history and prior treatment for prostate cancer

History of prostate cancer will be collected separately from the general medical history. This includes but is not limited to:

- Date of diagnosis
- Staging (performed at diagnosis)
- Relapse history
- Disease status at study entry
- Prior diagnostic and therapeutic procedures
- Prior prostate cancer treatments (any therapy that is ongoing should be reported as concomitant medication)

7.2.4 Body size descriptors

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Body size descriptors will be calculated from subject height and weight at the applicable baselines. Details will be described in the statistical analysis plan (SAP).

7.3 Efficacy

7.3.1 Efficacy variables

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

The complete list of variables to be analyzed for this study will be provided in the SAP.

The primary efficacy variable is SSE-FS.

The secondary efficacy variables are:

- OS
- Time to first SSE
- rPFS
- Time to radiological progression
- Pain improvement rate
- Time to pain progression

The exploratory efficacy variables include:

- Bone scan lesion area (BSLA)
- Bone scan time point response rate
- Bone scan best overall response rate
- Increase in analgesic use rate
- Time to increase in pain management
- Pain improvement without increase in analgesic use rate
- Time to pain progression or increase in analgesic use
- Change in last 24-hour analgesic use score
- Time to increase in physical symptoms of disease based on the NCCN-FACT FPSI-17 physical disease related symptoms (FPSI-DRS-P) subscale score measured up to 48 weeks after the start of treatment.
- Total ALP response rate

- Time to total ALP progression
- Percentage change in total ALP
- PSA response rate
- Time to PSA progression
- Palliative pain procedure use

7.3.2 Definition of efficacy variables

Section modified by Amendments 1 (Section 13.1) and 3 (Section 13.3).

In this study, time-to-event endpoints are defined with respect to 2 distinct start dates, randomization date and the date of 6th dose. Response and progression endpoints are defined with respect to 2 corresponding baselines, the screening (or pre-treatment) baseline and 6th dose date baseline. Details on definitions of starting points and baselines will be provided in the SAP or in the imaging charter or other central reviewer documentation.

Additional details on endpoints will be provided in the SAP.

7.3.3 Primary endpoint

Symptomatic skeletal event-free survival

Symptomatic skeletal event-free survival is defined as the time in days from the applicable start date to the first SSE or death, whichever occurs first, on or following the start date. Subjects not experiencing death or an SSE as of database cut-off will be censored at the last assessment for SSEs.

7.3.4 Secondary endpoints

7.3.4.1 Overall survival

Overall survival is defined the time in days from the applicable start date to the date of death due to any cause. Subjects who are still alive or who are lost to survival follow-up as of database cut-off date will be censored at the last known alive date on or prior to database cut-off date.

7.3.4.2 Time to first symptomatic skeletal event

Time to first SSE is defined as the time in days from the applicable start date to the first SSE on or following the start date. Subjects not experiencing an SSE as of database cut-off, whether or not surviving, will be censored at the last assessment for SSEs.

7.3.4.3 Radiological progression endpoints

Section modified by Amendments 1 (Section 13.1 and 3 (Section 13.3).

Radiological progression is radiological progression of soft-tissue disease or radiological progression of bone disease, whichever occurs first. Assessment of radiological progression will be made by independent central review.

Radiological progression of soft tissue disease is determined according to RECIST 1.1 based on MRI or CT scans (see Section 14.1). Radiological progression of osseous disease is determined according to adapted PCWG2 criteria based on whole body technetium-99 bone scans (30) (see Section 14.2). Radiological bone progression is determined if at least one of the following criteria is met:

- The first bone scan with ≥ 2 new lesions compared to baseline is observed < 12 weeks from randomization and is confirmed by a second bone scan taken ≥ 6 weeks later showing ≥ 2 additional new lesions (a total of ≥ 4 new lesions compared to baseline); or
- The first bone scan with ≥ 2 new lesions compared to baseline is observed ≥ 12 weeks from randomization and the new lesions are verified on the next bone scan ≥ 6 weeks later (a total of ≥ 2 new lesions compared to baseline).

Further details will be defined in the imaging charter and / or related central review documentation, and / or the SAP.

7.3.4.3.1 Radiological progression free survival

Radiological progression free survival is defined as the time in days from the applicable start date to the date of subsequent radiological disease progression or death from any cause (if death occurs before such progression). Subjects not experiencing death or radiological disease progression as of database cut-off will be censored at the last radiological disease progression assessment.

7.3.4.3.2 Time to radiological progression

Time to radiological progression is defined as the time in days from the applicable start date to the date of subsequent radiological progression. Subjects without radiological progression as of database cut-off date, whether or not surviving, will be censored at the last radiological progression assessment.

7.3.4.4 Pain endpoints

Section modified by Amendment 1 (Section 13.1) and 2 (Section 13.2).

The WPS is defined for each subject at baseline and at each applicable 4-week assessment date, as the mean of the "worst pain score" values in the last 24 hours from the preceding 7 days before each applicable visit or telephone contact per the BPI-SF recorded in the subject's reported outcome pain data.

Pain endpoints are defined with respect to each applicable baseline and start date.

The screening baseline for pain endpoints will be based on the pre-Dose 1, 7-day pain assessment (Day 7 will be done on the morning of the day of Dose 1, Day 1 of the protocol)

Additional details on pain endpoints will be provided in the SAP.

7.3.4.4.1 Pain improvement rate

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Pain improvement is defined for each baseline in subjects evaluable for pain improvement at that baseline, i.e., subjects entering the study with a WPS of at least 4 at the respective baseline assessment. Pain improvement with respect to each baseline is defined in each applicable evaluable subject at each applicable post-baseline assessment time point as a 30% and 2-point decrease in WPS over 2 consecutive measurements conducted at least 4 weeks apart.

Pain improvement rate is defined for each baseline and applicable post-baseline assessment time point as the number of subjects with pain improvement at the time point, divided by the total number of subjects evaluable for pain improvement with respect to the applicable baseline.

7.3.4.4.2 Time to pain progression

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Pain progression is defined for each baseline in subjects evaluable for pain progression at the applicable baseline, i.e., subjects with a WPS of ≤ 7 at the respective baseline assessment. Pain assessments will occur daily for one week, beginning a week prior to each visit and including the day of the visit. An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 daily questions. Pain progression is defined as the occurrence of a pain increase with respect to the applicable baseline.

A pain increase is defined as follows:

- For asymptomatic subjects (WPS 0 to < 1 at baseline), pain increase is defined as an increase of 2 or more points in the average (i.e., average of 7-day assessments) "worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart.

- For mildly symptomatic subjects (WPS 1-3 at baseline), pain increase is defined as an increase of 2 or more points in the average (i.e., average of 7-day assessments) "worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart and an average worst pain score of ≥ 4".

- For symptomatic subjects with WPS > 3 and ≤ 7 at baseline), pain increase is defined as an increase of 2 or more points in the average (i.e., average of 7-day assessments) "worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart.

The time to pain progression is defined for each applicable baseline for applicable subjects as the time (in days) from the respective baseline until occurrence of the first post-baseline pain progression event. Subjects without pain progression as of the last applicable post-baseline assessment, whether or not surviving, will be censored at the last applicable post-baseline assessment. Subjects with insufficient applicable baseline assessment(s) or without adequate post-baseline assessment(s) will be censored at the applicable baseline date. Additional censoring and other details will be described in the SAP.

7.3.5 Exploratory endpoints

Additional exploratory endpoints may be defined in the SAP.

7.3.5.1 Quantitated bone scan endpoints

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Further details will be defined in the imaging charter and /or related central review documentation, and / or the SAP.

7.3.5.1.1 Bone scan lesion area

Bone scan lesion area is defined for each subject at the screening baseline and each subsequent radiological assessment time point, as the sum of the pixel areas (cm^2) of the set of technetium-99 bone scan imaging pixels identified as bone lesion based on central review.

7.3.5.1.2 Bone scan time point response rate

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Bone scan time point response will be determined based on central review. For each applicable subject, at each applicable time point following each respective baseline, the time point BSLA will be compared to the respective baseline BSLA. The bone scan time point response with respect to the baseline will be assessed as described in Section 14.3.

7.3.5.1.3 Bone scan best overall response rate

Bone scan best overall response is defined for each applicable subject, with respect to each applicable baseline, as the best bone scan time point response (ordered as responder, stable disease, PD, unable to evaluate) to the respective baseline observed following the baseline and during the course of the study. Responder and stable disease responses will only be reported if observed prior to PD. No confirmation of responder or PD status will occur.

The bone scan best overall response rate is defined for each applicable treatment group, with respect to each applicable baseline, as the number of subjects with respective bone scan best overall response of responders, divided by the total number of subjects in the treatment group.

7.3.5.2 Time to increase in physical symptoms of disease based on FPSI-DRS-P

Section modified by Amendments 1 (Section 13.1) and 3 (Section 13.3).

Time to increase in physical symptoms of disease based on the NCCN-FACT FPSI-17 physical disease related symptoms (FPSI-DRS-P) subscale score measured up to Week 48 after start of treatment will be assessed using the NCCN-FACT FPSI-17 questionnaire (Section 14.8).

The NCCN-FACT FPSI-17 is a validated instrument that was developed to assess symptoms of prostate cancer, symptoms caused by the treatment of prostate cancer, and the health related quality of life of prostate cancer patients.(26) The instrument was developed in accordance with recent FDA guidance for the development of instruments for electronic patient-reported outcome (ePRO). The instrument contains 17 items, each of which utilizes a Likert scale with 5 possible responses. The ten items reflect disease related physical symptoms of disease and the responses on the items are be summed to calculate a disease related physical symptom subscale score. One item represents emotional symptoms of disease and the response to that item is used to calculate a disease related emotional symptom subscale score. Four items represent treatment related symptoms and the responses to these items are summed to calculate a treatment side effect subscale score. Finally, two items represent functional well-being and the responses to those items are summed to calculate a functional/well-being subscale score.

The NCCN-FACT FPSI-17 will be self-administered by the subject via an ePRO device.

Time to increase in physical symptoms of disease based on (FPSI-DRS-P) will be calculated with respect to baseline value collected prior to first dosing, based only on assessments through Week 48. Details, including definition of an increase, will be provided in the SAP.

7.3.5.3 Total alkaline phosphatase endpoints

Total ALP endpoints are determined based on the total ALP laboratory assessments collected as described in the assessment schedule.

A subject is evaluable for ALP endpoints if the subject had a non-missing total ALP assessment at the applicable baseline.

7.3.5.3.1 Total alkaline phosphatase response rate

Section modified as of Amendment 3 (Section 13.3).

Total ALP response is defined with respect to each applicable baseline, as a ≥ 30% reduction of the blood total-ALP level compared to the baseline value, confirmed by a second consecutive ALP value 4 or more weeks later but within 9 weeks, among evaluable subjects.

The total ALP response rate is defined for each applicable treatment group, with respect to each applicable baseline, as the number of subjects with total ALP response with respect to the baseline, divided by the total number of subjects evaluable for the respective total ALP response in the treatment group.

7.3.5.3.2 Time to total alkaline phosphatase progression

Section modified by Amendment 3 (Section 13.3).

Total ALP progression is defined with respect to each applicable baseline, as a ≥ 25% increase from baseline value, at least 12 weeks from baseline in subjects with no ALP decline from baseline; or ≥ 25% increase above the nadir value, which is confirmed by a second consecutive value obtained 3 or more weeks later but within 9 weeks in subjects with an initial ALP decline from the baseline.

The time to total ALP progression is defined as the time in days from the applicable start date to the date of first total ALP progression following the start date. Subjects not experiencing total ALP progression as of database cut-off, whether or not surviving, will be censored at the last total ALP lab assessment.

7.3.5.3.3 Percentage change in total alkaline phosphatase at 12 and 24 weeks

The percentage change in total ALP from screening baseline to 12 weeks and the percentage change in total ALP from screening baseline to 24 weeks will be calculated for each applicable evaluable subject, based on lab data collected as of the 12 and 24-week assessments, respectively.

7.3.5.4 Prostate specific antigen endpoints

Prostate specific antigen endpoints are determined based on the PSA laboratory assessments collected as described in the assessment schedule.

A subject is evaluable for PSA endpoints if the subject had a non-missing PSA laboratory assessment at the applicable baseline.

7.3.5.4.1 Prostate specific antigen response rate

Section modified by Amendment 3 (Section 13.3).

Prostate specific antigen response is defined in each evaluable subject with respect to each applicable baseline as a ≥ 30% reduction of the blood PSA level, compared to the baseline value, confirmed by a second subsequent PSA value with a ≥ 30% reduction from the applicable baseline approximately 4 or more weeks later but within 9 weeks.

Prostate specific antigen response rate is defined for each applicable treatment group with respect to each applicable baseline, as the number of subjects with PSA response with respect to the baseline, divided by the total number of subjects evaluable for the respective PSA response in the treatment group.

7.3.5.4.2 Time to prostate specific antigen progression

Section modified by Amendment 3 (Section 13.3).

Prostate specific antigen progression is defined with respect to each applicable baseline, as a

≥ 25% increase from baseline value and an increase in absolute value of ≥2 ng/mL, at least 12 weeks from the applicable baseline in subjects with no PSA decline from baseline; or ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir value, which is confirmed by a second consecutive value obtained 3 or more weeks later but within 9 weeks in subjects with an initial PSA decline from the baseline.

The time to PSA progression is defined as the time in days from the respective start date to the date of first subsequent PSA progression. Subjects without PSA progression as of database cut-off, whether or not surviving, will be censored at the last PSA lab assessment.

7.3.5.5 Exploratory pain and analgesic use endpoints

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

For purposes of determining exploratory increase in analgesic use, pain improvement without an increase in analgesic use, and pain progression without an increase in analgesic use, a daily analgesic use score will be calculated programmatically for each subject for each day, based on the subject's complete case report form (CRF) data on analgesic use. Analgesic use data will be coded using the World Health Organization (WHO) drug dictionary. Oral morphine equivalents (OMEs) will be calculated. Each day's analgesic use in OME units will be calculated using the applicable CRF-reported dates and date ranges. The AQA will be applied to obtain a daily analgesic use score. Details will be described in the SAP.

An increase in analgesic use is defined for each baseline in evaluable subjects, i.e., subjects with a valid AQA analgesic use score at the applicable baseline, as follows:

For subjects not on opioids at the applicable baseline, initiation of short or long-acting opioid use for pain will constitute an increase in analgesic use. For subjects being treated with ≤ 600 OME (oral morphine equivalents) of opioids at the applicable baseline, an increase by 1 point in the daily AQA score and increase ≥ 50% in daily OMEs will constitute an increase in analgesic use. For subjects being treated at the highest AQA level (> 600 OME/day) at the applicable baseline, an increase ≥ 50% in daily OMEs from that baseline will constitute an increase in analgesic use.

Additional details on analgesic use endpoints, including details on the applicable baselines, evaluability for daily analgesic use increase, calculation of daily analgesic use score(s) applicable to each baseline and post-baseline time point, and definition of baseline values and "increase" in daily analgesic use for purposes of these endpoints, will be provided in the SAP.

7.3.5.5.1 Increase in analgesic use rate

Section modified by Amendment 2 (Section 13.2).

Increase in analgesic use rate is defined for each applicable baseline as the number of subjects with an increase in analgesic use from that baseline divided by the number of subjects evaluable for analgesic use at that baseline.

7.3.5.5.2 Time to Increase in analgesic use

Section modified by Amendment 2 (Section 13.2).

Time to increase in analgesic use is defined for each applicable baseline for applicable subjects as the time (in days) from the respective baseline until occurrence of the first post-baseline increase in analgesic use pain progression event. Subjects without increase in analgesic use as of the last applicable post-baseline assessment, whether or not surviving, will be censored at the last applicable post-baseline assessment. Subjects with insufficient applicable baseline assessment(s) or without adequate post-baseline assessment(s) will be censored at the applicable baseline date. Additional censoring and other details will be described in the SAP.

7.3.5.5.3 Pain improvement rate without increase in analgesic use

Section modified by Amendment 2 (Section 13.2).

Pain improvement without increase in analgesic use is defined for each baseline in subjects evaluable for both pain improvement and increase in analgesic use at that baseline, as defined in Section 7.3.4.4.1 and Section 7.3.5.5.1 respectively, at the applicable baseline assessment. Pain improvement without increase in analgesic use is defined in each applicable evaluable subject at each applicable post-baseline assessment time point with respect to each baseline,

as a 30% and 2-point decrease in WPS over 2 consecutive measurements conducted at least 4 weeks apart, without an increase in analgesic use.

Pain improvement without increase in analgesic use rate is defined for each baseline and applicable post-baseline assessment time point as the number of subjects with pain improvement without increase in analgesic use at the time point, divided by the total number of subjects evaluable for pain improvement without increase in analgesic use with respect to the applicable baseline.

7.3.5.5.4 Time to pain progression or increase in analgesic use

Section modified by Amendment 2 (Section 13.2).

Time to pain progression is defined for each baseline in subjects evaluable for both pain progression and increase in analgesic use, as defined in Section 7.3.4.4.2 and Section 7.3.5.5.1, respectively, at the applicable baseline assessment.

The time to pain progression or increase in analgesic use is defined for each applicable baseline for applicable subjects as the time (in days) from the respective baseline until occurrence of the first post-baseline pain progression (pain increase) event or increase in analgesic use event, whichever occurs first. Subjects with neither pain progression nor an increase in analgesic use as of the last applicable post-baseline assessment, whether or not surviving, will be censored at the last applicable post-baseline assessment. Subjects not evaluable for both pain progression and increase in analgesic use, and subjects without adequate post-baseline assessment(s), will be censored at the applicable baseline date. Additional censoring and other details will be described in the SAP.

Change in the last 24-hour analgesic use score

Change in the last 24-hour analgesic use score is calculated based on the subject's analgesic use in the last 24 hours CRF data.

For each subject, each analgesic medication from analgesic use in the last 24 hour's data taken at applicable clinic visits (and in Arms A and B, at telephone contacts) will be coded using the WHO drug dictionary and OMEs will be calculated from the coded data.

For each subject and applicable visit or telephone contact, analgesic use in the last 24 hours will be scored using the AQA (see Section 14.9) based on the coded medications and corresponding OME quantities.

Details on coding and scoring will described in the SAP.

For each subject, for each applicable baseline and post-baseline time point, the subject's change in the last 24-hour analgesic use is defined as the difference between the subject's last 24 hour AQA score at the post-baseline time point and at the applicable baseline.

7.3.5.6 Additional pain and health related quality of life endpoints

Section modified by Amendments 1 (Section 13.1) and 3 (Section 13.3).

Subject-reported outcome data not described above, palliative pain relief procedure data, additional BPI-SF data collected at clinic visits, and pain data collected will be evaluated as described in the SAP.

7.4 Pharmacokinetics / pharmacodynamics

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

7.5 Safety

Section modified by Amendment 1 (Section 13.1).

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: AEs will be collected and recorded on an ongoing basis throughout the study as described in Section 7.5.1.
- Laboratory assessments: The following laboratory assessments with reference ranges, including investigator determinations, will be recorded in the source documentation and the eCRF:
    - CBC, including hematocrit, hemoglobin, RBC count, MCV, MCH, MCHC, WBC count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils
    - Chemistry panel, including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total ALP, AST, ALT, LDH (screening only), and albumin (screening only)

7.5.1 Adverse events

7.5.1.1 Definitions

Definition of adverse event

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.

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

In the following differentiation between medical history and AEs, the term "condition" may include abnormal symptoms, diseases, laboratory, or vital sign findings.

- Conditions that started before signing of ICF and for which no symptoms or treatment are present until signing of ICF are recorded as medical history (e.g., seasonal allergy without acute complaints).

- Conditions that started before signing of ICF and for which symptoms or treatment are present after signing of ICF, at *unchanged intensity*, are recorded as medical history (e.g., allergic pollinosis).

- Conditions that started or deteriorated after signing of informed consent will be documented as AEs.

Definition of serious adverse event (SAE)

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
     (i.e., elective or scheduled surgery arranged prior to the start of the study)
   - 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 medically important serious 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 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

The intensity of an AE is classified according to the grades specified by the NCI-CTCAE, version 4.03 (see Section 14.4).

7.5.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no"

An assessment of "no" would include:

1. The existence of a clear 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 there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge).
- Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- 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 may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism, and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a “reasonable causal relationship” to protocol-required procedure(s).

Possible answers are “yes” or “no”

7.5.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

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 2 (Section 13.2) and 4 (Section 13.4.1.2).

All AEs occurring from the time the subject signs the ICF until 30 days after the last dose of study medication must be recorded on the eCRF. Treatment-emergent AEs and all SAEs that occur during the treatment period and up to 30 days after the last administration of radium-223 dichloride must be reported on the appropriate eCRF.

A laboratory test abnormality should be reported as an AE if it is considered clinically relevant (e.g., causing the subject to withdraw from the study), requires treatment, causes apparent clinical manifestations, or is judged as relevant by the investigator. Laboratory abnormalities that are not considered clinically significant do not need to be entered as an AE. Laboratory abnormalities related to the disease under study (e.g., PSA, testosterone) do not need to be recorded as AEs. Each event should be described in detail along with start and stop dates (onset and resolution of event), intensity, temporal and causal relationship to investigational product and / or protocol-related procedures, possibly 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 and laboratory results with grades and causality assessments must be documented and retained in the source documentation.

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

All AEs and SAEs occurring beyond 30 days after the last treatment have to be reported if considered to be related to study medication or if related to an SSE (during active follow-up with clinic visits only). However, 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. In subjects who receive cytotoxic chemotherapy, all occurrences of febrile neutropenia or hemorrhage during their chemotherapy treatment must be reported as SAEs at any time and for up to 6 months thereafter. In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported 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 may need to be obtained from the primary provider.

Adverse events may be reported spontaneously by the subject or elicited through open (non-leading) questioning during each visit during the treatment period and for 30 days after the last dose. As far as possible, all AEs must be described by their duration (start and stop date), severity (graded according to the 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.

Subjects who sign the ICF and are randomized but who discontinue prior to receiving the first dose will not be followed for safety.

7.5.1.4 Reporting of serious adverse events

Section modified by Amendment 4 (Section 13.4.1.2).

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.

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.

All SAEs occurring during the observation period defined in Section 7.5.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the recipient detailed in the manual. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

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

In addition, during the long-term follow-up all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

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 / independent 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. The sponsor will send SUSARs to a site once the site initiation visit has occurred and will stop sending SUSARs to a site once the last subject EOT visit for that site (30 days after last dose) occurs.

7.5.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the IB. 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 study subject's partner during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

Bayer usually does not gather information of drug exposure via the father; however, if those cases are reported, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used.

7.5.3 Further safety

7.5.3.1 Laboratory evaluations

Section modified by Amendment 1 (Section 13.1).

Blood samples will be collected by a member of the investigator's team per the schedule of assessments. The same local laboratory should be used throughout the study for a given subject. The following laboratory assessments will be recorded with reference ranges:

- CBC, including hematocrit, hemoglobin, RBC count, MCV, MCH, MCHC, WBC count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils
- Chemistry panel, including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total ALP, AST, ALT, LDH (screening only), and albumin (screening only)

7.5.3.2 Physical examination

The physical examination (by means of inspection, palpation, auscultation) will be performed by a physician at the investigational site. A complete physical examination will be performed at the screening visit; a brief physical examination will be performed at all other visits. Brief physical examinations will include systems of primary relevance and those systems associated with symptoms. Full and brief physical examinations will be performed according to the standard of care.

7.5.3.3 Vital signs

Systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes.

7.5.3.4 Eastern Cooperative Oncology Group performance status

A screening ECOG PS of 0 to 2 must be confirmed and documented. The ECOG PS is defined in Section 14.5.

7.5.3.5 Body weight

Section modified by Amendment 2 (Section 13.2).

Body weight will be measured without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. At all sites (in US and outside US), weight is to be taken only once for each dose.

- For non-US sites, the weight should be performed within 72 hours prior to dosing.

- For US sites using the central PRD depot ONLY, subject weight for the dose day should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits. Body weight can be obtained at the local healthcare provider on a calibrated scale and the results sent by fax to the Principal Investigator with advanced notice and agreement from the Covance Medical Monitor for each subject. No other procedures can be done at the local healthcare provider.

7.6 Other procedures and variables

Not applicable.

7.7 Appropriateness of procedures / measurements

The procedures chosen for the evaluation of safety in this study population are consistent with the appropriate and ethical standards used in Phase II studies of oncology drugs.

Tumor progression will be assessed by MRI / CT scan of the abdomen and pelvis, chest X-ray, and whole body technetium-99 bone scan and it will be evaluated according to the PCWG2 criteria (see Section 14.2). All images should be obtained with the same technique (e.g., MRI or CT) as those obtained at screening.

8. Statistical methods and determination of sample size

8.1 General considerations

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Subjects will be randomized in a 1:1:1 ratio to one of:

- Treatment Arm A: Radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) intravenously every 28 days up to 6 doses (“standard dose”)

- Treatment Arm B: Radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) intravenously every 28 days up to 6 doses (“high dose”)

- Treatment Arm C: Radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) intravenously every 28 days up to 12 doses (“extended dosing”)

Randomization will be stratified by:

- Prior chemotherapy (≤ 1 regimen versus > 1 regimen)
- Total ALP (< 220 U/L versus ≥ 220 U/L).
- Average WPS of the BPI-SF (WPS ≤ 4 versus WPS > 4)

Analysis of the primary variables will be performed for each subgroup for individual stratification factors. Statistical analyses will be performed using SAS; the version used will be specified in the SAP.

8.2 Analysis sets

Section modified by Amendments 2 (Section 13.2) and 3 (Section 13.3).

The following 3 analysis sets will be defined:

Intent-to-treat (ITT): All randomized subjects. The ITT analysis set will be used in the analysis of all efficacy endpoints. Subjects will be included in all ITT analyses according to the treatment to which they were randomized.

Week 24 (W24): All ITT subjects in Arm A (standard dose) and Arm C (extended dosing) treated with radium-223 dichloride and eligible for further treatment at W 24(i.e., 7th injection). Week 24 applies to subjects who received the 6th injection without any dose delays. As dose delays are allowed per protocol, 6th injection can occur after Week 24 for subjects who had dose delays. Hence, this population is defined based on the number of injections not based on the timing. The W24 dataset will be used for the analysis of efficacy endpoints related to Comparison 2 and associated evaluations. Subjects will be included in W24 analyses according to the treatment to which they were randomized.

Safety: All randomized subjects who have received at least one study drug administration. This safety analysis set will be used in the analyses of all safety endpoints. Subjects will be included in the analyses according to the treatment they received.

8.3 Variables

Efficacy variables are listed in Section 7.3.1. Definitions for each efficacy variable are given in Section 7.3.2.

The primary efficacy variable is SSE-FS.

The safety variables are defined in Section 7.5 and listed in Section 8.4.4.

8.4 Statistical and analytical plans

8.4.1 Primary efficacy analysis

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), and 3 (Section 13.3).

Decision rules and adjustment of alpha for primary endpoints

The primary efficacy endpoints, SSE-FS, will be analyzed separately in 2 respective comparisons, as described below.

Both comparisons will be performed at the time of final analysis, after the latest of (1) approximately 135 SSE-FS events in subjects included in Comparison 1 as defined below; (2) approximately 75 SSE-FS events following the 6th dose in subjects included in Comparison 2 as defined below; and (3) the last subject has been followed for 30 days from last treatment. In the event the applicable number of events is not reached, the primary endpoint analysis will mature 7 years after the last subject has received last treatment.

No alpha adjustment for multiple comparisons will be performed in this Phase II study.

Comparison 1: Standard dose versus high dose: SSE-FS from randomization in radium-223 dichloride-naïve subjects

Comparison 1 will test the following hypotheses:

The Null Hypothesis (H0)1: In a population of radium-223 dichloride-naïve subjects with CRPC metastatic to the bone, population SSE-FS in subjects treated with a regimen of up to 6 doses of 80 kBq/kg (88 kBq/kg after implementation of NIST update) (high dose) radium-223 dichloride is equal to population SSE-FS in subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride, versus

The Alternative Hypothesis (HA)1: In a population of radium-223 dichloride-naïve subjects with CRPC metastatic to the bone, population SSE-FS in subjects treated with a regimen of up to 6 doses of 80 kBq/kg (88 kBq/kg after implementation of NIST update) (high dose) radium-223 dichloride is greater than population SSE-FS in subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride.

Comparison 1 will analyze SSE-FS with randomization date as start date.

Comparison 1 will pool SSE-FS in subjects in Treatment Arm A, with SSE-FS truncated at 24 weeks in subjects in Treatment Arm C, and compare this pooled value with SSE-FS in Treatment Arm B. Only ITT subjects will be included in this ITT analysis. In this study, extended dosing subjects (Treatment Arm C) will receive the same treatment regimen as standard dose subjects (Treatment Arm A) for the first 6 doses, with Dose 7 scheduled to start after 24 weeks. Accordingly, data from Treatment Arm C subjects arising during the first

24 weeks is relevant to this comparison and including it increases the analysis power under the study assumptions.

It will be performed using a log-rank test with a 1-sided alpha of 0.1 stratified by the randomization factors (previous chemotherapy [≤ 1 regimen versus > 1 regimen] and total ALP [< 220 U/L versus ≥ 220 U/L]). The high-dose regimen will be declared superior to the standard-dosing regimen if the 1-sided p-value from the stratified log-rank test is less than 0.1.

The hazard ratio (high dose / standard dose) will be computed together with 2-sided 80% and 95% confidence intervals using a stratified Cox regression model with treatment as a factor and previous chemotherapy (≤ 1 regimen versus > 1 regimen) and total ALP (< 220 U/L versus ≥ 220 U/L) as strata in the model for the ITT population. Kaplan-Meier survival distribution tables and plots will also be produced for both Treatment Arms A and B. Additional details will be provided in the SAP.

Comparison 2: No further radium-223 dichloride treatment versus extended dosing: SSE-FS analysis from the 6th dose in subjects receiving standard-dose regimen

Comparison 2 will test the following hypotheses:

H02: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST standard update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond the 6th dose in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (extended dose) radium-223 dichloride is equal to population SSE-FS beyond the 6th dose in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen, versus

HA2: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond the 6th dose in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (extended dose) radium-223 dichloride is greater than population SSE-FS beyond the 6th dose in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen.

Comparison 2 will be an analysis of SSE-FS from the 6th dose, in subjects surviving SSE-free to the 6th dose. It will compare subjects in Treatment Arm A with subjects in Treatment Arm C.

Comparison 2 will be performed using a log-rank test with a 1-sided alpha of 0.1 stratified by the randomization factors (previous chemotherapy [≤ 1 regimen versus > 1 regimen] and total ALP [< 220 U/L versus ≥ 220 U/L]). The extended dosing regimen will be declared superior

to the standard dosing regimen if the 1-sided p-value from the stratified log-rank test is less than 0.1.

8.4.2 Secondary efficacy analysis

Selected secondary variables will be tested. No multiple testing procedures to control overall alpha level will be performed in this Phase II study. All testing will be one-sided with a significance level of 0.10. Further details will be specified in the SAP.

Secondary efficacy analyses will be grouped as follows:

8.4.2.1 Analyses of pooled standard dose and high dose from randomization

Section modified by Amendment 1 (Section 13.1).

For the following secondary endpoint analyses, subjects will be classified into 2 treatment groups: (1) the "standard dose" treatment group, consisting of ITT subjects in Treatment Arm A pooled with subjects in Treatment Arm C, and (2) the "high dose" treatment group, ITT subjects in Treatment Arm B. For these analyses, the start date will be randomization, and the screening (or pre-treatment) baseline will be used. Only data truncated at 24 weeks will be included for Treatment Arm C subjects.

The following secondary efficacy time-to-event endpoints will have hypothesis testing performed to compare these treatment groups: OS, time to first SSE, time to radiological progression, and rPFS.

Other endpoints will be analyzed descriptively for each treatment group.

Other endpoints and analyses for these treatment groups may be defined in the SAP.

8.4.2.2 Analyses of standard dosing and extended dosing from the 6th dose

Section modified by Amendment 3 (Section 13.3).

For the following secondary endpoint analyses, subjects will be classified into 2 treatment groups: (1) the "standard dose" treatment group, consisting of applicable ITT subjects in Treatment Arm A, and (2) the "extended dosing" treatment group, consisting of applicable ITT subjects in Treatment Arm C. For these analyses except for rPFS, the 6th dose date will be used as the reference date. For rPFS, randomization date will be used as the reference date.

For secondary endpoint time-to-event analyses for these treatment groups, subjects included will have survived to the 6th dose without having experienced the applicable event, and will have completed and / or not been discontinued from treatment. Details defining these analyses will be provided in the SAP.

The following secondary efficacy time-to-event endpoints will have hypothesis testing performed to compare these treatment groups: OS, time to first SSE, and rPFS.

Other endpoints will be analyzed descriptively for each treatment group.

Other endpoints and analyses for these treatment groups may be defined in the SAP.

8.4.2.3 Analyses by treatment arm

Selected descriptive efficacy analyses and listings will be provided by randomized treatment arm. Details will be provided in the SAP.

8.4.2.4 Secondary endpoint analysis methods

All secondary endpoint hypothesis tests will be performed using a stratified log-rank test: For each log-rank test, the factors from the randomization will be used for stratification.

For time to event endpoints, Kaplan-Meier survival distribution tables and plots with 95% confidence intervals will be produced for each applicable treatment group.

Rates will be calculated with 95% confidence intervals for each treatment group.

8.4.3 Analysis of exploratory variables

Section modified by Amendment 1 (Section 13.1).

Analyses of exploratory variables will be defined in the SAP.

An exploratory analysis will be performed estimating and modeling SSE-FS efficacy in Treatment Arm B (high dose) versus Treatment Arm C (extended dosing). Analyses will be further described in the SAP. No formal comparison testing between Treatment Arm B and Treatment Arm C will be performed.

An exploratory analysis of the impact of baseline body size descriptors on the efficacy and safety of radium-223 dichloride will also be performed with respect to each applicable baseline. Details regarding the baseline body size descriptor definitions, analysis specifications, and applicable baseline definitions will be provided in the SAP.

8.4.4 Safety analysis

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

No formal interim analysis for safety is planned. A JSRC will review the safety data periodically. Details on the JSRC are described in Section 3.

The safety endpoints include:

- Incidence and severity of TEAEs and laboratory abnormalities graded by NCI-CTCAE 4.03 and coded by MedDRA
- Incidence of serious TEAEs
- Incidence of drug-related AEs in the follow-up period

Safety data evaluated will also include laboratory data, vital signs, and physical examination results.

Safety variables will be analyzed using frequency tables and descriptive statistics, or through listings.

The following safety analyses will be performed as follows:

1. Treatment-emergent safety events

   The treatment period for safety purposes for this study extends from the initiation of treatment until 30 days after the last administration of radium-223 dichloride. Events starting or worsening within the treatment period will be considered treatment-emergent.

   For the analysis of treatment-emergent safety events, subjects will be grouped by treatment arm as treated.

2. Safety events emerging during the standard-regimen treatment period

   For this analysis, subjects will be classified into 2 groupings, 50 kBq/kg (55 kBq/kg after implementation of NIST update) subjects (Treatment Arms A and C, pooled), and 80 kBq/kg (88 kBq/kg after implementation of NIST update) subjects (Treatment Arm B), as treated. It will be performed for selected safety endpoints for events emerging from start of treatment through the later of 24 weeks from treatment start or 30 days following completion of 6 doses of radium-223 dichloride treatment.

3. Safety events emerging following the standard-regimen treatment period

   This analysis will be performed in each treatment arm for events following the later of 24 weeks from treatment start or 30 days following completion of 6 doses of radium-223 dichloride treatment. It will be performed for selected safety endpoints collected during active follow-up after end of treatment through primary endpoint completion. This analysis will be performed by treatment group as treated.

4. Safety events emerging during long-term follow-up following primary endpoint completion.

Safety events emerging following primary endpoint completion and any events emerging during long-term follow-up, will be reported in a separate document(s) from the study Clinical Study Report.

Further details describing these analyses will be provided in the SAP.

8.5 Planned interim analyses

No formal interim analysis is planned, and no alpha adjustment to efficacy analyses for an interim analysis is required.

8.6 Determination of sample size

Section modified by Amendments 1 (Section 13.1), 2 (Section 13.2), and 3 (Section 13.3).

The sample size is calculated to have the indicated power, separately and with no multiple-testing adjustment, to detect one or both of the following:

- Comparison 1: A 50% increase in SSE-FS in subjects receiving a regimen 6 doses of 80 kBq/kg (88 kBq/kg after implementation of NIST update) radium-223 dichloride every 28 days (high dose) over subjects receiving a regimen of 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) radium-223 dichloride every 28 days (standard dose) in a population of radium-223 dichloride-naïve subjects, and / or

- Comparison 2: A 65% increase in SSE-FS following 24 weeks in subjects receiving a regimen of up to 6 additional doses of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) every 28 days (extended dose) over subjects receiving no further radium-223 dichloride treatment, in a population of subjects surviving SSE-free to 24 weeks who received a standard regimen of up to 6 doses of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) and who either completed standard treatment, or remained eligible to receive further radium-223 dichloride (not permanently discontinued from treatment) at 24 weeks.

The sample size calculations assume 30 subjects/month enrollment with 7 months ramp-up and a 3% loss to follow-up per month. The accrual period is anticipated to last approximately 16 months. Overall, 360 subjects are expected to be randomized. The primary endpoint cut-off, as defined in Section 8.4, is estimated to be reached in an average of 39 months.

Comparison 1 will analyze SSE-FS from randomization date in subjects randomized to standard dosing and high dose regimens, and SSE-FS truncated at 24 weeks in subjects randomized to the extended dose regimen. Subjects randomized to the standard dosing and extended dosing regimens will be pooled. Constant hazards are assumed with a median SSE-FS of 9 months throughout the study for the standard dosing regimen, a median SSE-FS of 9 months for the first 24 weeks from randomization for the extended dosing regimen, and a 50% improvement (median 13.5, hazard ratio 0.667) throughout the study for the high dose regimen. Simulations indicated an average of 186.6 events would occur for this comparison

at primary endpoint cut-off, and a 1-sided log-rank test with 0.10 significance gave approximately 90.5% power to test H01 versus HA1.

Comparison 2 will analyze SSE-FS from the 6th dose, in subjects surviving SSE-free to the 6th dose. (27,28) A median SSE-FS of 9 months with constant hazards is assumed for standard dose. Extended dosing is assumed to have the same SSE-FS efficacy as standard dosing for the first 24 weeks, and 65% improvement (hazard ratio 0.606) thereafter. With 240 of 360 subjects randomized to Treatment Arm A and Treatment Arm C, simulations indicated that 44.65% of randomized subjects (107.2 of 240) would have an SSE-FS event or loss to follow-up during the first 24 weeks, leaving an estimated 55.35% (132.8) surviving SSE-free and eligible for inclusion at 24 weeks. An average of 74.9 simulated events occurred for this comparison, and a 1-sided log-rank test with 0.10 significance gave approximately 80.6% power to test H02 versus HA2.

Simulations assume continuous event and censoring times. Last treatment is assumed to occur 44 weeks (10.12 months) after last subject accrued.

Primary endpoint power calculations were based on simulations programmed using SAS version 9.2 and used 10,000 replicates.

9. Data handling and quality assurance

9.1 Data recording

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the site. The site must implement processes to ensure this happens. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

Data recorded from "only screened subjects (screening failures)"

Data of 'only screened subjects' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, data to be recorded in the eCRF are demographic information (subject number, date of birth / age, sex, race, and ethnicity), the reason for premature discontinuation and date of last visit. These data will be transferred to the respective database.

For screening failures with an SAE, the following additional data should be collected in the eCRF, in addition to demographic information, primary reason for discontinuation and date of last visit:

- All information about the SAE
- All information related to the SAE such as:
  - Concomitant medication

- Medical history
- Other information needed for SAE complementary page

9.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor'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's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the 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

The data collection tool for this study will be a validated electronic system. Subject data necessary for analysis and reporting will be transmitted into a validated data system. Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g., IVRS / IWRS, laboratory).

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

9.4 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.

9.5 Archiving

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

Subject (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 notifies 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

Section modified by Amendments 2 (Section 13.2), 3 (Section 13.3), and 4 (Section 13.4.1.2).

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.

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and SAEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic anti-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. In addition, during the long-term follow-up, all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject.

Until the transition to the long term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up).

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 given by the sponsor for destruction.
- In case 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 5.2.1.

11.Ethical and legal aspects

11.1 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 under 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 IECs / 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 / 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.

11.2 Subject information and consent

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.

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 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 IEC / IRB has been obtained.

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the ICF and has done so, may he enter the study. Additionally, the investigator and other information provider (if any) 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 ICF statement is to remain in the investigator site file or, if locally required, in the subject'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.

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 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.

11.3 Publication policy

The sponsor is interested in the publication of the results of every study it performs.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator / institution.

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

11.4 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.

11.5 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 CRF, 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 Amendments 1 (Section 13.1) and 2 (Section 13.2).

1. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;26(7):1148-59.

2. Cancer Facts & Figures 2013. American Cancer Society. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf. Published 2013. Accessed 07 Mar 2013.

3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-1403.

4. Ye L, Kynaston HG, Jiang WG. Bone metastasis in prostate cancer: molecular and cellular mechanisms (Review). Int J Mol Med. 2007;20(1):103-11.

5. Lange PH, Vessella RL. Mechanisms, hypotheses and questions regarding prostate cancer micrometastases to bone. Cancer Metastasis Rev. 1998;17(4):331-6.

6. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-12.

7. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacobe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94:1458-68.

8. Smith MR, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, Saad F, et al.; Denosumab HALT Prostate Cancer Study Group. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med. 2009 361(8):745-55.

9. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364:1995-2005.

10. Scher HI, Fizazi K, Saad F, Taplin, M-E, Cora N. Sternberg CN, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187-97.

11. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant

prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147-54.

12. 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.

13. Henriksen G, Fisher DR, Roeske JC, Bruland OS, Larsen RH. Targeting of osseous sites with alpha-emitting 223Ra: comparison with the beta-emitter 89Sr in mice. J Nucl Med. 2003;44(2):252-9.

14. Bayer. Cellular effects of alpha particle radiation from radium-223, Alpharadin III. DNA damages, double strand breaks observed by γH2A.X flow cytometry.

15. Henriksen G, Breistol K, Bruland OS, Fodstad O, Larsen RH. Significant antitumor effect from bone-seeking, alpha-particle-emitting (223)Ra demonstrated in an experimental skeletal metastases model. Cancer Res. 2002;62(11):3120-5.

16. Bayer HealthCare AG. BAY 88-8223 Investigator's Brochure, 2012.

17. Bayer HealthCare, internal communication. Nov 2012.

18. Nilsson S, Larsen RH, Fossa SD, Balteskard L, Borch KW, Westlin JE, et al. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. Clin Cancer Res. 2005;11(12):4451-9.

19. Nilsson S, Franzén L, Parker C, Bolstad B, Ramdahl T, Thuresson M, et al. Alpha emitting radium-223: two years follow up from a randomized phase II study in patients with bone metastases from hormone refractory prostate cancer. EJC Supplements. 2009;7(2):412.

20. A phase III study of alpharadin (radium-223) in patients with symptomatic hormone refractory prostate cancer with skeletal metastases (ALSYMPCA). [database on the Internet]. Available from: http://clinicaltrials.gov/ct2/show/NCT00699751?term=ALSYMPCA&rank=1.

21. Parker C, Nilsson S, Heinrich D, O'Sullivan JM, Fossa SD, Chodacki A, et al. Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA). J Clin Oncol. 30, 2012 (suppl; abstr LBA4512).

22. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-23.

23. Parker CC, Pascoe S, Chodacki A, O'Sullivan JM, Germá JR, O'Bryan-Tear CG, et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium

chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. Eur Urol. 2013;63(2):189-97.

24. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. Ann Intern Med. 1999;130:461-70.

25. Levey AS, Stevens LA, Schid CH, Zhang YL, Castro AF 3rd, Feldman Hi, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009 May 5, 150(9): 604-12.

26. http://www.facit.org/FACITOrg/Questionnaires.

27. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012;366:1759-69.

28. Zinner RG, Saxman SB, Peng G, Monberg MJ, Ortuzar WI. Treatment rationale and study design for a randomized trial of pemetrexed/carboplatin followed by maintenance pemetrexed versus paclitaxel/carboplatin/bevacizumab followed by maintenance bevacizumab in patients with advanced non-small-cell lung cancer of nonsquamous histology. Clin Lung Cancer. 2010;11(5):352-7.

29. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23:129-38.

30. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2012;368(2):138-48.

31. Cessna JT, Zimmerman BE. Standardization of radium-223 by liquid scintillation counting. Appl Radiat Isot. 2010;68(7-8):1523-8.

32. Zimmerman BE, Bergeron DE, Cessna JT, Fitzgerald R, Pibida L. Revision of the NIST standard for ^{223}Ra: new measurements and review of 2008 data. J Res Natl Inst Stand Technol. 2015;120:37-57.

13. Protocol amendments

13.1 Amendment 1

Description of the amendment

Amendment 1 is an amendment to the original protocol dated 09 AUG 2013. Changes to the protocol include:

- Clarification of the comparisons performed and populations of inference for the primary objective
- Reduction of estimated time until CSR is produced with long-term safety evaluations reported separately.
- Addition of an exploratory objective to evaluate the quality of life based on the NCCN FACT-P Symptom Index-17 (NCCN-FACT FPSI-17) with associated data collection.
- Addition of a secondary analgesic use objective based on the Analgesic Quantification Algorithm (AQA).
- Addition of an exploratory objective to explore the impact of baseline body size descriptors on the efficacy and safety of study drug.
- Addition of an inclusion criteria to only include subjects who are at least 18 years of age.
- Addition of an inclusion criteria for sexually active males and/or their partners to use effective birth control during the treatment period and for 6 months after last dose of radium-223 dichloride.
- Revised definition of bone progression based on the adapted PCWG2 criteria for consistency across the radium-223 program following comments from the FDA on another related radium-223 study. This change affected the time points of radiological assessments.
- Provide for consistent collection of pain and analgesic use data in every treatment arm, every 28 weeks for the first 48 weeks.
- Added a clarification of when the primary analysis will be performed in the event that too few SSE events occur to trigger the primary analysis (135 SSE-FS events for Comparison 1 and 75 SSE-FS events for Comparison 2).
- Clarification of the safety analyses performed.

- Clarification of how and when the IVRS / IRWS will be used in the study so that study drug is shipped to the investigator sites on-time for the subject's next dose.

- Clarification of central review of radiological and quantitated bone scan endpoints.

- Added a study specific dose modification to mandate discontinuation of treatment with radium-223 dichloride in subjects who experience Grade 4 neutropenia lasting > 7 days despite adequate treatment.

- Changed the safety review during the study from an independent data monitoring committee to a joint safety review committee; membership may include investigators, sponsor team members, and/or independent members.

- Changed laboratory assessments from bilirubin to total bilirubin.

13.1.1 Overview of changes

Change 1:

Revised primary objectives to be co-primary objectives to evaluate efficacy in treating metastatic bone cancer in subjects with CRPC. Also clarified the descriptions of the populations in the two overall comparisons; the revised descriptions are as follows:

- The first co-primary objective compares subjects who receive radium-223 dichloride 50 kBq/kg every 28 days for up to 6 doses with radium-223 dichloride 80 kBq/kg every 28 days for up to 6 doses in radium-223 dichloride-naïve subjects.

- The second co-primary objective compares subjects who receive radium-223 dichloride 50 kBq/kg every 28 days for up to 6 additional doses compared to no further radium-223 dichloride treatment in subjects with CRPC metastatic to the bone who previously received radium-223 dichloride 50 kBq/kg every 28 days for up to 6 doses, and survived SSE free and are eligible for further radium-223 dichloride treatment.

Sections affected include:

- Synopsis - Study objectives

- Synopsis - Plan for statistical analysis

- 2. Study objectives

- 8.4.1 Primary efficacy analysis

- 8.6 Determination of sample size

Rationale: These changes were made to provide a clearer description of the comparisons and populations for the study co-primary and secondary objectives than the descriptions in the original protocol version 1.0 (dated 09 AUG 2013).

Change 2:

Added as an exploratory objective and endpoint to evaluate quality of life based on the NCCN-FACT FPSI-17 questionnaire.

Sections affected include:

- Synopsis - Study objectives
- Synopsis - Methodology
- 2. Study objectives
- 4.1 Design overview
- 7.1.1 Tabular overview, Table 7-1 Schedule of procedures
- 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C)
- 7.1.2.3 Doses 2 to 6 (Treatment Arms A and B)
- 7.1.2.4 Doses 2 to 12 (Treatment Arm C)
- 7.1.2.5 End of treatment visit
- 7.1.2.6.1 Active follow-up with clinic visits
- 7.3.1 Efficacy variables
- 7.3.5.2 Time to increase in physical symptoms of disease based on (FPSI-DRS-P) - new section
- 12. References
- 14.8 NCCN FACT-P Symptom Index-17 (NCCN-FACT FPSI-17) Questionnaire - new section

Rationale: The NCCN-FACT FPSI-17 questionnaire was added as per input received from Bayer Global Health Economics and Outcome Research and from external Pain Experts of the Radium 223 Pain Advisory Board.

Change 3:

Added a secondary objective that analgesic usage and change in analgesic use will be analyzed using the Analgesic Quantification Algorithm (AQA).

Sections affected included:

- Synopsis - Study objectives
- Synopsis - Methodology
- Synopsis - Primary / Secondary variables
- 1.2 Study rationale
- 2. Study objectives
- 4.1 Design overview
- 4.2 Primary and secondary variables
- 7.3.1 Efficacy variables
- 7.3.4.5 Change in analgesic use score - new section
- 7.3.5.5 Additional pain and health related quality of life endpoints
- 14.10 Analgesic Quantification Algorithm - new section

Rationale: A secondary endpoint for change in analgesic use supports its use in secondary endpoints for pain improvement/progression, and supports a separate descriptive evaluation of changes in analgesic use over time.

Change 4:

Added an exploratory objective and endpoint to explore the impact of baseline body size descriptors on efficacy and safety of radium-223 dichloride.

Section affected include:

- Synopsis - Study objectives
- 2. Study objectives
- 7.2.4 Body size descriptors - new section
- 8.4.3 Analysis of exploratory endpoints

Rationale: Post hoc analyses of the impact of body size on the efficacy and safety of radium-223 dichloride have previously been performed on the ALSYMPCA database. After reviewing the original protocol version 1.0 (dated 09 Aug 2013), the FDA requested that this be evaluated prospectively in this study as an exploratory objective and the Sponsor agrees. Due to the dosing regimen based on total body weight, the evaluation of the potential impact of other body size descriptors on the efficacy and safety of radium-223 dichloride may provide information relevant to the radium-223 treatment optimization program.

Change 5:

Added an inclusion criteria to include subjects who are at least 18 years of age and not expose adolescent subjects whose bone development may be adversely affected by radium-223 dichloride.

Sections affected include:

- Synopsis - Diagnosis and main criteria for inclusion
- 5.1.1 Inclusion criteria

Rationale: This change was made to be consistent with the approved label for Xofigo and to eliminate any exposure of potential, though unlikely, adolescent subjects whose bone development might be affected.

Change 6:

Added an inclusion criteria to only include male subjects who agree to use condoms, if sexually active, and/or their female partners to use effective methods of birth control to prevent pregnancy. This requirement complies with the US package insert.

Sections affected include:

- Synopsis - Diagnosis and main criteria for inclusion
- 5.1.1 Inclusion criteria

Rationale: This change was made to be consistent with the approved label for Xofigo and to prevent pregnancy in women of reproductive potential, female sexual partners of male subjects exposed to radium-223 dichloride.

Change 7:

Revised the definition of bone progression based on the PCWG2 criteria to being based on the adapted PCWG2 criteria. The reference to the adapted PCWG2 criteria was added. The time points of assessment of radiological progression were revised according to the new definition.

Sections affected included:

- Synopsis - Methodology
- 4.1 Design overview
- 7.1.1 Tabulated overview, Table 7-1 Schedule of procedures
- 7.1.2.3 Doses 2 to 6 (Treatment Arms A and B)
- 7.1.2.4 Doses 2 to 12 (Treatment Arm C)
- 7.1.2.5 End of treatment visit
- 7.1.2.6.1 Active follow-up with clinic visits
- 7.1.2.7.1 End of active follow-up with clinic visits
- 7.3.4.3 Radiological progression endpoints
- 7.3.5.1.3 Bone scan time point response rate
- 12 Reference list
- 14.2 Recommendations of the Prostate Cancer Clinical Trials Working Group for assessment of radiological progression
- 14.5 Bone scan assessment tool

Rationale: The definition of bone progression was revised to the adapted PCWG2 criteria to be consistent across the radium-223 dichloride program following recent comments from the FDA on another radium-223 dichloride study. Appropriate changes to the time points of the assessment of radiological progression were made and a reference to the new definition was also added.

Change 8:

Changed the exclusion criteria concerning treatment with an investigational drug by deleting "or planned treatment with an investigational drug during the treatment period or follow-up". Subjects would unlikely plan to be treated with another investigational drug years in advance and, if they do receive an investigation study drug during the treatment period or follow-up, then they would be excluded from the efficacy analysis because of receiving prohibited concomitant drugs.

Sections affected include:

- Synopsis - Diagnosis and main criteria for inclusion

- 5.1.2 Exclusion criteria

Rationale: Clarification.

Change 9:

Revised method and schedule of pain and analgesic use assessments to provide for additional daily electronic patient-reported outcome (ePRO) pain assessments for 7 days and telephone contacts to assess BPI-SF and analgesic use, in Arms A and B at Weeks 28, 32, 40, and 44. Consistent collection schedules through Week 48 supports deleting language characterizing data collected following Week 24 as exploratory.

Section affected:

- Synopsis - Methodology
- 4.1 Design overview
- 7.1.1 Tabulated overview, Table 7-1
- 7.1.2.5 End of treatment visit
- 7.1.2.6.1 Active follow-up with clinic visits
- 14.7 Brief Pain Inventory-Short Form

Rationale: Addresses FDA comment requesting a more consistent schedule of collecting pain data among the treatment arms to reduce bias in the results.

Change 10:

Changed the point when the primary endpoint will be performed by reducing minimum follow-up after last patient last treatment from 24 months to 1 month, and providing that in the event that too few SSE events (135 SSE events for Comparison 1 and 75 SEE events for Comparison 2) occur to trigger the primary analysis. This change reduces the estimated study duration and slightly reduces the estimated power.

Sections affected include:

- Synopsis - Plan for statistical analysis
- 4.3 End of study
- 8.4.1 Primary efficacy analysis
- 8.6 Determination of Sample Size

Rationale: Dependence of primary endpoint completion on safety follow-up is being relaxed to enable primary endpoint completion to mature earlier to support FDA post-marketing commitment deadlines. Safety events reported after primary endpoint completion will be reported in a separate document.

Change 11:

Revised randomization stratification to include to be stratified by worst pain score (WPS) of the BPI-SF (WPS ≤ 4 versus WPS > 4), and provided for collection of selected BPI-SF pain data for 4 days prior to randomization to calculating stratification value.

Sections affected include:

- Synopsis - Methodology
- 4.1 Design overview
- 6.1 Treatments to be administered
- 6.3 Treatment assignment
- 7.1.1 Tabulated overview, Table 7-1
- 7.1.2.1 Screening period
- 8.1 General considerations

Rationale: Pain added as randomization stratification factor to address FDA comment requesting a method to better ensure that baseline pain levels are consistent across the treatment arms. Not added to efficacy analysis stratification to avoid added risk of sparse cells.

Change 12:

Modified end of active follow-up to continue beyond minimum of 2 years from last treatment to earlier of first SSE or primary endpoint maturation in patients receiving clinic visits, while ending active follow-up at 2 years in all cases in subjects receiving telephone contact only.

Sections affected included;

- Synopsis - Methodology
- 4.1 Design overview
- 6.8 Post-study therapy

- 7.1.2.6 Active follow-up
- 7.1.2.6.1 Active follow-up with clinic visits
- 7.1.2.6.2 Active follow-up without scheduled clinic visits
- 7.1.2.7.1 End of active follow-up with clinic visits
- 7.1.2.7.2 End of active follow-up without scheduled clinic visits

Rationale: End of follow-up was made different for active follow-up with clinic visits and telephone-only active follow-up to reflect their different capacities. To ensure primary endpoint completion and adequate study power, patients in study need to continue follow-up for SSEs to first SSE if before primary endpoint completion, if after the two-year period selected to evaluate safety. As subjects without clinic visits cannot have primary endpoint SSE evaluations, telephone-only follow-up need occur only for 2-year safety period.

Change 13:

Changed the safety review during the study from an independent data monitoring committee to a joint safety review committee; membership may include investigators, sponsor team members, and/or independent members.

Sections affected included:

- Synopsis - Methodology
- 3 Investigators and other study personnel
- 4.3 Interim Analyses and Joint Safety Review Committee - new section
- 8.4.4 Safety analysis

Rationale: A Data Monitoring Committee, with a stringent membership requirement of only independent members, is not necessary for this open-label study. Therefore, a Joint Safety Review Committee (JSRC), whose membership requirements that are less stringent and can include investigators, sponsor members, and/or independent members, is adequate for this study. The JSRC's mandate will be limited to safety to reduce the possibility of any bias arising from study principal participation.

Change 14:

Added that Cardinal Health is the radio pharmacy that will prepare and dispense patient ready doses of radium-223 dichloride in the US.

Section affected:

- 6.4.4 Dose preparation

Rationale: Inclusion of important dose preparation information.

Change 15:

Revised text to be clearer on when and how IVRS / IWRS will be used to order study drug to be shipped to the investigator site so that the study drug is delivered on-time for the subject's next visit requiring study drug administration.

Sections affected included:

- 7.1.1 Tabular overview, Table 7-1 Schedule of procedures
- 7.1.2.1 Screening period

Rationale: Clarification

Change 16:

Added that on Study Day 1 visit, study eligibility must be reconfirmed for hematology tests if the results are greater than 72 hours prior to the first dose of study drug. This is not a new requirement. It was in Section 7.1.2.2, but stated differently.

Section affected include:

- 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C)

Rationale: Moved this text and restated to emphasize that hematology results should be reconfirmed to be within the entry criteria prior to the first dose of study medication.

Change 17:

A study specific radium-223 dose modification to mandate discontinuation of treatment in patients who experience grade 4 neutropenia lasting more than 7 days.

Section affected:

- 5.2.1 Withdrawal
- 6.4.7 Dose delays

Rationale: The study specific radium-223 dose modification was added as per FDA request. The addition of the dose modification was agreed with Bayer Global Pharmacovigilance in consideration of the higher doses and extended regimen investigated in this trial.

Change 18:

Modified definition of pain progression, pain improvement rate, and time to pain progression to refer to evaluability for analgesic use increase and decrease respectively.

Sections affected include:

- 7.3.4.4 Pain endpoints
- 7.3.4.4.1 Pain improvement rate
- 7.3.4.4.2 Time to pain progression

Rationale: Changed to be consistent with the radium-223 dichloride program and with FDA comment regarding population evaluable for pain endpoints, further clarifies the portion of patient population eligible for evaluation for each pain endpoint.

Change 19:

Modified safety analysis section to define treatment-emergent period, and to provide for an analysis of safety events arising after primary endpoint completion in a separate document from the CSR

Sections affected include:

- 8.4.4 Safety analysis

Rationale: Change clarifies treatment-emergent safety event analysis. As primary endpoint completion following amendment is expected to occur before the end of 2-year active safety follow-up, this provides for an analysis of events emerging after primary endpoint completion, as well as any long-term follow-up events in a separate document.

Change 20:

Added that IVRS / IWRS procedures can be found in the IVRS / IWRS manual.

Section affected:

- 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C)

Rationale: Clarification

Change 21:

Changed the terminology for “active safety follow-up” period to “active follow-up” period since efficacy assessments are also included in these visits. In addition, the terminology for

"extended active follow-up" period was changed to "long-term follow-up" period; this change was done to ensure the use of a consistent term across the radium-223 program. Another revision included changing "2 years of active follow-up" to "active follow-up".

Sections affected included:

- Synopsis - Methodology
- 4.1 Design overview
- 6.8 Post-study therapy
- 7.1.1 Tabulated overview, Table 7-1 Schedule of procedures
- 7.1.2.6 Active follow-up
- 7.1.2.7.2 End of active follow-up without scheduled clinic visits
- 7.1.2.8 Long-term follow-up to 7 years following last dose
- 7.1.2.8.1 Long-term follow-up (via telephone follow-up)
- 7.1.2.8.2 End of long-term follow-up
- 8.4.4 Safety analysis

Rationale: Clarification

Change 22:

Clarified handling of radiological progression and quantitated bone scan details.

Sections affected included:

- 7.3.2 Definition of efficacy variables
- 7.3.4.3 Radiological progression endpoints
- 7.3.5.1 Quantitated bone scan endpoints

Rationale: Clarifies central radiological reviewer is responsible for imaging endpoints including baselines. Permits details to be addressed in a separate document from the imaging charter.

Change 23:

Changed laboratory assessment from bilirubin to total bilirubin.

Sections affected:

- 7.1.1 Tabulated overview, Table 7-1 Schedule of procedures
- 7.1.2.1 Screening period
- 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C)
- 7.1.2.3 Doses 2 to 6 (Treatment Arms A and B)
- 7.1.2.4 Doses 2 to 12 (Treatment Arm C)
- 7.1.2.5 End of treatment visit
- 7.1.2.6.1 Active follow-up with clinic visits
- 7.1.2.7.1 End of active follow-up with clinic visits
- 7.5 Safety
- 7.5.3.1 Laboratory evaluations

Rationale: Bilirubin was changed to total bilirubin to clarify that direct and indirect bilirubin were not necessary.

Change 24:

Revised text for clarification purposes:

Section affected:

- Synopsis - Diagnosis and main criteria for inclusion
- Synopsis - Plan for statistical analysis
- 5.1.1 inclusion criteria
- 6.4.7 Dose delays
- 7.1.1 Tabulated overview, Table 7-1 Schedule of procedures
- 7.1.2.1 Screening period
- 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C)
- 7.1.2.3 Doses 2 to 6 (Treatment Arms A and B)

- 7.1.2.4 Doses 2 to 12 (Treatment Arm C)
- 7.1.2.5 End of treatment visit
- 7.1.2.6.1 Active follow-up with clinic visits
- 7.3.2 Definition of efficacy variables
- 7.2.5.5 Additional pain and health-related quality of life
- 8.4.2.1 Analyses of pooled standard dose and high dose from randomization
- 8.4.4 Safety analysis

Rationale: Original text was not clear, revised text is clearer.

Change 25:

The list of abbreviations was updated to reflect the usage of abbreviations in the amended protocol:

Section affected:

- List of abbreviations

Rationale: Update abbreviation definitions

Change 26:

Revised Section 7.1.1 Tabular overview, Table 7-1 Schedule of procedures to reflect all the changes described above in Changes 1 to 21.

Rationale: Updated Table 7-1 Schedule of procedures to be consistent with Changes 1 to 21.

Change 27:

Updated Section 12 Reference list to include new reference “22” cited in Section 1.1 Background.

Rationale: Updated reference list to include an additional reference cited in the amended protocol.

Change 28:

Editorial revisions were made throughout the amended protocol.

Sections affected:

- Synopsis - Diagnosis and main criteria for inclusion
- Synopsis - Plan for statistical analysis
- 2 Study objectives
- 3 Investigators and other study personnel

13.1.2 Changes to the protocol text

General format conventions:

- Deleted text = ~~deleted text~~
- Added text = <u>added text</u>

Change 1:

Synopsis - Study objectives and Section 2 Study objectives:

Paragraph 1:

Old text:

~~Each of~~ the following objectives will be used to compare radium-223 dichloride 50 kBq/kg every 28 days for up to 6 doses ~~to~~ radium-223 dichloride 80 kBq/kg every 28 days for up to 6 doses ~~and to~~ radium-223 dichloride 50 kBq/kg every 28 days ~~for~~ up to ~~12~~ doses.

New text:

<u>T</u>he following objectives will be used to compare radium-223 dichloride 50 kBq/kg every 28 days for up to 6 doses <u>with</u> radium-223 dichloride 80 kBq/kg every 28 days for up to 6 doses <u>in radium-223 dichloride-naïve subjects; and, in subjects receiving</u> radium-223 dichloride 50 kBq/kg every 28 days <u>up to 6 doses, to compare a regimen of</u> up to a <u>further 6</u> doses <u>of radium-223 dichloride 50 kBq/kg every 28 days with no further radium-223 dichloride treatment</u>.

Paragraph 2:

Old text:

Primary objective:

- To evaluate efficacy as measured by SSE-FS of radium-223 dichloride 50 kBq/kg every 28 days for up to 6 doses compared to radium-223 dichloride 80 kBq/kg every 28 days for up to 6 doses, ~~and compared to radium-223 dichloride 50 kBq/kg every 28 days for up to 12 doses~~ in subjects with CRPC metastatic to bone

New text:

Co-primary objective**s**:

- To evaluate efficacy as measured by symptomatic skeletal event-free survival (SSE-FS) of radium-223 dichloride 50 kBq/kg every 28 days for up to 6 doses compared to radium-223 dichloride 80 kBq/kg every 28 days for up to 6 doses in subjects with castration-resistant prostate cancer (CRPC) metastatic to the bone not previously receiving radium-223 dichloride; and

- To evaluate efficacy as measured by SSE-FS of radium-223 dichloride 50 kBq/kg every 28 days for up to 6 additional doses compared to no further radium-223 dichloride treatment in subjects with CRPC metastatic to the bone who previously received radium-223 dichloride 50 kBq/kg every 28 days for up to 6 doses, and survived SSE-free and are eligible for further radium-223 dichloride treatment

Synopsis - Plan for statistical analysis and Section 8.4.1 Primary efficacy analysis:

Comparison 1 and comparison 2 subheadings and text:

Old text:

Comparison 1: Standard dose versus high dose: SSE-FS from randomization

Comparison 1 will test the following hypotheses:

H01: ~~Population SSE-FS from randomization in~~ subjects ~~treated~~ with high dose radium-223 dichloride is equal to population SSE-FS ~~from randomization~~ in subjects treated with standard dose radium-223 dichloride, versus

HA1: ~~Population SSE-FS from randomization~~ in subjects treated with high dose radium-223 dichloride is greater than population SSE-FS ~~from randomization~~ in subjects treated with standard dose radium-223 dichloride

Comparison 2: ~~Standard dose~~ versus extended ~~dose~~: SSE-FS analysis from 24 weeks

Comparison 2 will test the following hypotheses:

H02: Population SSE-FS ~~from~~ 24 weeks in subjects treated with extended dose radium-223 dichloride is equal to population SSE-FS ~~from~~ 24 weeks in subjects ~~treated with~~ standard dose ~~radium-223 dichloride~~, versus

HA2: ~~Population~~ SSE-FS ~~from~~ 24 weeks in subjects treated with extended dose radium-223 dichloride is greater than population SSE-FS ~~from~~ 24 weeks in subjects ~~treated with standard dose~~ radium-223 dichloride

New text:

Comparison 1: Standard dose versus high dose: SSE-FS from randomization in radium-223 dichloride-naïve subjects

Comparison 1 will test the following hypotheses:

H01: In a population of radium-223 dichloride-naïve subjects with CRPC metastatic to the bone, population SSE-FS in subjects treated with a regimen of up to 6 doses of 80 kBq/kg (high dose) radium-223 dichloride is equal to population SSE-FS in subjects treated with a regimen of up to 6 doses of 50 kBq/kg (standard dose) radium-223 dichloride, versus

HA1: In a population of radium-223 dichloride-naïve subjects with CRPC metastatic to the bone, population SSE-FS in subjects treated with a regimen of up to 6 doses of 80 kBq/kg (high dose) radium-223 dichloride is greater than population SSE-FS in subjects treated with a regimen of up to 6 doses of 50 kBq/kg (standard dose) radium-223 dichloride.

Comparison 2: No further radium-223 dichloride treatment versus extended dosing: SSE-FS analysis from 24 weeks in subjects receiving standard dose regimen

Comparison 2 will test the following hypotheses:

H02: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond 24 weeks in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (extended dose) radium-223 dichloride is equal to population SSE-FS beyond 24 weeks in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen, versus

HA2: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond 24 weeks in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (extended dose) radium-223 dichloride is greater than

population SSE-FS beyond 24 weeks in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen**.**

Section 8.6 Determination of sample size:

Paragraph 1:

Old text:

The sample size is calculated to have the indicated power, separately and with no multiple testing adjustment, to detect one or both of the following:

- Comparison 1: A 50% increase in SSE-FS in subjects receiving a regimen 6 doses of 80 kBq/kg radium-223 dichloride every 28 days (high dose) over subjects receiving a regimen of 6 doses of 50 kBq/kg radium-223 dichloride every 28 days (standard dose), and / or

- Comparison 2: A 65% increase in SSE-FS following 24 weeks in subjects receiving a regimen of ~~12~~ doses of 50 kBq/kg radium 223 dichloride every 28 days (~~high~~ dose) over subjects receiving a regimen of 6 doses of 50 kBq/kg radium 223 dichloride ~~every 28 days (standard dose), in subjects surviving SSE-FS to 24 weeks~~ and who either completed ~~6 doses of radium 223 dichloride~~, or remained eligible to receive further radium 223 dichloride (not permanently discontinued from treatment) at 24 weeks.

New text:

The sample size is calculated to have the indicated power, separately and with no multiple-testing adjustment, to detect one or both of the following:

- Comparison 1: A 50% increase in SSE-FS in subjects receiving a regimen 6 doses of 80 kBq/kg radium-223 dichloride every 28 days (high dose) over subjects receiving a regimen of 6 doses of 50 kBq/kg radium-223 dichloride every 28 days (standard dose) in a population of radium-223 dichloride-naïve subjects, and / or

- Comparison 2: A 65% increase in SSE-FS following 24 weeks in subjects receiving a regimen of up to 6 additional doses of 50 kBq/kg radium-223 dichloride every 28 days (extended dose) over subjects receiving no further radium-223 dichloride treatment, in a population of subjects surviving SSE-free to 24 weeks who received a standard regimen of up to 6 doses of 50 kBq/kg radium-223 dichloride and who either completed standard treatment, or remained eligible to receive further radium-223 dichloride (not permanently discontinued from treatment) at 24 weeks.

Change 2:

Synopsis - Study objectives and Section 2 Study objectives:

Exploratory objectives, 3rd bullet:

Added text:

- Time to increase in physical symptoms of disease based on the NCCN FACT-P Symptom Index-17 (NCCN-FACT FPSI-17) physical disease related symptoms (FPSI-DRS-P) subscale score measured up to Week 48 after the start of treatment

Synopsis - Methodology and Section 4.1 Design overview:

Paragraphs 8 and 9, new text

The NCCN-FACT FPSI-17 questionnaire will be completed by the patient in all treatment arms every clinic visit starting on Dose 1, Day 1 up to Week 48 visit. In treatment Arms A and B only the NCCN-FACT FPSI-17 questionnaire will also be completed on the day of each telephone contact at Weeks 28, 32, 40 and 44.

Both the pain assessment using the BPI-SF questionnaire and the NCCN-FACT FPSI-17 questionnaire will be self-administered by the patient using a handheld device.

Section 2 Study objectives:

Exploratory objectives, 3rd bullet:

Added text:

- Time to increase in physical symptoms of disease based on the NCCN FACT-P Symptom Index-17 physical disease related symptoms (FPSI-DRS-P) subscale score measured up to Week 48 after the start of treatment

Section 7.1.1 Tabular overview, Table 7-1 Schedule of procedures:

See **Change 26**

Section 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C), 3rd bullet;
Section 7.1.2.3 Doses 2 to 6 (Treatment Arms A and B), 2nd bullet;
Section 7.1.2.4 Doses 2 to 12 (Treatment Arm C), 2nd bullet;
Section 7.1.2.5 End of treatment visit, 2nd bullet; and
Section 7.1.2.6.1 Active follow-up with clinic visits, 6th paragraph, last bullet

Added text:

- NCCN-FACT FPSI-17 questionnaire, using a handheld device, is also self-administered at the beginning of the visit and should be checked for completion at the visit prior to treatment (see Section 14.8). ***In Section 7.1.2.6.1*** **only** - ***added text at end of previous sentence:*** (Treatment Arms A and B only)

Section 7.1.2.6.1 Active follow-up with clinic visits:

Paragraph 2, last sentence, new text:

Pain data, ... and NCCN-FACT FPSI-17 questionnaires will also be collected as detailed below.

Paragraph 3, 2nd bullet:

Added text:

- NCCN-FACT FPSI-17 questionnaire is also administered at the beginning of the visit and should be checked for completion at the visit prior to treatment (see Section 14.8). (Treatment Arms A and B only).

Section 7.3.1 Efficacy variables:

Paragraph 4, 5th bullet:

New text:

- Time to increase in physical symptoms of disease based on the NCCN-FACT FPSI-17 physical disease related symptoms (FPSI-DRS-P) subscale score measured up to 48 weeks after the start of treatment.

Section 7.3.5.2 Time to increase in physical symptoms of disease based on (FPSI-DRS-P):

New section:

Time to increase in physical symptoms of disease based on the NCCN-FACT FPSI-17 physical disease related symptoms (FPSI-DRS-P) subscale score measured up to Week 48 after start of treatment will be assessed using the NCCN-FACT FPSI-17 questionnaire (Section 14.8).

The NCCN-FACT FPSI-17 is a validated instrument that was developed to assess symptoms of prostate cancer, symptoms caused by the treatment of prostate cancer, and the health related quality of life of prostate cancer patients.(26) The instrument was developed in accordance with recent FDA guidance for the development of instruments for electronic patient-reported outcome (ePRO). The instrument contains

17 items, each of which utilizes a Likert scale with 5 possible responses. The ten items reflect disease related physical symptoms of disease and the responses on the items are be summed to calculate a disease related physical symptom subscale score. One item represents emotional symptoms of disease and the response to that item is used to calculate a disease related emotional symptom subscale score. Four items represent treatment related symptoms and the responses to these items are summed to calculate a treatment side effect subscale score. Finally, two items represent functional well-being and the responses to those items are summed to calculate a functional/well-being subscale score.

The NCCN-FACT FPSI-17 will be self-administered by the subject via an ePRO device.

For each applicable baseline, time to increase in physical symptoms of disease based on (FPSI-DRS-P) will be calculated with respect to that baseline, based only on assessments through Week 48. Details, including definition of an increase, will be provided in the SAP.

Section 12 Reference list:

New reference:

25. http://www.facit.org/FACITOrg/Questionaires.

Section 14.8 NCCN FACT-P Symptom Index (NCCN-FACT FPSI-17) Questionnaire:

New section which includes a copy of the NCCN-FACT FPSI-17.

Change 3:

Synopsis - Study objectives and Section 2 Study objectives:

Secondary objectives, 8th bullet:

New text:

- To evaluate change in analgesic use as measured by the Analgesic Quantification Algorithm (AQA)

Synopsis - Methodology:

Paragraph 10, new text:

The AQA score will be calculated programmatically from the assessments of analgesic use in the last 24 hours.

Synopsis - Primary / Secondary variables and Section 7.3.1 Efficacy variables:

Paragraph 3, 7th bullet:

New text:

- Change in analgesic use

Section 7.3.1 Efficacy variables:

Paragraph 4, 10th bullet:

Deleted text:

- ~~Analgesic use~~

Section 1.2 Study rationale:

Paragraph 4, last sentence:

Added text:

Additional secondary objectives include pain improvement rate and time to progression based on subjects' self-assessment of pain, change in analgesic use based on subjects' analgesic use in the last 24 hours as evaluated by the Analgesic Quantification Algorithm (AQA).

Section 4.1 Design overview:

Paragraph 11:

New text:

The AQA score will be calculated programmatically from the assessments of analgesic use in the last 24 hours (See Section 14.9).

Section 4.2 Primary and secondary variables:

Paragraph 3:

Old text:

Secondary efficacy variables will be OS, time to first SSE, rPFS, time to radiological progression, pain improvement rate, ~~and~~ time to pain progression.

New text:

Secondary efficacy variables will be OS, time to first SSE, rPFS, time to radiological progression, pain improvement rate, time to pain progression, and change in analgesic use.

Section 7.3.4.5 Change in the last 24-hour analgesic use score - new section:

New text:

Change in the last 24 hour analgesic use score is calculated based on the subject's analgesic use in the last 24 hours CRF data.

For each subject, each analgesic medication from analgesic use in the last 24 hour's data taken at applicable clinic visits (and in Arms A and B, at telephone contacts) will be coded using the WHO drug dictionary and OMEs will be calculated from the coded data.

For each subject and applicable visit or telephone contact, analgesic use in the last 24 hours will be scored using the AQA (see Section 14.9) based on the coded medications and corresponding OME quantities.

Details on coding and scoring will described in the SAP.

For each subject, for each applicable baseline and post-baseline time point, the subject's change in the last 24-hour analgesic use is defined as the difference between the subject's last 24 hour AQA score at the post-baseline time point and at the applicable baseline.

Section 7.3.5.5 Additional pain and health related quality of life endpoints:

Deleted text:

Subject-reported outcome data not described above, ~~analgesic use data,~~ palliative pain relief procedure data, additional BPI-SF data collected at clinic visits, and pain data collected following the Week 24 assessment, will be evaluated as described in the SAP.

Section 14.9 Analgesic Quantification Algorithm - new section:

New text:

Analgesic Quantification Algorithm Score Categories

0 No analgesic

1 Non-opioid analgesics

2 Weak opioids (i.e., meperidine, codeine, tramadol)

3 Strong opioids ≤75 mg OME/d

4 Strong opioids >75-150 mg OME/d

5 Strong opioids > 150-300 mg OME/d

6 Strong opioids > 300 mg-600 mg OME/d

7 Strong opioids > 600 mg OME/d

OME, oral morphine equivalents; d, day.

References for the AQA:

Chung K, Barlev A, Braun A, Qian Y, Zagari M. Development of the Analgesic Quantification Algorithm (AQA): a new scale to assess analgesic use. Poster presented at: Joint 15th Congress of the European Cancer Organization and 34th Congress of the European Society for Medical Oncology; September 20-24, 2009; Berlin, Germany.

Charles S. Cleeland PhD1,†,*, Jean-Jacques Body MD, PhD2, Alison Stopeck MD3, et al. (2013). Pain outcomes in patients with advanced breast cancer and bone metastases: Results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer, Volume 119, Issue 4, pages 832–838.

Change 4:

Synopsis - Study Objectives and Section 2 Study objectives:

Exploratory objectives, 2nd bullet

New text:

- To explore the impact of patient body size on the efficacy and safety of radium-223 dichloride

Section 7.2.4 Body size descriptors - new section:

New text:

Body size descriptors will be calculated from patient height and weight at the applicable baselines. Details will be described in the statistical analysis plan (SAP).

Section 8.4.3 Analysis of exploratory variables:

Paragraph 3, new text:

An exploratory analysis of the impact of baseline body size descriptors on the efficacy and safety of radium-223 dichloride will also be performed with respect to each applicable baseline. Details regarding the baseline body size descriptor definitions,

analysis specifications, and applicable baseline definitions will be provided in the SAP.

Change 5:

Synopsis - Diagnosis and main criteria for inclusion and Section 5.1.1 Inclusion criteria:

Main inclusion criteria, 3rd bullet:

New text:

- Subjects must be ≥ 18 years of age.

Change 6

Synopsis - Diagnosis and main criteria for inclusion and Section 5.1.1 Inclusion criteria:

Main criteria for inclusion, 9th bullet:

New text:

- Sexually active males agree to use condoms and/or their female partners of reproductive potential to use a method of effective birth control during treatment and for 6 months following the completion of treatment with radium-223 dichloride.

Change 7:

Synopsis - Methodology (paragraph 5) and Section 4.1 Design overview (paragraph 6):

Added text:

Radiological assessment, including whole body technetium-99 bone scan, MRI / CT scan of the abdomen and pelvis, and chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), will be performed at Week 8, Week 16, Week 24, then every 12 weeks for 2 years after the subject's last dose of radium-223 dichloride or until radiologic progression. If progression is detected by bone scan, a confirmatory bone scan is required at least 6 weeks later. Radiological assessments will continue .....

Section 7.1.1 Tabulated overview, Table 7-1 Schedule of procedures:

See **Change 26**

Section 7.1.2.3 Doses 2 to 6 (Treatment Arms A and B):

Paragraph 1, 18th bullet:

Old text:

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed ~~12~~ weeks after the start of treatment (i.e., ~~within 7 days prior to starting~~ Dose ~~4~~ and ~~documented at the visit~~)

New text:

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed at 8 weeks and 16 weeks after the start of treatment (i.e., on Dose 3 and Dose 5 visits)
    - Bone scans will be assessed by adapted PCWG2 criteria (30). Per adapted PCWG2 criteria, confirmation of bone progression by a 2nd scan ≥ 6 weeks later is required in all cases. A SPECT or MRI (with and without contrast media) should be obtained to clarify any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression. The patient should remain on study treatment in the interim unless the investigator determines that there is immediate need to initiate cytotoxic chemotherapy.

Section 7.1.2.4 Doses 2 to 12 (Treatment Arm C):

Paragraph 1, 18th bullet:

Old text:

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed ~~every 12~~ weeks ~~during~~ the treatment ~~period~~ (i.e., ~~within 7 days prior to starting~~ Dose ~~4~~, 7, and 10 and ~~documented at the visit~~)

New text:

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone

scan will be performed at 8 weeks, 16 weeks, 24 weeks, and 36 weeks after the start of treatment (i.e., on Dose 3, 5, 7 and 10 Visits).

- Bone scans will be assessed by adapted PCWG2 criteria (30). Per adapted PCWG2 criteria, confirmation of bone progression by a 2nd scan ≥ 6 weeks later is required in all cases. A SPECT or MRI (with and without contrast media) should be obtained to clarify any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression. The patient should remain on study treatment in the interim unless the investigator determines that there is immediate need to initiate cytotoxic chemotherapy.

Section 7.1.2.5 End of treatment visit:

Paragraph 1, 16th bullet:

Old text:

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone ~~within 7 days prior to~~ the EOT visit ~~and documented at the visit~~, if the last tumor evaluation is older than 4 weeks

New text:

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan on the EOT visit, if the last tumor evaluation is older than 4 weeks

    - Per adapted PCWG2 criteria, confirmation of bone progression by a 2nd scan ≥ 6 weeks later is required in all cases. A SPECT or MRI (with and without contrast media) should be obtained to clarify any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression.

Section 7.1.2.6.1 Active follow-up with clinic visits (paragraph 3, 15th bullet, 1st sub-bullet) and ***Section 7.1.2.7.1 End of active follow-up with clinic visits*** (paragraph 1, 11th bullet, 1st sub-bullet)***:***

Added text:

- Per adapted PCWG2 criteria (29), confirmation of bone progression by a 2nd scan ≥ 6 weeks later is required in all cases. A SPECT or MRI

(with and without contrast media) should be obtained to clarify any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression.

Section 7.3.4.3 Radiological progression endpoints:

Paragraph 1:

Old text:

Radiological progression is radiological progression of soft-tissue disease or radiological progression of bone disease, whichever occurs first. Assessment of radiological progression will be made ~~at the site level~~.

New text:

Radiological progression is radiological progression of soft-tissue disease or radiological progression of bone disease, whichever occurs first. Assessment of radiological progression will be made by independent central review.

Paragraph 2:

Added text:

Radiological progression of soft tissue disease is determined according to RECIST 1.1 based on MRI or CT scans (see Section 14.1). Radiological progression of osseous disease is determined according to adapted PCWG2 criteria based on whole body technetium-99 bone scans (30) (see Section 14.2). Radiological bone progression is determined if at least one of the following criteria is met:

- The first bone scan with ≥ 2 new lesions compared to baseline is observed < 12 weeks from randomization and is confirmed by a second bone scan taken ≥ 6 weeks later showing ≥ 2 additional new lesions (a total of ≥ 4 new lesions compared to baseline); or

- The first bone scan with ≥ 2 new lesions compared to baseline is observed ≥ 12 weeks from randomization and the new lesions are verified on the next bone scan ≥ 6 weeks later (a total of ≥ 2 new lesions compared to baseline).

Section 7.3.5.1.3 Bone scan time point response rate:

Paragraph 1, 2nd sentence:

Old text:

The bone scan time point response with respect to the baseline will be assessed as described in Section ~~14.5~~.

New text:

The bone scan time point response with respect to the baseline will be assessed as described in Section 14.3.

Section 12 Reference list:

Reference "29", added text:

29. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2012;368(2):138-48.

Section 14.2 Recommendations of the Prostate Cancer Clinical Trials Working Group for assessment of radiological progression

Table 14-4:

Old table:

Table 14-4 Radiological progression free survival definition per modified Response Evaluation Criteria in Solid Tumors, version 1.1, or progression by bone scan as adapted by Prostate Cancer Clinical Trials Working Group 2 criteria

Site	Criteria for radiological progression
Soft tissue	Soft tissue progression is determined by modified RECIST, version 1.1: • Only lymph nodes with short axis ≥ 2 cm can be selected as a target lesion
Bone	Progressive disease by bone scan ~~is defined as follows:~~ • ~~First scheduled assessment 12 weeks after the start of treatment with radium-223 dichloride~~ – ~~≥ 2 new bone lesions plus 2 additional at confirmation ("2 + 2") performed 6 or more weeks later~~ – ~~The date of progression is the date of the first scan that shows the change~~ • ~~Subsequent assessments > 12 weeks after start of treatment with radium-223 dichloride~~ – ~~≥ 2 new bone lesions~~

Abbreviations: RECIST = Response Evaluation Criteria in Solid Tumors

New table:

Table 14-4 Radiological progression free survival definition per modified Response Evaluation Criteria in Solid Tumors, version 1.1, or progression by bone scan as adapted by Prostate Cancer Clinical Trials Working Group 2 criteria

Site	Criteria for radiological progression
Soft tissue	Soft tissue progression is determined by modified RECIST, version 1.1: • Only lymph nodes with short axis ≥ 2 cm can be selected as a target lesion
Bone	Progressive disease by bone scan as adapted from PCWG2 Consensus Criteria:

- < 12 weeks after randomization: ≥ 2 new bone lesions plus 2 additional at confirmation ("2+2")
- ≥ 12 weeks after randomization: ≥ 2 new bone lesions with subsequent confirmation

If progression is detected by bone scan, a confirmatory bone scan is required at least 6 weeks later. A SPECT or MRI (with and without contrast media) should be obtained to confirm any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression.

Abbreviations: RECIST = Response Evaluation Criteria in Solid Tumors

14.5 Bone scan assessment tool

Deleted section.

Change 8:

Synopsis - Diagnosis and main criteria for inclusion and Section 5.1.2 Exclusion criteria:

Main criteria for exclusion, 6th bullet:

Deleted text:

- Treatment with an investigational drug within the 4 weeks prior to randomization~~, or planned treatment with an investigational drug during the treatment period or follow-up~~

Change 9:

Synopsis - Methodology:

Paragraph 6:

Old text:

Pain endpoints will be based on subject-reported outcome data. Pain will be assessed by means of selected questions from the ~~Brief Pain Inventory Short Form~~ (BPI-SF) daily for ~~the 7 days~~ immediately prior to ~~Dose 1, Day 1,~~ and then for Treatment Arms A and B, daily for 7 days prior to each scheduled dosing visit through Week 24 ~~and~~ for the 7 days prior to Weeks 36 and 48, ~~or~~ for Treatment Arm C, daily for 7 days prior to each scheduled dosing visit through Week 48. ~~Analgesic use will be collected and it will be assessed by the treating physician at each visit for all treatment arms from Dose 1, Day 1 until the Week 48 visit. Pain will also be assessed by means of the BPI SF questionnaire for all treatment arms at each clinic visit from Dose 1, Day 1 until the Week 48 visit.~~

New text:

Pain endpoints will be based on subject-reported outcome data. Pain data will be collected every 4 weeks through week 48 in all treatment arms using a handheld device. Pain will be assessed by means of selected questions from the BPI-SF daily for 4 days immediately prior to randomization, in order to stratify patients by worst pain score (WPS) ≤ 4 or > 4, and then as follows:

- for Treatment Arms A and B, daily for 7 days prior to each scheduled dosing visit from Dose 1, Day 1 through Week 24. During the Active Follow-up, pain data will be collected for the 7 days prior to Week 36 and 48 visits, and for 7 days prior to each telephone contact at Weeks 28, 32, 40 and 44.

- for Treatment Arm C, daily for 7 days prior to each scheduled dosing visit from Dose 1, Day 1 through Week 48.

Pain will also be assessed by means of the BPI-SF questionnaire every clinic visit from Dose 1, Day 1 visit until the Week 48 visit. In treatment Arms A and B only, the BPI-SF questionnaire will also be completed on the day of each telephone contact at Weeks 28, 32, 40 and 44.

Section 4.1 Design overview:

Paragraph 7

Old text:

Pain endpoints will be based on subject-reported outcome data. Pain will be assessed by means of selected questions from the BPI-SF daily for the 7 days immediately prior to Dose 1, Day 1, and then for Treatment Arms A and B, daily for 7 days prior to each scheduled dosing visit through Week 24 ~~and~~ for the 7 days prior to Weeks 36 and 48, ~~and for~~ Treatment Arm C, daily for 7 days prior to each scheduled dosing visit through Week 48. ~~Analgesic use will be collected and it will be assessed by the treating physician at each visit for all treatment arms from Dose 1, Day 1 until the Week 48 visit.~~ Pain will also be assessed by means of the BPI SF questionnaire for all treatment arms at each clinic visit from Dose 1, Day 1 until the Week 48 visit.

New text:

Pain endpoints will be based on subject-reported outcome data. Pain will be assessed by means of selected questions from the BPI-SF daily for 4 days immediately prior to randomization, in order to stratify patients by worst pain score (WPS) ≤ 4 or > 4, for the 7 days immediately prior to Dose 1, Day 1, and then for Treatment Arms A and B, daily for 7 days prior to each scheduled dosing visit through Week 24, for the 7 days prior to Weeks 36 and 48 visits and for 7 days prior to each telephone contact at Weeks 28, 32, 40 and 44. For Treatment

Arm C, pain data will be collected daily for 7 days prior to each scheduled dosing visit through Week 48. Pain will also be assessed by means of the BPI-SF questionnaire for all treatment arms at each clinic visit from Dose 1, Day 1 until the Week 48 visit and for treatment Arms A and B on the day of each telephone contact at Weeks 28, 32, 40 and 44.

Synopsis - Methodology and Section 4.1 Design overview:

Paragraph 10, new text:

Analgesic use will be collected throughout the study. In addition analgesic use over the 24-hour period prior to the day of the visit will be collected by the study investigator at each visit for all treatment arms from Dose 1, Day 1 until the Week 48 visit, and analgesic use over the 24-hour period prior to each telephone contact (in Arms A or B) will be collected by the study investigator at the telephone contact at Weeks 28, 32, 40 and 44.

Section 7.1.1 Tabulated overview, Table 7-1:

See **Change 26**.

Section 7.1.2.1 Screening period:

Paragraph 2, 19th bullet, new text:

- When a subject is determined to be eligible, the subject will be trained on daily Patient-reported outcome (PRO) pain data collection using a handheld device. Eligible subjects will then complete the pain assessment daily
    - for the 4 days immediately prior to randomization. The average of the daily WPS over the 4-day period will be used for stratification (WPS ≤4 versus WPS >4). 4 days of daily WPS data must be taken before randomization can occur.
    - for the 7 days prior to Dose 1, Day 1.

Section 7.1.2.5 End of treatment visit:

Paragraph 1, 17th bullet:

Old text:

- After the visit, subjects will complete the pain assessment daily for the 7 days prior to the Week ~~36~~ (Treatment Arm A and B only).

New text:

- After the visit, subjects will complete the pain assessment daily for the 7 days prior to the Week 28 telephone contact (Treatment Arms A and B only).

Section 7.1.2.6.1 Active follow-up with clinic visits:

Paragraph 2, new text:

In addition to the visits at Weeks 36 and 48 the subjects in Treatment Arms A and B will receive telephone contacts at Weeks 28, 32, 40, and 44 to assess for possible SSE risks and will continue PRO data collection. Pain data, 24-hour analgesic use, BPI and NCCN-FACT FPSI-17 questionnaires will also be collected as detailed below.

Paragraph 3, 16th bullet:

Old text:

- After the Week 36 visit, subjects will complete the pain assessment ~~using~~ daily for the 7 days prior to the Week ~~48 visit~~.

New text:

- After the Week 36 visit, subjects will complete the pain assessment daily for the 7 days prior to the Week 40 telephone contact.

Paragraphs 4 to 6:

Added text:

Telephone contact for SSE risks and PRO pain and analgesic use data collection at Weeks 28 (±7 days), 32 (±7 days), 40 (±7 days), and 44 (±7 days), subjects in Treatment Arms A and B only.

The subjects will receive telephone contacts at Weeks 28, 32, 40, and 44 assessing for possible SSE risks. Subjects exhibiting symptoms indicative of possible SSEs will be encouraged to visit the clinic early to assess SSE status. Symptomatic skeletal events will not be determined over the phone.

In the intervals between the visits, the subjects will continue to be followed for PRO pain data collection and analgesic use data collection as follows:

- Pain will be assessed daily for 7 days prior to each telephone contact at Weeks 28, 32, 40 and 44 and the daily PRO pain input data will be reviewed for completeness at the telephone contact.

- 24-hour analgesic use will be collected by the study investigator at each telephone contact at Weeks 28, 32, 40 and 44.

- The BPI-SF questionnaire will be completed on the day of each telephone contact (should be completed prior to the contact and should be checked for completion at the contact; see Section 14.7

- NCCN-FACT FPSI-17 questionnaire will be completed on the day of each telephone contact (should be completed prior to the contact and should be checked for completion at the telephone contact; (see Section 14.8).

Section 14.7 Brief Pain Inventory-Short Form:

Paragraph 3:

Old text:

Assessment of the worst pain score (WPS) via Question 3, ~~of~~ average pain score via Question 5~~, and pain interference with general activity score via Question 9A~~ on the BPI-SF will occur daily for 7 days prior to each scheduled visit from the Dose 1, Day 1 visit through the Week 48 visit. The data will be collected and checked for completeness at each visit.

New text:

Assessment of the worst pain score (WPS) via Question 3 and average pain score via Question 5 on the BPI-SF will occur daily for 4 days immediately prior to randomization and for 7 days prior to each scheduled visit from the Dose 1, Day 1 visit through the Week 48 visit. The data will be collected and checked for completeness at each visit. In Treatment Arms A and B only, pain will also be assessed daily for 7 days prior to each telephone contact at Weeks 28, 32, 40 and 44 and the daily PRO pain input data will be reviewed for completeness at the telephone contact.

Paragraph 5

Added text:

The BPI-SF will be self-administered by the subject at Dose 1, Day 1 (before the start of study treatment) through the Week 48 visit. In Treatment Arms A and B only the BPI-SF questionnaire will also be completed on the day of each telephone contact at Weeks 28, 32, 40 and 44 and checked for completion at the telephone contact.

Paragraph 9:

Old text:

"Your doctor would like to better understand how you feel, how well you are able to do your usual activities, and how you rate your health. To help us better

understand these things about you, we will ask you to answer ~~3~~ questions related to the worst pain in the last 24 hours, the average level of pain, and how pain ~~interferes with your activities~~ for 7 days prior to each scheduled treatment visit and at the end of treatment visit. We will ask you to complete this questionnaire about your health at each of these visits.

New text:

"Your doctor would like to better understand how you feel, how well you are able to do your usual activities, and how you rate your health. To help us better understand these things about you, we will ask you to answer 2 questions related to the worst pain in the last 24 hours and the average level of pain, for 7 days prior to each scheduled treatment visit and at the end of treatment visit. We will ask you to complete this questionnaire about your health at each of these visits. Depending on which treatment you are assigned, you may also be requested to answer these 2 questions during the first 6 months of the follow-up period, for 7 days prior to the visits or telephone contacts and to complete the BPI-SF questionnaire on the day of the visits or on the day of the telephone contacts.

Paragraph 12:

Old text:

At the beginning of each visit, please check that the subject has answered the questions related to the WPS, the average pain score, ~~and pain interference with general activity score~~ in the 7 days prior to the visit. Thank the subject once you have reviewed the responses.

New text:

At the beginning of each visit or at each telephone contact (Treatment Arms A and B only), please check that the subject has answered the questions related to the WPS and the average pain score, in the 7 days prior to the visit. Thank the subject once you have reviewed the responses.

Change 10:

Synopsis - Plan for statistical analysis (paragraph 3); and
Section 8.4.1 Primary efficacy analysis (paragraph 2):

Old text:

Both comparisons will be performed at the time of final analysis, after the latest of (1) approximately 135 SSE-FS events in subjects included in Comparison 1 as defined below; (2) approximately 75 SSE-FS events following Week 24 in subjects included in Comparison 2 as defined below, and (3) the last subject has been followed for ~~2 years~~ from last treatment.

New text:

Both comparisons will be performed at the time of final analysis, after the latest of (1) approximately 135 SSE-FS events in subjects included in Comparison 1 as defined below; (2) approximately 75 SSE-FS events following Week 24 in subjects included in Comparison 2 as defined below, and (3) the last subject has been followed for 30 days from last treatment. In the event the applicable number of events is not reached, the primary endpoint analysis will mature 7 years after the last subject has received last treatment.

Section 4.4 End of study:

Paragraph 2:

Old text:

The primary endpoint cut-off will be reached at the later of 1) 135 SSE-FS events in subjects included in Comparison 1 as defined in Section 8.4 below, and 2) 75 SSE-FS events following Week 24 in subjects included in Comparison 2 as defined in Section 8.4 below, and 3) the last subject has been followed for ~~2 years~~ from last treatment.

New text:

The primary endpoint cut-off will be reached at the later of 1) 135 SSE-FS events in subjects included in Comparison 1 as defined in Section 8.4 below, and 2) 75 SSE-FS events following Week 24 in subjects included in Comparison 2 as defined in Section 8.4 below, and 3) the last subject has been followed for 30 days from last treatment. In the event the applicable number of events is not reached, the primary endpoint analysis will mature 7 years after the last subject has received last treatment.

Section 8.6 Determination of Sample Size:

Paragraphs 2 to 4:

Old text:

The sample .....randomized. The primary endpoint cut-off, as defined in Section 8.4, is estimated to be reached in an average of ~~55~~ months.

Comparison 1 will analyze SSE-FS..... regimen. Simulations indicated an average of ~~197.9~~ events would occur for this comparison at primary endpoint cut-off, and a 1-sided log-rank test with 0.10 significance gave approximately ~~92~~% power to test H01 versus HA1.

Comparison 2 will analyze SSE-FS .....
.....eligible for inclusion at 24 weeks. An average of ~~80.6~~ simulated events occurred for this comparison, and a 1-sided log-rank test with 0.10 significance gave approximately ~~84~~% power to test H02 versus HA2.

New text:

The sample .....randomized. The primary endpoint cut-off, as defined in Section 8.4, is estimated to be reached in an average of 39 months.

Comparison 1 will analyze SSE-FS.....
.regimen. Simulations indicated an average of 186.6 events would occur for this comparison at primary endpoint cut-off, and a 1-sided log-rank test with 0.10 significance gave approximately 90.5% power to test H01 versus HA1.

Comparison 2 will analyze SSE-FS .....
.....eligible for inclusion at 24 weeks. An average of 74.9 simulated events occurred for this comparison, and a 1-sided log-rank test with 0.10 significance gave approximately 80.6% power to test H02 versus HA2.

Change 11:

Synopsis - Methodology (paragraph 2)***;***
Section 4.1 Design overview (paragraph 2)***;***
Section 6.1 Treatments to be administered (paragraph 2)***;***
Section 6.3 Treatment assignment (paragraph 3)**;**
Section 7.1.1 Tabulated overview, Table 7-1 (footnote "l")**;** and
Section 7.1.2.1 Screening period (paragraph 4, 2nd sentence)***:***

Added text:

The randomization will be permuted-block, stratified by use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total ALP (< 220 U/L versus ≥ 220 U/L), and by average worst pain score (WPS) of the Brief Pain Inventory Short Form (BPI-SF) (WPS ≤4 versus WPS >4).

Section 7.1.2.1 Screening period

Paragraph 2, 19th bullet:

Added text:

- When a subject is determined to be eligible, the subject will be trained on daily Patient-reported outcome (PRO) pain data collection using a handheld device. Eligible subjects will then complete the pain assessment daily

- for the 4 days immediately prior to randomization. The average of the daily WPS over the 4-day period will be used for stratification (WPS ≤4 versus WPS >4); 4 days of daily WPS data must be taken before randomization can occur.

- for the 7 days prior to Dose 1, Day 1.

Paragraph 4, 2nd sentence:

Old text:

The randomization will be permuted-block, stratified by the use of prior chemotherapy (≤ 1 regimen versus > 1 regimen~~) and~~ by total ALP (< ~~200~~ U/L versus ≥ 220 U/L~~)~~.

New text:

The randomization will be permuted-block, stratified by the use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total ALP (< 220 U/L versus ≥ 220 U/L), and by the average of the daily WPS of the screening BPI-SF (WPS ≤4 versus WPS >4).

Section 8.1 General considerations

Paragraph 2, 3rd bullet:

New text:

- Average WPS of the BPI-SF (WPS ≤4 versus WPS >4)

Change 12:

Synopsis - Methodology (paragraph 13) and ***Section 4.1 Design overview*** (paragraph 11):

Old text:

~~All safety data will be collected beyond~~ the EOT visit, ~~and~~ subjects will come to the clinic for safety and ~~SSE~~ evaluations every 12 weeks for 2 years ~~of~~ active follow-up. ~~Every~~ effort will be made to follow subjects through clinic visits; however, phone contact will be undertaken for subjects unable to come to the clinic. ~~The active follow-up period will continue for 2 years after the subject's last dose of radium-223 dichloride or until the primary efficacy analysis matures, whichever occurs last~~.

New text:

> Following the EOT visit, subjects will enter the active follow-up period and will come to the clinic for selected safety and efficacy evaluations every 12 weeks for at least 2 years following last study treatment. Subjects not experiencing an SSE by 2 years following last study treatment will continue active follow-up until the subject experiences an SSE or the primary endpoint matures, whichever occurs first. During active follow-up, every effort will be made to follow subjects through clinic visits; however, phone contacts will be undertaken for subjects unable to come to the clinic.

Synopsis - Methodology (paragraph 14) and ***Section 4.1 Design overview*** (paragraph 13):

Old text:

> After the ~~2 years of~~ active follow-up, subjects will enter the extended follow-up period and will be followed via telephone follow-up at 6-month intervals for investigator-reported, radium-223 dichloride-related SAEs, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies, and survival up to 7 years after the last dose of radium-223 dichloride or until death. Once a separate extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical trials, has been implemented, the study subjects surviving after the end of the ~~2 years of~~ active follow-up will be transitioned to this separate extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned.

New text:

> After the active follow-up, subjects will enter the long-term follow-up period and will be followed via telephone follow-up at 6-month intervals for investigator-reported, radium-223 dichloride-related SAEs, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies, and survival up to 7 years after the last dose of radium-223 dichloride or until death. Once a separate extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical trials, has been implemented, the study subjects surviving after the end of the active follow-up will be transitioned to this separate extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned.

Section 6.8 Post-study therapy:

Old text:

> Subjects will have an EOT visit 30 (± 7) days following the last dose of study drug, including early discontinuation of study drug, and will be followed every 12 weeks for safety and SSE evaluations. Every effort will be made to follow subjects through clinic visits; however, phone contact will be undertaken for subjects unable to come to

the clinic. The active ~~safety~~ follow-up period will continue for 2 years after the subject's last dose of radium-223 dichloride or until the primary efficacy analysis matures, whichever occurs last. After the ~~2 years of~~ active follow-up, subjects will enter the ~~extended active~~ follow-up period and will be followed via telephone follow-up at 6-month intervals for investigator-reported, radium-223 dichloride-related SAEs, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies, and survival up to 7 years after the last dose of radium-223 dichloride or until death. Once a separate extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical trials, has been implemented, the study subjects surviving after the end of the ~~2 years of~~ active follow-up will be transitioned to this separate extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned.

New text:

Subjects will have an EOT visit 30 (± 7) days following the last dose of study drug, including early discontinuation of study drug, and will be followed every 12 weeks for safety and SSE evaluations. Every effort will be made to follow subjects through clinic visits; however, phone contact will be undertaken for subjects unable to come to the clinic. The active follow-up period will continue for 2 years after the subject's last dose of radium-223 dichloride or until the primary efficacy analysis matures, whichever occurs last. After the active follow-up, subjects will enter the long term follow-up period and will be followed via telephone follow-up at 6-month intervals for investigator-reported, radium-223 dichloride-related SAEs, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies, and survival up to 7 years after the last dose of radium-223 dichloride or until death. Once a separate extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical trials, has been implemented, the study subjects surviving after the end of the active follow-up will be transitioned to this separate extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned.

Section 7.1.2.6 Active follow-up:

Paragraph 1, last sentence:

Added text:

<u>However, in the event an SSE is identified at an unscheduled clinic visit in an active follow-up subject, an unscheduled-visit SSE should be recorded regardless of whether the subject is receiving clinic visits or telephone-only follow-up.</u>

Section 7.1.2.6.1 Active follow-up with clinic visits:

Paragraph 1:

Old text:

The subject should return to the clinic every 12 weeks (± 14 days) following the EOT visit ~~for 2 years following the last study treatment~~ or until the primary efficacy analysis matures, whichever ~~comes last, preferably in the morning. Active follow-up may continue past 2~~ years ~~if the subject has not had a SSE and the required number of events has not taken place~~.

New text:

The subject should return to the clinic every 12 weeks (± 14 days) following the EOT visit until the subject experiences a symptomatic skeletal event or until the primary efficacy analysis matures, whichever occurs first; provided that active follow-up will not last less than 2 years or more than 7 years following the subject's last study treatment.

Section 7.1.2.6.2 Active follow-up without scheduled clinic visits:

Paragraph 1, 2nd sentence:

Old text:

Subjects will be contacted by telephone every 12 weeks (± 14 days) for 2 years following the last study treatment ~~or until death, whichever comes last,~~ to determine the following:

New text:

Subjects who cannot travel to the clinic will be contacted by telephone every 12 weeks (± 14 days) for 2 years following the last study treatment to determine the following:

Section 7.1.2.7.1 End of active follow-up with clinic visits:

Paragraph 1:

Deleted text:

~~The active follow-up period will continue for 2 years after the subject's last dose of radium 223 dichloride or until the primary efficacy analysis matures, whichever occurs last.~~ The subject should return to the clinic for the end of follow-up with clinic visits, preferably in the morning, and the following assessments will be performed:

Section 7.1.2.7.2 End of active follow-up without scheduled clinic visits:

Paragraph 1:

Old text:

The active follow-up period will continue for 2 years after the subject's last dose of radium-223 dichloride ~~or until death, whichever occurs last~~. The end of active follow-up procedures for subjects who are in the active follow-up period without clinic visits will include the following:

New text:

The active follow-up period <u>without clinic visits</u> will continue for 2 years after the subject's last dose of radium-223 dichloride. The end of active follow-up procedures for subjects who are in the active follow-up period without clinic visits will include the following:

Change 13:

Synopsis - Methodology:

Paragraph 12, 1st sentence:

Old text:

A~~n independent Data Monitoring~~ Committee will conduct safety reviews at regular intervals.

New text:

A <u>Joint Safety Review Committee</u> will conduct safety reviews at regular intervals.

Section 3 Investigators and other study personnel:

Last paragraph:

Old text:

~~**Independent Data Monitoring Committee**~~

~~An independent DMC will conduct safety reviews at regular intervals. There is no formal interim analysis planned. The main objective of these safety reviews is to ensure subject safety and to identify whether any protocol modifications are needed.~~

New text:

Joint Safety Review Committee

A Joint Safety Review Committee (JSRC), which may contain sponsor, investigator, and/or independent members, will conduct safety reviews at regular intervals. There is no formal interim analysis planned. The objective of these safety reviews is to ensure subject safety and to identify whether any protocol modifications are needed. The JSRC will not evaluate efficacy. Details on the JSRC and its safety review monitoring will be described in a separate JSRC charter.

Section 4.3 Interim Analyses and Joint Safety Review Committee (new section):

New text:

4.3 Interim Analyses and Joint Safety Review Committee

No formal interim analysis is planned. A JSRC, which may contain sponsor, investigator, and/or independent members, will conduct safety reviews at regular intervals. The objective of these safety reviews is to ensure subject safety and to identify whether any protocol modifications are needed. The JSRC will not evaluate efficacy. Details on the JSRC and its safety review monitoring will be described in a separate JSRC charter.

Section 8.4.4 Safety Analysis:

Paragraph 1:

Old text:

No formal interim analysis for safety is planned. A~~n independent DMC~~ will review the safety data periodically. Details on the ~~DMC~~ are described in Section 3.

New text:

No formal interim analysis for safety is planned. A JSRC will review the safety data periodically. Details on the JSRC are described in Section 3.

Change 14:

Section 6.4.4 Dose preparation:

Paragraph 2, new text:

A radio pharmacy will prepare a patient ready dose for dispensing to the patient. In the US, Cardinal Health is the radio pharmacy that will dispense the patient ready dose.

Change 15:

Section 7.1.1 Tabular overview, Table 7-1 Schedule of procedures:

See **Change 26**.

Section 7.1.2.1 Screening period:

Paragraph 3:

Old text:

The IVRS / IWRS will be used to register ~~subject~~ eligibility ~~and request~~ /~~ confirm~~ study drug doses. Once the subject eligibility is approved and registered in the IVRS / IWRS, the initial shipment ~~will~~ be triggered. The order date for the next dose ~~cannot be earlier~~ than the pre-defined ~~country~~ lead time.

New text:

The IVRS / IWRS will be used to register requests for eligibility / study drug doses. Once the subject eligibility is approved and registered in the IVRS / IWRS, including entry of required demographic and stratification information, the initial drug shipment may be prepared. Additional IxRS transactions for dose orders may be required; follow the country-specific guidance in the manual. The latest order date for the next dose is no later than the pre-defined lead time (number of days from order received to delivery to site in the country) prior to the planned dosing date. The planned date for the next dose must be specified, when the dose is requested in the IVRS / IWRS. At Doses 1 through 5, the site should order the next dose in the IVRS / IWRS, as soon as the current visit's dose is registered in the IVRS / IWRS. The latest order date for the next dose is no later than the pre-defined lead time (number of days from order received to delivery to site in the country) prior to the planned dosing date. The planned date for the next dose must be specified, when the dose is requested in the IVRS / IWRS. For subject visit registrations in the IVRS / IWRS, see the IVRS / IWRS manual.

Change 16:

Section 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C):

Moved text and revised:

Old text (paragraph 1, 4th bullet, sub-bullet):

- ~~Hematology results should be reviewed and it should be confirmed that the values are still within the treatment ranges (ANC ≥ 1.5 x 109/L, platelet count ≥ 100 x 109/L, and hemoglobin ≥ 9.0 g/dL).~~

New text (paragraph 1, 1st bullet):

- Reconfirmation of eligibility: hematology results obtained within 72 hours of Dose 1, Day 1 should be reviewed and it should be confirmed that the values are still within the treatment ranges (absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 9.0 g/dL).

Change 17:

Section 5.2.1 Withdrawal:

Paragraph 1, 6th bullet:

Old text:

- If the subject experiences Grade 3 ~~or 4~~ neutropenia or thrombocytopenia lasting > 2 weeks despite adequate treatment. Blood transfusions and biologic response modifiers, such as GM-CSF or G-CSF can be used for the treatment of hematological abnormalities during the treatment period

New text:

- If the subject experiences Grade 3 neutropenia or Grades 3 or 4 thrombocytopenia lasting > 2 weeks or Grade 4 neutropenia lasting >7 days despite adequate treatment. Blood transfusions and biologic response modifiers, such as GM-CSF or G-CSF can be used for the treatment of hematological abnormalities during the treatment period

Section 6.4.7 Dose delays:

Myelosuppression, 2nd bullet (new 3rd bullet):

Old text:

- If a subject experiences sustained CTCAE Grade 3 ~~or 4~~ neutropenia or thrombocytopenia (see Table 6-1) lasting > 2 weeks despite adequate treatment, the subject must be discontinued from treatment with radium-223 dichloride.

New text:

- If a subject experiences sustained CTCAE Grade 3 neutropenia or sustained CTCAE Grades 3 or 4 thrombocytopenia (see Table 6-1) lasting > 2 weeks despite adequate treatment, the subject must be discontinued from treatment with radium-223 dichloride.

- If a subject experiences sustained CTCAE Grade 4 neutropenia (see Table 6-1) lasting > 1 week despite adequate treatment, the subject must be discontinued from treatment with radium-223 dichloride.

Change 18:

Section 7.3.4.4 Pain endpoints:

Old text:

The ~~worst pain score (~~WPS~~)~~ is defined for each subject at baseline and at each applicable 4-week assessment date, as the mean of the "worst pain score" values in the last 24 hours from the preceding 7 days before each ~~scheduled~~ visit per the BPI-SF recorded in the subject's reported outcome pain data.

~~Secondary~~ pain endpoints are defined with respect ~~to the screening period~~ baseline ~~with randomization date as~~ start date, ~~and are~~ based on data collected as of the Week 24 assessment.

Additional details on pain endpoints, including ~~analgesic use~~ details, will be provided in the SAP.

New text:

The WPS is defined for each subject at baseline and at each applicable 4-week assessment date, as the mean of the "worst pain score" values in the last 24 hours from the preceding 7 days before each applicable visit or telephone contact per the BPI-SF recorded in the subject's reported outcome pain data.

Pain endpoints are defined with respect to each applicable baseline and start date.

The screening baseline for pain endpoints will be based on the pre-Dose 1, 7-day pain assessment.

For purposes of determining pain improvement and pain progression, a daily analgesic use score will be calculated programmatically for each subject for each day, based on the subject's complete CRF data on analgesic use. Analgesic use data will be coded using the WHO drug dictionary. Oral morphine equivalents will be calculated. Each day's analgesic use in OME units will be calculated using the applicable CRF-reported dates and date ranges. The AQA will be applied to obtain a daily analgesic use score. Details will be described in the SAP.

Additional details on pain endpoints, including details on the applicable baselines, evaluability for daily analgesic use increase, calculation of daily analgesic use score(s) applicable to each baseline and post-baseline time point, and definition of baseline values and "increase" in daily analgesic use for purposes of these endpoints, will be provided in the SAP.

Section 7.3.4.4.1 Pain improvement rate:

Added text:

Pain improvement is defined for each baseline in subjects evaluable for pain improvement at that baseline, i.e., subjects entering the study with a WPS of at least 4 and evaluable for analgesic use increase at the respective baseline assessment. Pain improvement with respect to each baseline is defined in each applicable evaluable subject at each applicable post-baseline assessment time point as a 30% and 2-point decrease in WPS over 2 consecutive measurements conducted at least 4 weeks apart, without an increase in analgesic use.

Pain improvement rate is defined for each baseline and applicable post-baseline assessment time point as the number of subjects with pain improvement at the time point, divided by the total number of subjects evaluable for pain improvement with respect to the applicable baseline.

Section 7.3.4.4.2 Time to pain progression:

Old text:

Pain progression is defined in subjects evaluable for pain progression, i.e., subjects ~~entering the study~~ with a WPS of at most 7. A pain progression event consists of an increase of ≥ 30% and 2 points in WPS over 2 consecutive measurements conducted at least 4 weeks apart, without a decrease in analgesic use, ~~based on the included assessments~~.

The time to pain progression is defined as the time (in days) from ~~randomization date~~ until occurrence of the first pain progression event. Subjects without pain progression as of the last ~~included~~ ~~pain~~ assessment, ~~whether or not surviving,~~ will be censored at the ~~last included pain assessment~~.

New text:

Pain progression is defined for each baseline in subjects evaluable for pain progression at the applicable baseline, i.e., subjects with a WPS of ≤ 7 at the respective baseline assessment. Pain assessments will occur daily for one week, beginning a week prior to each visit and including the day of the visit. An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 daily questions. Pain progression is defined as the occurrence of either a pain increase or an increase in pain management with respect to the applicable baseline, whichever occurs first.

A pain increase is defined as follows:

- For asymptomatic patients (WPS 0 to < 1 at baseline), pain increase is defined as an increase of 2 or more points in the average (i.e., average of 7-day assessments) "worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart

- For mildly symptomatic patients (WPS 1-3 at baseline), pain increase is defined as an increase of 2 or more points in the average (i.e., average of 7-day assessments) "worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart and an average worst pain score of ≥ 4"

- For symptomatic patients with WPS > 3 and ≤ 7 at baseline), pain increase is defined as an increase of 2 or more points in the average (i.e., average of 7-day assessments) "worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart.

An increase in pain management is defined as follows:

For patients not on opioids at the applicable baseline, initiation of short or long-acting opioid use for pain will constitute an increase in pain management. For patients being treated with ≤ 600 OME (oral morphine equivalents) of opioids at the applicable baseline, an increase by 1 point in the daily AQA score and increase ≥ 50% in daily OMEs will constitute an increase in pain management. For patients being treated at the highest AQA level (> 600 OME/day) at the applicable baseline, an increase ≥ 50% in daily OMEs from that baseline will constitute an increase in pain management.

The time to pain progression is defined for each applicable baseline for applicable subjects as the time (in days) from the respective baseline until occurrence of the first post-baseline pain progression event. Subjects without pain progression as of the last

applicable post-baseline assessment, whether or not surviving, will be censored at the last applicable post-baseline assessment. Subjects with insufficient applicable baseline assessment(s) or without adequate post-baseline assessment(s) will be censored at the applicable baseline date. Additional censoring and other details will be described in the SAP.

Change 19:

Section 8.4.4 Safety analysis:

Paragraph 5

Old text:

1. Treatment-emergent safety events

   ~~This analysis will be performed for safety events observed through the end of treatment visit. For this analysis, subjects will be grouped by treatment arm as treated.~~

3. Safety events emerging following the standard-regimen treatment period

   This analysis will be performed in each treatment arm for events following the later of 24 weeks from treatment start or 30 days following completion of 6 doses of radium-223 dichloride treatment. It will be performed for selected safety endpoints collected during active ~~safety~~ follow-up after end of treatment. This analysis will be performed by treatment group as treated.

New text:

1. Treatment-emergent safety events

   The treatment period for this study extends from the initiation of treatment until 30 days after the last administration of radium-223 dichloride. Events starting or worsening within the treatment period will be considered treatment-emergent.

   For the analysis of treatment-emergent safety events, subjects will be grouped by treatment arm as treated.

3. Safety events emerging following the standard-regimen treatment period

   This analysis will be performed in each treatment arm for events following the later of 24 weeks from treatment start or 30 days following completion of 6 doses of radium-223 dichloride treatment. It will be performed for selected safety endpoints collected during active follow-up after end of treatment

through primary endpoint completion. This analysis will be performed by treatment group as treated.

4. Safety events emerging during long-term follow-up following primary endpoint completion

   Safety events emerging following primary endpoint completion and any events emerging during long-term follow-up, will be reported in a separate document(s) from the study Clinical Study Report.

Change 20:

Added that IVRS / IWRS procedures can be found in the IVRS / IWRS manual.

Section 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C):

Last paragraph, 2nd sentence:

Added text:

The order date for the next dose cannot be earlier than the pre-defined country lead time, see IVRS / IWRS manual.

Change 21:

Changed the terminology for "active safety follow-up" period to "active follow-up" period since efficacy assessments are also included in these visits. In addition, the terminology for "extended active follow-up" period was changed to "long-term follow-up" period; this change was done to ensure the use of a consistent term across the radium-223 program.

- Synopsis - Methodology
- Section 4.1 Design overview
- Section 6.8 Post-study therapy
- Section 7.1.1 Tabulated overview, Table 7-1 Schedule of procedures
- Section 7.1.2.6 Active follow-up
- Section 7.1.2.7.1 End of active follow-up with clinic visits
- Section 7.1.2.7.2 End of active follow-up without scheduled clinic visits
- Section 7.1.2.8 Long-term follow-up to 7 years following last dose
- Section 7.1.2.8.1 Long-term follow-up (via telephone follow-up)

- Section 7.1.2.8.2 End of long-term follow-up
- Section 8.4.4 Safety analysis

Change 22:

Section 7.3.2 Definition of efficacy variables:

3rd sentence:

New text:

Details on definitions of starting points and baselines will be provided in the SAP or in the imaging charter or other central reviewer documentation.

Section 7.3.4.3 Radiological progression endpoints:

1st paragraph, 2nd sentence:

Old text:

Assessment of radiological progression will be made ~~at the site level~~.

New text:

Assessment of radiological progression will be made by independent central review.

3rd paragraph:

New text:

The central reviewer will determine the applicable baseline values for and assess radiological progression with respect to each applicable baseline.

4th paragraph:

Added text:

Further details will be defined in the imaging charter and / or related central review documentation, and / or the SAP.

Section 7.3.5.1 Quantitated bone scan endpoints:

Added text:

Further details will be defined in the imaging charter and / or related central review documentation, and / or the SAP.

Change 23:

Section 7.1.1 Tabulated overview, Table 7-1 Schedule of procedures:

See **Change 26**.

Section 7.1.2.1 Screening period (paragraph 2, 8th bullet, 2nd sub-bullet);
Section 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C) (paragraph 1, 6th bullet, 2nd sub-bullet):
Section 7.1.2.3 Doses 2 to 6 (Treatment Arms A and B) (paragraph 1, 4th bullet, 2nd sub-bullet);
Section 7.1.2.4 Doses 2 to 12 (Treatment Arm C (paragraph 1, 4th bullet, 2nd sub-bullet)***;***
Section 7.1.2.5 End of treatment visit (paragraph 1, 4th bullet, 2nd sub-bullet)***;***
Section 7.1.2.6.1 Active follow-up with clinic visits (paragraph 3, 4th bullet, 2nd sub-bullet)***;***
Section 7.1.2.7.1 End of active follow-up with clinic visits (paragraph 1, 2nd bullet, 2nd sub-bullet)
Section 7.5 Safety (paragraph 1, 2nd bullet, 2nd sub-bullet)***;*** and
Section 7.5.3.1 Laboratory evaluations (paragraph 1, 2nd bullet)***:***

Added text:

- Chemistry panel, including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, <u>total</u> bilirubin……..

Change 24:

Synopsis - Diagnosis and main criteria for inclusion (paragraph 2) ***and***
Section 5.1.1 inclusion criteria (paragraph 1)***:***

4th bullet:

Old text:

- Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2. In case of ECOG PS 2, the PS ~~has to~~ be due to metastatic prostate cancer to the bone.

New text:

- Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2. In case of ECOG PS 2, the PS <u>must</u> be due to metastatic prostate cancer to the bone.

7th bullet, "d":

Added text:

d. Total bilirubin level ≤ 1.5 x institutional upper limit of normal (ULN) (< 3 x ULN for subjects with documented Gilbert's syndrome)

Synopsis - Plan for statistical analysis:

Last paragraph:

Old text:

The following secondary efficacy time-to-event endpoints will have hypothesis testing performed to ~~compare~~ the ~~treatment groups~~: OS, time to first SSE, time to radiological progression, and rPFS. Other endpoints, including safety and tolerability variables, will be analyzed descriptively for each treatment group.

New text:

Comparison 2 will be performed using a log-rank test with a 1-sided alpha of 0.1 stratified by the randomization factors (previous chemotherapy [≤ 1 regimen versus > 1 regimen] and total ALP [< 220 U/L versus ≥ 220 U/L]). The extended dosing regimen will be declared superior to the standard dosing regimen if the 1-sided p-value from the stratified log rank test is less than 0.1.

The following secondary efficacy time-to-event endpoints will have hypothesis testing performed with comparisons analogous to those for the primary endpoint: OS, time to first SSE, time to radiological progression, and rPFS. Other endpoints, including safety and tolerability variables, will be analyzed descriptively for each treatment group.

Section 6.4.7 Dose delays:

Under Myelosuppression, paragraph 1, 4th bullet:

Added text:

- Blood transfusions are acceptable during the treatment period, but erythropoietin is not allowed. Use of biologic response modifiers, such as GM-CSF or G-CSF, is allowed in the management of acute toxicity during the treatment period. Such drugs (and transfusions) cannot be used for 4 weeks prior to screening and during the screening period, or prior to the start of treatment.

Section 7.1.1 Tabulated overview, Table 7-1 Schedule of procedures (footnote "o");
Section 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C) (paragraph 1, 13**th** bullet);
Section 7.1.2.3 Doses 2 to 6 (Treatment Arms A and B) (paragraph 1, 10th bullet);
Section 7.1.2.4 Doses 2 to 12 (Treatment Arm C) (paragraph 1, 10th bullet);
Section 7.1.2.5 End of treatment visit (paragraph 1, 10th bullet); and
Section 7.1.2.6.1 Active follow-up with clinic visits (paragraph 3, 9th bullet);

Revised text from "treating physician" to "study investigator".

Section 7.1.1 Tabulated overview, Table 7-1 Schedule of procedures:

Footnotes "i", "j", and "k": added text:

"using a handheld device", see **Change 26.**

Section 7.1.2.2 Initial visit-Dose 1, Day 1 (Treatment Arms A, B, and C) (paragraph 1, 2nd bullet);
Section 7.1.2.3 Doses 2 to 6 (Treatment Arms A and B) (paragraph 1, 1st bullet)***;***
Section 7.1.2.4 Doses 2 to 12 (Treatment Arm C) (paragraph 1, 1st bullet)***;*** and
Section 7.1.2.5 End of treatment visit (paragraph 1, 1st bullet)***:***

Added text:

- BPI-SF questionnaire using a handheld device (should be self-administered at the beginning of each visit through Week 48 and should be checked for completion at the visit; see Section 14.7).

Section 7.1.2.6.1 Active follow-up with clinic visits:

Paragraph 3, 1st sentence:

Added text:

The following assessments will be performed during the clinic visits:

Paragraph 9:

Added text:

If a subject is no longer able to travel to the clinic due to deteriorating status, the subject will enter the active follow-up without visits and will be followed by telephone.

Paragraph 10:

Old text:

If a subject has a SSE in the active ~~safety~~ follow-up period, he will continue the ~~2-year~~ active ~~safety~~ follow-up period.

New text:

If a subject has an SSE in the active follow-up period, he will continue the active follow-up period for 2 years from last study treatment. If a subject becomes unable to travel to the clinic after 2 years after his last treatment, he will enter long-term follow-up.

Section 7.3.2 Definition of efficacy variables

Paragraph 1, 2nd sentence:

Added text:

Response and progression endpoints are defined with respect to 2 corresponding baselines, the screening (or pre-treatment) baseline and 24 weeks.

Section 7.2.5.5 Additional pain and health-related quality of life endpoints:

Revised title of section:

Added text:

7.3.5.5 Additional pain and health related quality of life endpoints

Section 8.4.2.1 Analyses of pooled standard dose and high dose from randomization

Paragraph 1, 2nd sentence:

Added text:

For these analyses, the start date will be randomization, and the screening (or pre-treatment) baseline will be used.

Section 8.4.4 Safety analysis:

Paragraph 5, 3rd subsection:

Added text:

3. Safety events emerging following the standard-regimen treatment period

This analysis will be performed in each treatment arm for events following the later of 24 weeks from treatment start or 30 days following completion of 6 doses of radium 223 dichloride treatment. It will be performed for selected safety endpoints collected during active follow-up after end of treatment through primary endpoint completion. This analysis will be performed by treatment group as treated.

Change 25:

List of abbreviations:

New text:

AQA	Analgesic Quantification Algorithm
CR	Complete response
ePRO	Electronic patient-reported outcome
FPSI-DRS-P	FACT-P Symptom Index-17 physical disease related symptoms
HA	The Alternative Hypothesis
H0	The Null Hypothesis
JSRC	Joint Safety Review Committee
MBq	Megabecquerel, SI unit of radioactivity
mCi	milli-curie
NCCN	National Comprehensive Cancer Network
NCCN-FACT FPSI-17	NCCN-FACT-P Symptom Index-17
OMEs	Oral morphine equivalents
PRO	Patient-reported outcome
U/L	Units/liter

Change 26:

Section 7.1.1 Tabular overview, Table 7-1 Schedule of procedures:

Old table/text:

Table 7.1.1-1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active ~~Safety~~ Follow-up				~~Extended active~~ follow-up	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months	~~End of extended active~~ follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Informed consent	X																									
Inclusion / exclusion criteria[f]	X	X[g]						X[g]																		
Demographic data	X																									
Medical and disease history	X																									
Height	X																									
Weight[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Randomization[i]	X																									
Pain assessment[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]					
Training on daily PRO pain collectionl[l]	X																									
Review daily PRO pain input		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]					
BPI-SF[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]					
Analgesic use ~~evaluation~~[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]					
Vital signs[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Table 7.1.1-1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active ~~Safety~~ Follow-up				~~Extended active~~ follow-up	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months	~~End of extended active~~ follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Physical examination[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Chemistry panel and CBC[q]	X	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]				
PSA	X	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X	X	X				
Testosterone	X																									
Whole body technetium-99 bone scans[t]	X				~~X~~						~~X~~			X			X			X[u]	X	X				
Documentation of bone metastases[v]	X																									
MRI / CT scan abdomen and pelvis, chest X-ray[t]	X				X						X			X			X			X[u]	X	X				
IVRS / IWRS[w]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X								
Radium-223 dichloride administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Oral hydration[x]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Subject contact card[y]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Subject and family instructions[z]	X	X						X																		

Table 7.1.1-1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active ~~Safety~~ Follow-up				~~Extended active~~ follow-up	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months	~~End of extended active~~ follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Record SSEs	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[bb]	X[bb]				
Record concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Record limited concomitant medication[cc]																					X	X				
Record therapy for prostate cancer other than radium-223 dichloride		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[dd]	X	X	X		
Record new primary malignancies		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs and SAEs[ee]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Record radium-223 dichloride related AEs and SAEs[ff]																					X	X	X	X		
Record radium-223 dichloride related SAEs[gg]																									X	X

Table 7.1.1-1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active ~~Safety~~ Follow-up				~~Extended active~~ follow-up	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[c]	Day 1, Week 0^d	Day 1, Week 4^d	Day 1, Week 8^d	Day 1, Week 12^d	Day 1, Week 16^d	Day 1, Week 20^d	Day 1, Week 0^d	Day 1, Week 4^d	Day 1, Week 8^d	Day 1, Week 12^d	Day 1, Week 16^d	Day 1, Week 20^d	Day 1, Week 24^d	Day 1, Week 28^d	Day 1, Week 32^d	Day 1, Week 36^d	Day 1, Week 40^d	Day 1, Week 44^d	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months	~~End of extended active~~ follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Record SSE-related AEs and SAEs[ff]																					X	X				
Survival status																							X	X	X	X

Abbreviations: AE = adverse event; BPI-SF = Brief Pain Inventory Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; IVRS / IWRS = interactive voice / web response system; MRI = magnetic resonance imaging; PCWG2 = Prostate Cancer Clinical Trials Working Group 2; PS = performance status; PSA = prostate specific antigen; q6 = every 6; q12 = every 12; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SSE = symptomatic skeletal event; wk = week

a. Once a subject switches from active ~~safety~~ follow-up with clinical visits to active ~~safety~~ follow-up without clinical visits, the subject will not be allowed to switch back. A subject with a possible SSE may, and is encouraged to, return to the clinic at any time to assess for the presence of an SSE.

b. Once a separate, extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical studies, has been implemented, the study subjects surviving after the end of the 2 years of active follow-up will be transitioned to this separate, extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned.

c. The maximum period for rescreening screen failed subjects is 35 days (14 days screening + 7-day window + 14 days for rescreening) from signing the ICF to randomization. Rescreening of a subject requires prior approval of the Bayer-designated medical representative (see Section 5.1). Eligibility should be confirmed within 14 ± 7 days of randomization.

d. The subject should return to the clinic in advance of the scheduled dose visit such that results of the laboratory assessment are available within 72 hours prior to dosing (each dose period is 28 ± 7 days after the prior dose of radium-223 dichloride).

e. Subjects who can no longer travel to the clinical site or who receive further anticancer therapy will only be followed up by telephone (active follow-up without clinic visits). Symptomatic skeletal events will not be collected over the phone.

f. The study record or subject's clinical record must clearly show that informed consent was obtained prior to any other study procedures being performed. Eligibility should be confirmed during the screening period and reconfirmed prior to dosing at Dose 1, Day 1.

g. Reconfirmation of eligibility and registration in the IVRS / IWRS: hematology results obtained within 72 hours of Dose 1, Day 1 should be reviewed and it should be confirmed that the values are still within the treatment ranges (absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 9.0 g/dL).

h. Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. At all sites (in US and outside US), weight is to be taken only once for each dose. For non-US sites and US sites not using the central PRD depot, the weight should be performed within 72 hours prior to dosing. For US sites using the central PRD depot ONLY, subject weight for the dose day should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits. Please note this is applicable to all dosing visits.

i. Randomization will be permuted-block, stratified by the use of prior chemotherapy (≤ 1 regimen versus > 1 regimen~~) and~~ by total alkaline phosphatase (< 220 U/L versus ≥ 220 U/L~~)~~. This assessment will occur when the second call is made to the IVRS / IWRS to order drug: ≥ 10 to 14 days prior to study treatment administration.

j. Pain will be assessed ~~daily~~ during the screening period for the 7 days prior to Dose 1, Day 1 ~~and~~ then daily for 7 days prior to each scheduled treatment visit through the end of Week 48. Subjects will complete the daily pain assessment. The daily PRO pain input results should be reviewed at the visit to check for completeness.

k. For Treatment Arms A and B only ~~at~~ Weeks 36 and 48 only.

l. When a subject is determined to be eligible, the subject will be trained on daily PRO pain data collection. The subject will then complete the pain assessment daily for the 7 days prior to Dose 1, Day 1.

m. The BPI-SF questionnaire will be completed at each clinic visit from Dose 1, Day 1 until the Week 48 visit. For further details, see Section 14.7.

n. Analgesic use will be collected and it will be assessed by the ~~treating physician~~.

o. Systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes.

p. After a complete physical examination at screening, subsequent physical examinations may be 'brief,' but should include any systems with symptoms. All physical examinations will be performed by a physician according to the standard of care.

q. Complete blood count, including hematocrit, hemoglobin, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be collected. Chemistry panel including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, bilirubin, total alkaline phosphatase, aspartate transaminase,

alanine transaminase, lactate dehydrogenase (screening only), and albumin (screening only).

r. Laboratory assessments should be performed within 72 hours of the visit and the results assessed and documented prior to dosing.

s. The PSA result for each dosing visit may be assessed post-dose.

t. Radiological / progression (according to PCWG2 criteria) will be assessed by means of whole body technetium-99 bone scan, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and MRI / CT scan of the abdomen and pelvis. Baseline tumor assessment should be performed within 14 (± 7) days of randomization. If standard of care bone scan and / or MRI / CT scan of the abdomen and pelvis and chest X-ray within 8 weeks of randomization are available, they do not need to be repeated at baseline. If they are not available, they should be performed within 14 days ± 7 days of randomization (i.e., during the screening period). Subsequent tumor assessment should be performed every 12 weeks during treatment, ~~within 7 days prior to the EOT visit, and every 12 weeks during the active follow-up period with clinic visits~~ for 2 years after the subject's last dose of radium-223 dichloride or until radiological progression (according to PCWG2 criteria or RECIST guidelines), or death, whichever comes first. All images should be obtained with the same technique (e.g., CT or MRI) as those obtained at screening. Schedule deviations of ± 2 weeks for imaging / tumor evaluations are allowed.

u. Imaging is not required at the EOT visit if the subject discontinued due to radiological progression or the last tumor evaluation is not older than 4 weeks.

v. Bone imaging should be within 8 weeks of randomization. If no prior documentation is available, a whole body technetium-99 bone scan will be obtained at screening (within 14 ± 7 days of randomization).

w. The IVRS / IWRS will be used to register ~~subject~~ eligibility ~~and request~~ / ~~confirm~~ study drug doses. Once the subject eligibility is approved and registered in the IVRS / IWRS, the initial shipment ~~will be triggered~~. ~~Subsequent doses should be ordered as soon as the current visit's dose is registered in the IVRS / IWRS~~. The planned date for the next dose must be specified, when the dose is requested in the IVRS / IWRS. The order date for the next dose ~~cannot be earlier~~ than the pre-defined ~~country~~ lead time.

x. The subject should be encouraged to arrive at the clinic well-hydrated on each dosing day and to drink ad libitum after each dose of radium-223 dichloride. The subject should avoid drinking or eating within 1 hour before and after administration of the study drug.

y. The subject contact card is to be provided at each dosing visit for the subject to carry with him until the next visit.

z. Subject and family instructions should be reviewed with the subject during screening through Dose 1, Day 1.

aa. Subjects identified with possible SSEs will be asked to come to the clinic for an SSE evaluation. An SSE risk questionnaire will be developed. Symptomatic skeletal events will not be identified over the telephone.

bb. If a subject has an SSE in the active ~~safety~~ follow-up period, he will continue ~~the~~ 2~~-year active safety follow-up period~~. At Weeks 28, 32, 40, and 44, subjects in Treatment Arms A and B will receive telephone contacts assessing for possible SSE risks. Subjects exhibiting symptoms indicative of possible SSEs will be encouraged to visit the clinic early to assess SSE status. Symptomatic skeletal events will not be determined over the phone.

cc. ~~Limited~~ concomitant medication, including narcotic pain medication, will be recorded during the active follow-up with clinic visits period. Contrast agents will only be captured as concomitant medication if there is an AE or SAE related to administration of contrast media.

dd. Subjects who receive further anticancer therapy during the active follow-up period will have an end of active follow-up with clinic visits and

will enter the active follow-up without clinic visits (telephone follow-up).

ee. All AEs and SAEs will be assessed and recorded from the time the ICF is signed until 30 days after the last dose of study medication. All AEs should be assessed and documented prior to each dose of radium-223 dichloride.

ff. Any AEs and SAEs occurring beyond 30 days after the last treatment must be documented and reported if considered to be related to study medication or if related to an SSE. However, 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.

gg. Any SAEs must be documented and reported if considered to be related to study medication. However, 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.

New table/text:

Table 7-1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[e]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Informed consent	X																									
Inclusion / exclusion criteria[f]	X	X[g]						X[g]																		
Demographic data	X																									
Medical and disease history	X																									
Height	X																									
Weight[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Training on daily PRO pain collection[i]	X																									
Pain assessment[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X[k]					
Randomization[l]	X																									
Review daily PRO pain input	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X[k]					
BPI-SF[m]	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X[k]					

Table 7-1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
NCCN FACT-P Symptom Index-17 Questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]					
24-hour Analgesic use collection[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]					
Vital signs[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Physical examination[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Chemistry panel and CBC[r]	X	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]				
PSA	X	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X	X	X				
Testosterone	X																									
Whole body technetium-99 bone scans[u]	X			X		X				X		X		X			X			X[u]	X	X				
Documentation of bone metastases[w]	X																									

Table 7-1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
MRI / CT scan abdomen and pelvis, chest X-ray[u]	X			X		X				X		X		X			X			X[v]	X	X				
IVRS / IWRS[x]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X								
Radium-223 dichloride administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Oral hydration[y]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Subject contact card[z]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Subject and family instructions[aa]	X	X						X																		
Record SSEs	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[bb]	X[cc]	X[cc]				
Record concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Record limited concomitant medication[dd]																					X	X				

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Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Record therapy for prostate cancer other than radium-223 dichloride		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[ee]	X	X	X	X	
Record new primary malignancies		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs and SAEs[ff]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Record radium-223 dichloride related AEs and SAEs[gg]																					X	X	X	X		
Record radium-223 dichloride related SAEs[hh]																									X	X
Record SSE-related AEs and SAEs[gg]																					X	X				

Table 7-1 Schedule of procedures

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Survival status																							X	X	X	X

Abbreviations: AE = adverse event; BPI-SF = Brief Pain Inventory Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; IVRS / IWRS = interactive voice / web response system; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PCWG2 = Prostate Cancer Clinical Trials Working Group 2; PRO = Patient-reported outcome; PS = performance status; PSA = prostate specific antigen; q6 = every 6; q12 = every 12; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SSE = symptomatic skeletal event; US = United States; wk = week; WPS = worst pain score.

[a] Once a subject switches from active follow-up with clinical visits to active follow-up without clinical visits, the subject will not be allowed to switch back. A subject with a possible SSE may, and is encouraged to, return to the clinic at any time to assess for the presence of an SSE.

[b] Once a separate, extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical studies, has been implemented, the study subjects surviving after the end of the 2 years of active follow-up will be transitioned to this separate, extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned.

[c] The maximum period for rescreening screen failed subjects is 35 days (14 days screening + 7-day window + 14 days for rescreening) from signing the ICF to randomization. Rescreening of a subject requires prior approval of the Bayer-designated medical representative (see Section 5.1). Eligibility should be confirmed within 14 ± 7 days of randomization.

[d] The subject should return to the clinic in advance of the scheduled dose visit such that results of the laboratory assessment are available within 72 hours prior to dosing (each dose period is 28 ± 7 days after the prior dose of radium-223 dichloride).

[e] Subjects who can no longer travel to the clinical site or who receive further anticancer therapy will only be followed up by telephone (active follow-up without clinic visits). Symptomatic skeletal events will not be collected over the phone.

[f] The study record or subject's clinical record must clearly show that informed consent was obtained prior to any other study procedures being performed. Eligibility should be confirmed during the screening period and reconfirmed prior to dosing at Dose 1, Day 1.

[g] Reconfirmation of eligibility and registration in the IVRS / IWRS: hematology results obtained within 72 hours of Dose 1, Day 1 should be reviewed and it should be confirmed that the values are still within the treatment ranges (absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 9.0 g/dL).

[h.] Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. At all sites (in US and outside US), weight is to be taken only once for each dose. For non-US sites and US sites not using the central PRD depot, the weight should be performed within 72 hours prior to dosing. For US sites using the central PRD depot ONLY, subject weight for the dose day should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits. Please note this is applicable to all dosing visits.

[i.] When a subject is determined to be eligible, the subject will be trained on daily PRO pain data collection using a handheld device. The subject will then complete the pain assessment daily for 4 days prior to randomization and then for the 7 days prior to Dose 1, Day 1.

[j.] Pain will be assessed during the screening period daily for 4 days prior to randomization and for the 7 days prior to Dose 1, Day 1, then daily for 7 days prior to each scheduled treatment visit through the end of Week 48. Subjects will complete the daily pain assessment using a handheld device. The daily PRO pain input results should be reviewed at the visit to check for completeness.

[k.] For Treatment Arms A and B only, pain data will be collected daily using the handheld device for 7 days prior to Weeks 36 and 48 visits, and daily for 7 days prior to each telephone contact at Weeks 28, 32, 40 and 44. For Treatment Arms A and B only the BPI-SF and the NCCN FACT-P Symptom Index-17 (NCCN-FACT FPSI-17) questionnaires will be completed on the day of the Week 36 and 48 visits and on the day of each telephone contact at Weeks 28, 32, 40 and 44. Twenty-four (24) hour analgesic use will be collected by the study investigator at Week 36 and 48 Visits and at each telephone contact (in Arms A and B) at Weeks 28 (±7 days), 32 (±7 days), 40 (±7 days), and 44 (±7 days).

[l.] The randomization will be permuted-block, stratified by the use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total alkaline phosphatase (< 220 U/L versus ≥ 220 U/L), and by average WPS of the BPI-SF (WPS ≤4 versus WPS >4). This assessment will occur when the second call is made to the IVRS / IWRS to order drug: ≥ 10 to 14 days prior to study treatment administration.

[m.] The BPI-SF questionnaire will be completed at each clinic visit from Dose 1, Day 1 until the Week 48 visit and for Treatment Arms A and B only, on the day of each telephone contact at Weeks 28, 32, 40 and 44. For further details, see Section 14.7.

[n.] Prior to randomization, the subject will use the hand-held device to complete selected questions from the BPI-SF questionnaire, Question 3, worst pain in the last 24 hours will be completed for at least 4 days during a period of no more than 1 week prior to randomization. The average of the 4 days will be used as the randomization stratification value.

[o.] Twenty-four (24)-hour analgesic use will be collected and it will be assessed by the study investigator until the Week 48 visit. Twenty-four (24)-hour analgesic use will also be collected by the study investigator at each telephone contact (in Arms A and B) or visit at Weeks 28, 32, 40, and 44.

p. Systolic / diastolic blood pressure, respiratory rate, body temperature, and heart rate will be measured after the subject has rested for at least 5 minutes.

q. After a complete physical examination at screening, subsequent physical examinations may be 'brief,' but should include any systems with symptoms. All physical examinations will be performed by a physician according to the standard of care.

r. Complete blood count, including hematocrit, hemoglobin, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be collected. Chemistry panel including serum creatinine, sodium, potassium, chloride, calcium, phosphorous, magnesium, total bilirubin, total alkaline phosphatase, aspartate transaminase, alanine transaminase, lactate dehydrogenase (screening only), and albumin (screening only).

s. Laboratory assessments should be performed within 72 hours of the visit and the results assessed and documented prior to dosing.

t. The PSA result for each dosing visit may be assessed post-dose.

u. Radiological / progression (according to PCWG2 criteria) will be assessed by means of whole body technetium-99 bone scan, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and MRI / CT scan of the abdomen and pelvis. Baseline tumor assessment should be performed within 14 (± 7) days of randomization. If standard of care bone scan and / or MRI / CT scan of the abdomen and pelvis and chest X-ray within 8 weeks of randomization are available, they do not need to be repeated at baseline. If they are not available, they should be performed within 14 days ± 7 days of randomization (i.e., during the screening period). Subsequent tumor assessment should be performed at Week 8, Week 16, Week 24 and every 12 weeks thereafter for up to 2 years after the subject's last dose of radium-223 dichloride or until radiological progression (according to PCWG2 criteria or RECIST guidelines), or death, whichever comes first. If progression is detected by bone scan, a confirmatory bone scan is required at least 6 weeks later. All images should be obtained with the same technique (e.g., CT or MRI) as those obtained at screening. Schedule deviations of ± 2 weeks for imaging / tumor evaluations are allowed.

v. Imaging is not required at the EOT visit if the subject discontinued due to radiological progression or the last tumor evaluation is not older than 4 weeks.

w. Bone imaging should be within 8 weeks of randomization. If no prior documentation is available, a whole body technetium-99 bone scan will be obtained at screening (within 14 ± 7 days of randomization).

x. The IVRS / IWRS will be used to register requests for eligibility / study drug doses. Once the subject eligibility is approved and registered in the IVRS / IWRS, including entry of required demographic and stratification information, the initial drug shipment may be prepared. Additional IVRS / IWRS transactions for dose orders may be required; follow the country-specific guidance in the IVRS / IWRS manual. The latest order date for the next dose is no later than the pre-defined lead time (number of days from order received to delivery to site in the country) prior to the planned dosing date. The planned date for the next dose must be specified, when the dose is requested in the IVRS / IWRS. At Doses 1 through 5, the site should order the next dose in the IVRS / IWRS, as soon as the current visit's dose is registered in the IVRS / IWRS. The latest order date for the next dose is no later than the pre-defined lead time (number of days from order received to delivery to site in the country) prior to the planned dosing date. For subject visit registrations in the IVRS / IWRS, see the IVRS / IWRS manual.

y. The subject should be encouraged to arrive at the clinic well-hydrated on each dosing day and to drink ad libitum after each dose of radium-223 dichloride. The subject should avoid drinking or eating within 1 hour before and after administration of the study drug.

z. The subject contact card is to be provided at each dosing visit for the subject to carry with him until the next visit.

aa. Subject and family instructions should be reviewed with the subject during screening through Dose 1, Day 1.

bb. Subjects identified with possible SSEs will be asked to come to the clinic for an SSE evaluation. An SSE risk questionnaire will be developed. Symptomatic skeletal events will not be identified over the telephone.

cc. If a subject has an SSE in the active follow-up period, he will continue active follow-up for 2 years following last study treatment. At Weeks 28, 32, 40, and 44, subjects in Treatment Arms A and B will receive telephone contacts assessing for possible SSE risks. Subjects exhibiting symptoms indicative of possible SSEs will be encouraged to visit the clinic early to assess SSE
status. Symptomatic skeletal events will not be determined over the phone.

dd. Except for complete analgesic use information recorded through Week 48, limited concomitant medication, including narcotic pain medication, will be recorded

during the active follow-up with clinic visits period. Contrast agents will only be captured as concomitant medication if there is an AE or SAE related to administration of contrast media.

ee. Subjects who receive further anticancer therapy during the active follow-up period will have an end of active follow-up with clinic visits and will enter the active follow-up without clinic visits (telephone follow-up). Subjects who receive further anticancer therapy after 2 years from last study treatment will enter long-term follow-up.

ff. All AEs and SAEs will be assessed and recorded from the time the ICF is signed until 30 days after the last dose of study medication. All AEs should be assessed and documented prior to each dose of radium-223 dichloride.

gg. Any AEs and SAEs occurring beyond 30 days after the last treatment must be documented and reported if considered to be related to study medication or if related to an SSE. However, 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.

hh. Any SAEs must be documented and reported if considered to be related to study medication. However, 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.

Change 27:

Section 12 Reference List:

Reference 22, new text (cited in Section 1.1 Background):

22. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-23.

25. http://www.facit.org/FACITOrg/Questionnaires.

29. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2012;368(2):138-48.

Change 28:

Synopsis - Diagnosis and main criteria for inclusion:

Paragraph 1, 7th bullet, item "g":

Old text:

g. Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m2 according to the Modification of Diet in Renal Disease abbreviated formula (~~Levey AS, et al. Ann Intern Med. 1999;130:461-70~~) (see Section 14.~~7~~)

Next text:

g. Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m2 according to the Modification of Diet in Renal Disease abbreviated formula (24) (see Section 14.6)

Synopsis - Plan for statistical analysis:

Next to last paragraph:

Deleted text (correction of 1-sided alpha value):

Comparison 2 will be performed using a log-rank test with a 1-sided alpha of 0.1~~%~~ stratified by the randomization factors (previous chemotherapy [≤ 1 regimen versus > 1 regimen] and total ALP [< 220 U/L versus ≥ 220 U/L]). The extended dosing regimen will be declared superior to the standard dosing regimen if the 1-sided p-value from the stratified log rank test is less than 0.1~~%~~.

Section 2 Study objectives:

Paragraph 3, 1st bullet (defined abbreviation):

Added text:

- The use of external beam radiotherapy (EBRT) to relieve skeletal symptoms

Paragraph 4, 2nd bullet (defined abbreviation):

Added text:

- To evaluate overall survival (OS)

Section 3 Investigators and other study personnel:

Paragraph 1:

Deleted text (duplication):

Global Clinical Leader for the study:

~~Global Clinical Leader for the study:~~
PPD

Paragraph 3 (correction of title and address):

Added text:

European Principal Investigator for the study:

PPD
Italy
Tel: PPD

13.2 Amendment 2

Description of the amendment

Amendment 2 is an amendment to the integrated protocol version 2.0 dated 19 NOV 2013. Changes to the protocol include:

- Added CKD-EPI equation as an alternative method for calculation of estimated glomerular filtration rate (eGFR).
- Updated calculations for GFR.

- Updated the definition of measureable lymph nodes from a 2-cm cutoff to a 1.5-cm cutoff.
- Clarified when pain assessments will be collected throughout study.
- Removed ± 7 day window for dose delays.
- Reorganized the inclusion criterion to specify serum PSA ≥ 2 ng/mL as an inclusion criterion for castration-resistant disease.
- Added additional prior therapies and medical history that should be recorded on the eCRF.
- Updated sponsor's medical expert.
- Updated sponsor's medically responsible person.
- Updated text for long-term study follow-up period.
- Clarified duration between doses.
- Updated global clinical leader contact information.
- Clarified text regarding reporting of adverse events of neutropenia and hemorrhage.
- Clarified continued treatment for subjects with disease progression.
- Clarified withdrawal and dose delay for non-hematological thrombocytopenia and neutropenia.
- Clarified maximum period allowed for screening.
- Clarified tumor assessment scan timeline.
- Updated US site information on weight measurement.
- Added when treatment period is considered to begin for efficacy purposes.
- Tumor assessment timing was updated to be consistent throughout protocol.
- Clarified laboratory abnormalities related to assessments and documentation of adverse events.
- Updated current drug manufacturer.
- Revised efficacy variables related to analgesic use and pain management and changed the term "pain management" to "analgesic use."
- Updated the radium-223 dichloride dosing and dose calibration to reflect the revised NIST standard.
- Updated the list of abbreviations to reflect the usage of abbreviations in the amended protocol.
- Changed "patient" to "subject".
- Updated information on obtaining body weight.

- Removed dosing restriction with bisphosphonates
- Removed bone scan lesion index.
- Moved change in analgesic use from secondary objective and secondary variable to exploratory objective and exploratory endpoints.
- Clarified terminology by replacing toxicity with adverse event in dose delays.
- Clarified terminology for concomitant cytotoxic chemotherapy.
- Added sponsor's study medical expert to the list of investigator(s) and other study personnel.
- Revised text for consistency.
- Added an additional efficacy analysis set (W24).
- Changed terminology from "population" to "analysis set".

13.2.1 Overview of changes

Change 1:

Added CKD-EPI equation as an alternative method for calculation of eGFR.

Sections affected:

- Synopsis - Diagnosis and main criteria for inclusion
- 5.1.1 Inclusion Criteria
- 12. Reference List

Rationale: This change allows sites to use either the standard MDRD equation or the recent and more accurate CKD-EPI equation.

Change 2:

Updated calculations for GFR.

Sections affected:

- 14.6 Calculation for glomerular filtration rate

Rationale: This updated section provides background information and guidance regarding GFR assessment using current methods.

Change 3:

Updated the definition of measureable lymph nodes from a 2-cm cutoff to a 1.5-cm cutoff.

Sections affected:

- 14.1 Response evaluation criteria in solid tumors, version 1.1
- 14.2 Recommendations of the prostate cancer clinical trials working group for assessment of radiological progression

Rationale: This change is consistent with the RECIST 1.1 definition of measurable malignant lymph nodes.

Change 4:

Clarified when pain assessments will be collected throughout study.

Sections affected:

- 4.1 Study design
- 7.1.1 Tabulated overview
- 7.1.2.1 Screening period
- 7.1.2.3 Initial visit - Dose 1, Day 1 (Treatment arms A, B, C)
- 7.1.2.4 Doses 2 to 6 (Treatment arms A and B)
- 7.1.2.5 Doses 2 to 12 (Treatment arm C)
- 7.1.2.6 End of Treatment
- 7.1.2.7.1 Active follow-up with clinic visits
- 7.3.4.4 Pain Endpoints

Rationale: This change was made to eliminate ambiguity in the protocol wording.

Change 5:

Removed ± 7 day window for dose delays.

Sections affected:

- 5.2.1 Withdrawal
- 6.4.7 Dose delays

Rationale: This change was made to correct an error.

Change 6:

Reorganized the inclusion criterion to specify serum PSA ≥ 2 ng/mL as an inclusion criterion for castration-resistant disease.

Sections affected:

- Synopsis - Diagnosis and main criteria for inclusion
- 5.1.1 Inclusion criteria

Rationale: As a separate inclusion criterion, the serum PSA limit implies that all subjects have to meet the criterion, but it is possible for a subject to have CRPC without a high PSA. This reorganization was instituted to clarify that PSA ≥ 2 ng/mL is a possible symptom of CRPC rather than its own qualification criterion.

Change 7:

Added additional prior therapies and medical history that should be recorded on eCRF.

Sections affected:

- 6.9.1 Prior therapy
- 7.2.2 Medical history

Rationale: To collect clinical information for the purpose of identifying and accounting for factors that may influence the interpretation of radiographic images by central review.

Change 8:

Updated sponsor's medical expert.

Sections affected:

- Title page

Rationale: Provide most up to date contact information.

Change 9:

Updated sponsor's medically responsible person.

Sections affected:

- Signature page

Rationale: Provide most up to date signatory.

Change 10:

Updated text for long-term study follow-up period.

Sections affected:

- Synopsis - Methodology
- 4.1 Design overview

- 6.8 Post-study therapy
- 7.1.2.7.1 Active follow-up with clinic visits
- 7.1.2.8.1 End of active follow-up with clinic visits
- 7.1.2.8.2 End of active follow-up without scheduled clinic visits
- Section 7.1.2.9 Long-term follow-up to 7 years following last dose
- 10. Premature termination of the study

Rationale: Provide updated information regarding long-term follow-up study that has now started.

Change 11:

Clarified duration between doses.

Sections affected:

- Synopsis - Methodology
- 4.1 Design overview

Rationale: Clarify the text.

Change 12:

Updated global clinical leader contact information.

Sections affected:

- 3. Investigators and other study personnel

Rationale: Provide most up to date contact information.

Change 13:

Clarified text regarding reporting of adverse events of neutropenia and hemorrhage.

Sections affected:

- 7.5.1.3 Assessments and documentation of adverse events

Rationale: Wording should be consistent with the long-term follow-up study.

Change 14:

Clarified continued treatment for subjects with disease progression.

Sections affected:

- 6.4.7 Dose Delays

Rationale: For clarity.

Change 15:

Clarified withdrawal and dose delay for non-hematological thrombocytopenia and neutropenia.

Sections affected:

- 5.2.1 Withdrawal
- 6.4.7 Dose delays

Rationale: For clarity.

Change 16:

Clarified maximum period allowed for screening.

Sections affected:

- 5.1 Eligibility
- 6.4.7 Dose delays

Rationale: For clarity.

Change 17:

Clarified tumor assessment scan timeline.

Sections affected:

- 7.1.2.1 Screening period

Rationale: For clarity.

Change 18:

Updated US site information on weight measurement.

Sections affected:

- 7.1.1 Tabulated overview
- 7.1.2.1 Screening period
- 7.1.2.3 Initial visit - Dose 1, Day 1 (Treatment arms A, B, C)
- 7.1.2.4 Doses 2 to 6 (Treatment arms A and B)

- 7.1.2.5 Doses 2 to 12 (Treatment arm C)
- 7.5.3.5 Body weight

Rationale: All US sites using central PRD depot.

Change 19:

Added when treatment period is considered to begin for efficacy purposes.

Sections affected:

- Synopsis: Methodology
- 4.1 Design Overview
- 7.1.1 Tabulated Overview
- 7.1.2.2 Randomization
- 8.4.4 Safety analysis

Rationale: For clarity.

Change 20:

Updated tumor assessment timing to be consistent throughout protocol.

Sections affected:

- 7.1.2.4 Doses 2 to 6 (Treatment arms A and B)
- 7.1.2.5 Doses 2 to 12 (Treatment Arm C)

Rationale: For consistency.

Change 21:

Clarified laboratory abnormalities related to assessments and documentation of adverse events.

Sections affected:

- 7.5.1.3 Assessments and documentation of adverse events

Rationale: For clarity.

Change 22:

Updated current drug manufacturer.

Sections affected:

- 6.2 Identity of study treatment

Rationale: Bayer acquired Algeta.

Change 23

Revised efficacy variables related to analgesic use and pain management and changed the term “pain management” to “analgesic use.”

Sections affected:

- 7.3.1 Efficacy variables
- 7.3.4.4 Pain endpoints
- 7.3.4.4.1 Pain improvement rate
- 7.3.4.4.2 Time to pain progression
- 7.3.4.5 Change in the last 24 hour analgesic use score (section relocated to 7.3.5.5.5)
- 7.3.5.5 Exploratory pain and analgesic use endpoints (section added)

Rationale: For consistency with updated objectives.

Change 24:

Updated the radium-223 dichloride dosing and dose calibration to reflect the revised NIST standard.

Sections affected:

- Title Page
- Synopsis: Title
- Synopsis: Study objectives
- Synopsis: Doses
- Synopsis: Methodology
- Synopsis plan for statistical analysis
- 1.2 Study rationale
- 2. Study objectives
- 4.1 Design overview
- 6.1 Treatments to be administered
- 6.2 Identity of study treatments
- 6.3 Treatment assignment

- 6.4.1 Dose calibration
- 6.4.3 Dose calculation
- 7.1.2.2 Randomization
- 8.1 General considerations
- 8.4.1 Primary efficacy analysis
- 8.4.4 Safety Analyses
- 8.6 Determination of sample size
- 12. Reference list

Rationale: The quantification of radium-223 radioactivity in Xofigo® is based on the primary standardization performed by the US NIST. The NIST Standard Reference Material is used to calibrate the instruments in production and quality control of both the drug substance and drug product. Additionally, the calibrated instruments in production at the IFE, Norway are used to prepare the NIST traceable radium-223 reference material, which are then sent to the treatment sites (e.g., nuclear medicine laboratory physicians or technicians) for dial-setting of their dose calibrators, to allow verification of the patient dose. A reassessment of the primary standardization was initiated by the NIST. A discrepancy of approximately 10% between the published NIST primary standardization (NIST 2010 [31]) and current measurements was confirmed and a revised NIST primary reference standard has been issued (NIST update [32]). As a result of the revised NIST primary standardization, an adaption of the numerical description of patient dose and the description of radioactive concentration of the drug product solution becomes necessary. This concerns Xofigo® for commercial use and product used in clinical trials.

After the implementation of the new standard (NIST update [32]) the numerical description of the patient dose will be adjusted from 50 kBq/kg to 55 kBq/kg, and the numerical description of the radioactivity in the vial will be changed from 1,000 kBq/mL to 1,100 kBq/mL. A respective variation application and substantial amendment to our clinical trial agreements have been initiated. The current standard (NIST 2010 [31]), dial setting and dose will remain in effect until a unique implementation date in Q2 2016 as agreed with FDA and European Medicines Agency. All clinical sites using radium-223 dichloride will be notified in writing about the exact date of implementation prior to the effective date.

Justification for changing the dose to 55 kBq/kg body weight:

A systematic approximately 10% error in the radium-223 NIST standardization (NIST 2010 [31]) means that the current patient dose and the dose documented as safe and efficacious throughout development is 55 kBq/kg body weight and not 50 kBq/kg body weight as declared during clinical trials and in the marketing authorization application / new drug application. However, as this is a systematic error, the actual dose has been the same all the time. In order to keep the actual dose for patients identical to what has been documented and administered so far, also when implementing the new official standard, the nominal value of

the patient dose will be changed to 55kBq/kg body weight (NIST update [32]). This change keeps the same accuracy in the nominal value of the dose. Thus, there will be no actual change in the patient dose (amount of radioactivity), it will be only a change in the dose nominal value when corrected according to the new official radium-223 NIST standard. All sites will continue to use the current dial setting (NIST 2010 [31]) for the activity measurements until the implementation date in Q2 2016.

Justification for changing the description of the radioactivity in the vial to 1,100 kBq/mL:

A systematic approximately 10% error in the radium-223 NIST standard (NIST 2010 [31]) means that the Xofigo® solution for injection with a radioactivity concentration claim of 1,000 kBq/mL, which has been tested in pivotal clinical trials and is currently marketed, actually has a concentration of 1,100 kBq/mL. If the drug product concentration is adjusted to 1,100 kBq/mL, the total activity in the vial (6 mL) must be changed from 6,000 kBq/vial to 6,600 kBq/vial (changed from 6.0 MBq/vial to 6.6 MBq/vial in many countries). Xofigo® solution for injection produced according to the new NIST standardization (NIST update [32]), is the same product as before. NOTE: All product received by sites will be labelled with the current standard activity of 1000 kBq/mL until the implementation date in Q2 2016.

Now that the new radium-223 standard has been published, Bayer has applied for labeling and packaging changes, in accordance with the new standards, with each Health Authority for which Bayer holds a marketing application for radium-223 dichloride. Once all approvals have been received, the updated standard will be applied to all active protocols that include radium-223 dichloride, including this one, and the verification of the patient dose in treatment sites has to be performed using up-dated dial-settings of dose calibrators.

The change in the NIST radium-223 standard has no impact on subjects; subjects are receiving, and will continue to receive, the same actual dose that was studied in ALSYMPCA and is associated with the proven safety and efficacy of radium-223 dichloride, though the stated nominal radiation dose received is being updated to reflect the new standard. Subjects who are on-treatment at the time the new NIST calibration standard goes into effect will be notified of this change and will be required to sign a Patient Information Sheet to acknowledge that they have received information on the updated NIST standard calibration. All subjects randomized after the new calibration standard in effect will sign a revised Informed Consent Form that contains the updated NIST standard calibration.

Note: throughout this document the dose of radium-223 dichloride is given as 50 kBq/kg, which is based on the original NIST standardization (NIST 2010 [31]); however, when NIST issues the updated radium-223 dichloride standardization, the dose administered will actually be 55 kBq/kg (based on a change to the reference standard (NIST update [32]) only), though the volume of radium-223 dichloride given to each subject will remain the same.

Change 25

The list of abbreviations was updated to reflect the usage of abbreviations in the amended protocol.

Sections affected:

- List of abbreviations

Rationale: For consistency.

Change 26

Changed “patient” to “subject”.

Sections affected:

- Synopsis: Study objectives
- Synopsis: Methodology
- 2. Study objectives
- 4.1 Design overview
- 6.4.1 Dose calibration
- 6.4.4 Dose preparation
- 7.2.4 Body-size descriptors
- 7.3.4.4.2 Time to pain progression
- 7.3.5.5 Exploratory pain and analgesic use endpoints

Rationale: For consistency.

Change 27

Updated information on obtaining body weight.

Sections affected:

- 7.5.3.5 Body weight

Rationale: For clarification.

Change 28

Removed dosing restriction with bisphosphonates.

Sections affected:

- 6.9.2 Concomitant medication

Rationale: For Ra-223 dichloride, there is no evidence of a pharmacokinetic or PD interaction that would warrant a two-hour interval between injections.

Change 29

Removed bone scan lesion index.

Sections affected:

- 7.3.1 Efficacy variables
- 7.3.5.1.2 Bone scan lesion index (removed)

Rationale: It is not performed by central imaging as per charter.

Change 30

Moved change in analgesic use from secondary objective and secondary variable to exploratory objective and exploratory endpoints.

Sections affected:

- Synopsis: Study objectives
- Synopsis: Primary/secondary variables
- 2. Study objectives

Rationale: Objectives updated.

Change 31

Clarified terminology by replacing “toxicity” with “adverse event” in dose delays.

Sections affected:

- 6.4.7 Dose delays

Rationale: For clarification.

Change 32

Clarified terminology for concomitant cytotoxic chemotherapy.

Sections affected:

- Synopsis: Background treatment / concomitant medications / prohibited therapies
- Synopsis: Diagnosis and main criteria for exclusion

- 5.1.2 Exclusion criteria
- 5.2.1 Withdrawal
- 6.4.7 Dose Delays
- 6.9.1 Prior therapy
- 6.9.2 Concomitant medication
- 7.1.2.4 Doses 2 to 6 (Treatment Arms A and B)
- 7.1.2.5 Doses 2 to 12 (Treatment Arm C)
- 7.1.2.7.2 Active follow-up without scheduled clinic visits

Rationale: For clarification.

Change 33

Added sponsor's study medical expert to the list of investigator(s) and other study personnel.

Sections affected:

- 3. Investigator(s) and other study personnel

Rationale: For clarification.

Change 34

Revised text for consistency.

Sections affected:

- 5.1 Eligibility
- 7.1.2.1 Screening Period

Rationale: For consistency.

Change 35

Added analysis set (W24).

Section affected:

- 8.2 Analysis sets

Rationale: Two efficacy analysis sets are needed because of study design performing 2 separate comparisons, but only one set was defined in the original protocol.

Change 36

Changed terminology from "population" to "analysis set".

Sections affected:

- Synopsis: Plan for statistical analysis
- 8.2 Analysis sets

Rationale: To make terminology within the statistical analyses sections consistent.

13.2.2 Changes to the protocol text

Change 1:

Synopsis - Diagnosis and main criteria for inclusion and Section 5.1 Inclusion criteria:

Old text:

g. Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m2 according to the Modification of Diet in Renal Disease abbreviated formula (see Section 14.6) (24)

New text:

g. Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m2 according to either the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation or the Modification of Diet in Renal Disease abbreviated formula (see Section 14.6) (24, 25).

Added text:

25. Levey AS, Stevens LA, Schid CH, Zhang YL, Castro AF 3rd, Feldman Hi, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009 May 5, 150(9): 604-12

Change 2:

Section 14.6 Calculation for glomerular filtration rate

Entire section:

Old text:

~~In accordance with established nephrology practice and guidelines, renal function at screening and throughout the study will be assessed by means of the estimated GFR, calculated using the abbreviated MDRD study formula.~~

~~This equation of 4 variables (serum creatinine level, age, sex, and ethnicity) is recommended by the National Kidney Foundation for use in individuals 18 years or older. The formula is as follows:~~

~~GFR (mL / min / 1.73 m2) = k x 186 x [serum creatinine] 1.154 x [age] 0.203~~

~~Where k = 1 (men) or 0.742 (women), GFR indicates glomerular filtration rate, and serum creatinine is measured in mg/dL.~~

~~Subjects with a screening GFR < 30 mL/min/1.73 m2 calculated by this method will not be allowed to participate in the study.~~

New text:

Baseline kidney function will be assessed using the glomerular filtration rate as calculated using either the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, or, when this method is not available, the Modification of Diet in Renal Disease (MDRD) equation.

The MDRD calculation is an established method of estimating GFR based on 4 variables: serum creatinine level, age, sex, and ethnicity. This method has historically been the National Kidney Foundation's recommended method of estimating the GFR in individuals 18 years or older.

The MDRD Study Equation:

GFR (mL/min/1.73m2) = k x 186 x [serum creatinine]-1.154 x [age]-0.203

Where k = 1 (men) or 0.742 (women), serum creatinine is measured in mg/dL.

In an effort to improve upon the MDRD equation, the Chronic Kidney Disease Epidemiology Collaboration developed an updated calculation, the CKD-EPI creatinine equation, using the same variables as the MDRD equation. This new calculation has been validated and is considered to be more accurate than the MDRD equation. The National Kidney Foundation now recommends using the CKD-EPI Creatinine Equation for estimating GFR.

The CKD-EPI calculation is based on a serum creatinine value that was obtained through use of isotope dilution mass spectrometry (IDMS), a standardized serum creatinine assay. Therefore, the CKD-EPI equation is only valid if the laboratory used a calibration method for serum creatinine that is traceable to IDMS. The IDMS has been adopted by laboratories globally and is widely available. If it is not clear whether your laboratory uses this serum creatinine reference method, please contact the laboratory for confirmation.

CKD-EPI Equation

• Conventional Units (creatinine as mg/dL; age in years):

GFR (mL/min/1.73m2) = 175 x (serum creatinine)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if African American)

• International System of Units (SI) Units (creatinine as µmol/L; age in years):

GFR (mL/min/1.73m2) = 175 x (serum creatinine/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if African American)

The standard MDRD calculation should be used for any serum creatinine values that are not based on the IDMS assay.

For convenience and accuracy, a GFR calculator may be used for this study at the following URL at the National Kidney Foundation's web site: http://www.kidney.org/professionals/KDOQI/gfr_calculator

Change 3:

Section 14.1 Response evaluation criteria in solid tumors, version 1.1:

Paragraph 2, 1st bullet:

Old text:

- Only lymph nodes with short axis ≥ ~~2~~ cm can be selected as target lesions.

New text:

- Only lymph nodes with short axis ≥ 1.5 cm can be selected as target lesions.

Paragraph 4:

Old text:

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ ~~2~~ cm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.

New text:

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 1.5 cm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.

Paragraph 6:

Old text:

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (pathological lymph nodes with short axis ≥ 1 cm to < ~~2~~ cm) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, and lymphangitic involvement of skin or lung are all non-measurable.

New text:

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (pathological lymph nodes with short axis ≥ 1 cm to < 1.5 cm) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, and lymphangitic involvement of skin or lung are all non-measurable.

Section 14.2 Recommendations of the Prostate Cancer Clinical Trials Working Group for assessment of radiological progression:

Criteria for radiological progression:

Old text:

- Only lymph nodes with short axis ≥ ~~2~~ cm can be selected as a target lesion

New text:

- Only lymph nodes with short axis ≥ 1.5 cm can be selected as a target lesion

Change 4:

Section 4.1 Study design

7th paragraph:

Old text:

Pain endpoints will be based on subject-reported outcome data. Pain will be assessed by means of selected questions from the BPI-SF daily for 4 days immediately prior to randomization, in order to stratify subjects by worst pain score (WPS) ≤ 4 or > 4, for ~~the 7 days immediately prior to Dose 1, Day 1, and then for Treatment Arms A and B, daily for 7 days prior to each scheduled dosing visit through Week 24, for the 7 days prior to Weeks 36 and 48 visits and for 7 days prior to each telephone contact at Weeks 28, 32, 40 and 44. For Treatment Arm C, pain data will be collected daily for 7 days prior to each scheduled dosing visit through Week 48.~~ Pain will also be assessed by means of the BPI SF questionnaire for all treatment arms at each clinic visit from Dose 1, Day 1 until

the Week 48 visit and for treatment Arms A and B on the day of each telephone contact at Weeks 28, 32, 40 and 44.

New text:

Pain endpoints will be based on subject-reported outcome data. Pain will be assessed by means of selected questions from the BPI-SF daily for 4 days immediately prior to randomization, in order to stratify subjects by WPS ≤ 4 or > 4, and then daily for 6 days prior to Cycle 1, Day 1 or subsequent visits including telephone contacts, as applicable, plus the day of the visit or telephone contact until Week 48. Pain will also be assessed by means of the BPI-SF questionnaire for all treatment arms at each clinic visit or telephone contact from Dose 1, Day 1 until the Week 48 visit and for treatment Arms A and B on the day of each telephone contact at Weeks 28, 32, 40, and 44.

Section 7.1.1 Tabulated overview:

Footnote i, footnote j, and footnote k:

Old text:

i. When a subject is determined to be eligible, the subject will be trained on daily PRO pain data collection using a handheld device. The subject will then complete the pain assessment daily for 4 days prior to randomization and then ~~for the 7 days prior to Dose 1, Day 1.~~

j. Pain will be assessed during the screening period daily for 4 days prior to randomization and ~~for the 7 days prior to Dose 1, Day 1, then daily for 7 days prior to each scheduled treatment visit through the end of Week 48~~. Subjects will complete the daily pain assessment using a handheld device. The daily PRO pain input results should be reviewed at the visit to check for completeness.

k. For Treatment Arms A and B only, pain data will be collected daily using the handheld device for ~~7 days~~ prior to Week 36 and 48 visits, and daily for ~~7 days~~ prior to each telephone contact at Weeks 28, 32, 40, and 44. For Treatment Arms A and B only the BPI SF and the NCCN FACT-P Symptom Index-17 (NCCN-FACT FPSI-17) questionnaires will be completed on the day of the Week 36 and 48 visits and on the day of each telephone contact at Weeks 28, 32, 40, and 44. Twenty-four (24) hour analgesic use will be collected by the study investigator at Week 36 and 48 Visits and at each telephone contact (in Arms A and B) at Weeks 28 (±7 days), 32 (±7 days), 40 (±7 days), and 44 (±7 days).

New text:

i. When a subject is determined to be eligible, the subject will be trained on daily PRO pain data collection using a handheld device. The subject will then

complete the pain assessment daily for 4 days prior to randomization and then daily for one week (6 days prior to Cycle 1, Day 1 or subsequent visits, as applicable, plus the morning of the visit).

j. Pain will be assessed during the screening period daily for 4 days prior to randomization and daily for one week (6 days prior to Cycle 1, Day 1 or subsequent visits, as applicable, plus the day of the visit). Subjects will complete the daily pain assessment using a handheld device. The daily PRO pain input results should be reviewed at the visit to check for completeness.

k. For Treatment Arms A and B only, pain data will be collected daily using the handheld device for one week (6 days prior to the applicable visit, plus the day of the visit) prior to Week 36 and 48 visits, and daily for one week (6 days prior to the applicable phone call, plus the day of the phone call) prior to each telephone contact at Weeks 28, 32, 40, and 44. For Treatment Arms A and B only the BPI SF and the NCCN FACT-P Symptom Index-17 (NCCN-FACT FPSI-17) questionnaires will be completed on the day of the Week 36 and 48 visits and on the day of each telephone contact at Weeks 28, 32, 40, and 44. Twenty-four (24) hour analgesic use will be collected by the study investigator at Week 36 and 48 Visits and at each telephone contact (in Arms A and B) at Weeks 28 (±7 days), 32 (±7 days), 40 (±7 days), and 44 (±7 days).

Section 7.1.2.1 Screening Period:

19th Bullet :

Old text:

- for the 7 days prior to Dose 1, Day 1 (Day 7 will be done on the day of Dose 1, Day 1 of the protocol).

New text:

- for 6 full days prior to the dosing visit plus the morning of the day of the dosing visit prior to Dose 1, Day 1.

Section 7.1.2.3 Initial visit - Dose 1, Day 1 (Treatment arms A, B, C)

Last bullet:

Old text:

- Subjects will complete the pain assessment daily for ~~the 7 days~~ prior to Dose ~~2,~~ Day 1.

New text

- Subjects will complete the pain assessment daily for 6 days prior to the dosing visit plus the morning of the dosing visit prior to Dose 1, Day 1

Section 7.1.2.4 Doses 2 to 6 (Treatment arms A and B) and Section 7.1.2.5 Doses 2 to 12 (Treatment arm C)

19th bullet:

Old text:

- ~~After each visit,~~ subjects will complete the pain assessment daily for ~~the 7 days prior to next dose, Day 1 or for the 7 days prior to the EOT visit.~~

New text:

- Subjects will complete the pain assessment daily <u>for 6 days prior to the dosing visit plus the morning of the dosing visit</u>

Section 7.1.2.6 End of treatment visit

17th bullet:

Old text:

- ~~After the visit,~~ subjects will complete the pain assessment daily for the ~~7 days~~ prior to the Week 28 telephone contact (Treatment Arms A and B only).

New text:

- Subjects will complete the pain assessment daily for <u>6 days prior to plus the morning of</u> the Week 28 telephone contact (Treatment Arms A and B only).

Section 7.1.2.7.1 Active follow-up with clinic visits

6th paragraph, 1st bullet:

Old text:

- Pain will be assessed daily for ~~7 days~~ prior to each telephone contact at Weeks 28, 32, 40, and 44 and the daily PRO pain input data will be reviewed for completeness at the telephone contact.

New text:

- Pain will be assessed daily for <u>6 days prior to the visit plus the morning of</u> each telephone contact at Weeks 28, 32, 40, and 44 and the daily PRO pain input data will be reviewed for completeness at the telephone contact.

Section 7.3.4.4 Pain Endpoints:

Paragraph 3:

Old text:

The screening baseline for pain endpoints will be based on the pre-Dose 1, 7-day pain assessment.

New text:

The screening baseline for pain endpoints will be based on the pre-Dose 1, 7-day pain assessment. (Day 7 will be done on the day of Dose 1, Day 1 of the protocol.)

Change 5:

Section 5.2.1 Withdrawal:

3rd bullet:

Old text:

- A dose delay of more than 4 weeks (maximum of 8 weeks ~~[± 7 days]~~ between 2 injections)

New text:

- A dose delay of more than 4 weeks (maximum of 8 weeks between 2 injections)

Section 6.4.7 Dose Delays:

Logistical difficulties, Paragraph 3:

Old text:

A dose delay of more than 4 weeks (maximum of 8 weeks ~~[± 7 days]~~ between 2 injections) will lead to study drug discontinuation.

New text:

A dose delay of more than 4 weeks (maximum of 8 weeks between 2 injections) will lead to study drug discontinuation.

Change 6:

Synopsis - Diagnosis and main criteria for inclusion and 5.1.1 Inclusion Criteria:

2nd bullet:

Old text:

C. Serum PSA progression defined as 2 subsequent increases in PSA over a previous reference value ~~(a minimum of 2 ng/mL [µg/L])~~ **OR**

New text:

c. Serum PSA progression defined as 2 subsequent increases in PSA over a previous reference value, with a PSA value of ≥ 2 ng/mL at the time of the second increase, OR

Change 7:

Section 6.9.1 Prior therapy:

3rd bullet:

Old text:

- All other prior medications, including pain medications and taken in the 30 days prior to start of study treatment (Dose 1) will be recorded in the subject's medical record and in the appropriate eCRF. The generic or trade name, indication, dosage, and start and stop dates must be recorded.

New text:

- All other prior medications, including but not limited to pain medications, antibiotics, steroids, bisphosphonates, iron therapy, or radiation therapy taken in the 30 days prior to start of study treatment (Dose 1) will be recorded in the subject's medical record and in the appropriate eCRF. The generic or trade name, indication, dosage, and start and stop dates must be recorded.

Section 7.2.2 Medical history:

3rd bullet:

Old text:

Considered relevant to the study up to

New text:

Considered relevant to the study up to 6 months prior to screening: History of fractures, trauma, osteomyelitis, joint and dental infections, cellulitis, edema, arthritis, metabolic bone disease, or limitation of function; history of orthopedic

(e.g., presence and location of prosthetic implants) and non-orthopedic (e.g., ileal conduit) surgery that might affect the results of bone scintigraphy; history of recent scintigraphy, especially with 131I, 67Ga, or 111In.

Change 8:

Title page

Old text:

Sponsor's medical expert:	PPD ~~Bayer S.p.A. V.le Certosa 210~~ ~~20156 Milan, Italy~~ PPD

New text:

Sponsor's medical expert:	PPD PPD Milano V.le Certosa 210 20156 Milano - Italia Phone: PPD

Change 9:

Signature page

Old text:

Name:		Role:	Global Clinical Leader, PPD

New text:

Name:	PPD PPD	Role:	Global Clinical Leader, PPD

Change 10:

Synopsis – Methodology (14th paragraph), Section 4.1 Design overview (14th paragraph), Section 6.8 Post-study therapy (1st paragraph), Section 7.1.2.8.1 End of active follow-up with clinic visits (3rd paragraph), Section 7.1.2.8.2 End of active follow-up without scheduled clinic visits (3rd paragraph):

Old text:

~~After the active follow-up, subjects will enter the long term follow-up period and will be followed via telephone follow-up at 6-month intervals for investigator-reported, radium-223 dichloride related SAEs, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies, and survival up to 7 years after the last dose of radium-223 dichloride or until death. Once a separate extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical trials, has been implemented, the study subjects surviving after the end of the active follow-up will be transitioned to this separate extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned.~~

New text:

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and SAEs, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies including leukemias and solid tumors, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject.

Until the transition to the long term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up).

Section 4.1 Design Overview

Added Text:

Active follow-up period *with* clinic visits:

Subjects who discontinue study treatment and who did not have an SSE will enter an active follow-up period with clinic visits. These subjects will be evaluated every 12 weeks (± 7 days) for pain endpoints, radiological progression, SSEs, survival, treatment-related AEs and serious adverse events (SAEs), and the initiation of other anti-cancer therapies. In addition, subjects who receive cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice. During this period, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs, regardless of the investigator's causality assessment.

The active follow-up period with clinic visits extends from the discontinuation of the treatment period until the subject experiences an SSE, can no longer travel to the clinic, receives further treatment with cytotoxic chemotherapy for prostate cancer, other systemic radioisotopes, hemibody EBRT, or other investigational drugs, dies, is lost to follow-up, or withdraws informed consent and actively objects to collection of further data.

Active follow-up period *without* clinic visits:

Subjects from the treatment period or the active follow-up period with clinic visits who can no longer travel to the clinical site will be followed for survival, treatment-related AEs and SAEs, SSEs, pain endpoints, and the initiation of other anti-cancer therapies with a phone call every 12 weeks (± 7 days). In addition, subjects who receive cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice. During this period, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs, regardless of the investigator's causality assessment.

The active follow-up period **without** clinic visits extends from the EOT period or the end of active follow-up with clinic visits until the subject experiences an SSE, dies, is lost to follow-up, or withdraws informed consent and actively objects to collection of further data.

The maximum duration of the active follow-up is 7 years from the last dose of radium-223 dichloride received by the subject.

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported radium-223 dichloride-related AEs and SAEs, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies, including leukemias and solid tumors, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-

up, subjects will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject.

Until the transition to the long term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up).

Section 7.1.2.7.1. Active Follow-up with clinic visits:

Old text:

The subject should return to the clinic every 12 weeks (± 14 days) following the EOT visit until the subject experiences a symptomatic skeletal event or until the primary efficacy analysis matures, whichever occurs first~~; provided that active follow-up will not last less than 2 years or more than 7 years following the subject's last study treatment.~~

In addition to the visits at Weeks 36 and 48, the subjects in Treatment Arms A and B will receive telephone contacts at Weeks 28, 32, 40, and 44 to assess for possible SSE risks and will continue PRO data collection. Pain data, 24-hour analgesic use, BPI and NCCN-FACT FPSI-17 questionnaires will also be collected as detailed below.

New text:

The subject should return to the clinic every 12 weeks (± 14 days) following the EOT visit until the subject experiences a symptomatic skeletal event or until the primary efficacy analysis matures, whichever occurs first. Active follow-up will continue for 2 years in this study and not more than 7 years total including the long term follow-up study (if the subject has signed the ICF).

To the extent possible, subjects discontinuing treatment prematurely should nonetheless complete the Week 8, 16, 24, 36, and 48 clinic visits and any applicable tumor assessments scheduled with respect to treatment start. Similarly, subjects in Treatment Arms A and B should receive Week 28, 32, 40, and 44 telephone contacts at the regularly scheduled time with respect to treatment start.

In addition to the visits at Weeks 36 and 48 (from the start of treatment) the subjects in Treatment Arms A and B will receive telephone contacts at Weeks 28, 32, 40, and 44 (from the start of treatment) to assess for possible SSE risks and will continue PRO data collection. Pain data, 24-hour analgesic use, BPI and NCCN-FACT FPSI-17 questionnaires will also be collected as detailed below.

Section 7.1.2.9 Long-term follow-up to 7 years following last dose

Old text:

This period starts when subjects have completed the active follow-up period and ends 7 years after the last dose of radium-223 dichloride or when the subject dies. ~~Once a separate extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical trials, has been implemented, the study subjects surviving after the end of the active follow-up will be transitioned to this separate extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned.~~

New text:

This period starts when subjects have completed the active follow-up period and ends 7 years after the last dose of radium-223 dichloride or when the subject dies. All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and SAEs, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies including leukemias and solid tumors, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject.

Until the transition to the long term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up).

Section 10. Premature termination of the study:

Old text:

~~• If a separate extended safety follow-up protocol is implemented, the study subjects surviving after the end of the active follow-up will be transitioned to this separate extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned.~~

New text:

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and SAEs, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies including leukemias and solid tumors, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

Transition of all subjects into the separate long-term follow-up study will begin following the later of primary endpoint completion or 2 years after the last radium-223 dichloride treatment is administered to the last treated subject.

Until the transition to the long term follow-up study begins, some subjects may begin long-term follow-up in this study. This study will end when all subjects have transitioned into the long-term follow-up study or discontinued from this study for another reason (e.g., Consent Withdrawn, Lost to Follow-up).

Change 11:

Synopsis - Methodology and Section 4.1 Design overview

3rd paragraph:

Old text:

The treatment period begins at the time of randomization. During the treatment period, study medication is administered every 28 days and may be delivered in an outpatient setting.

New text:

The treatment period begins at the time of randomization. During the treatment period, study medication is administered every 28 days (±7 days) from Dose 1 and may be delivered in an outpatient setting.

Change 12:

Section 3 Investigators and other study personnel

1st paragraph:

Old text:

Global Clinical Leader for the study:

PPD

Bayer HealthCare Pharmaceuticals, Inc.
100 Bayer Blvd.
PO Box 915
Whippany, New Jersey 07981
Tel: PPD

New text:

Global Clinical Leader for the study:

PPD

Bayer HealthCare Pharmaceuticals, Inc.
100 Bayer Blvd.
PO Box 915
Whippany, New Jersey 07981
Tel: PPD

Change 13:

Section 7.5.1.3 Assessments and documentation of adverse events

4th paragraph:

Old text:

All AEs and SAEs occurring beyond 30 days after the last treatment have to be reported if considered to be related to study medication or if related to an SSE (during active follow-up with clinic visits only). However, 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. If a subject is unable to provide required details for events of interest, this information may need to be obtained from the primary provider.

New text:

All AEs and SAEs occurring beyond 30 days after the last treatment have to be reported if considered to be related to study medication or if related to an SSE (during active follow-up with clinic visits only). However, 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. In subjects who receive cytotoxic chemotherapy: all occurrences of febrile neutropenia or hemorrhage during their chemotherapy treatment must be reported as SAEs at any time and for up to 6 months thereafter. If a subject is unable to provide required details for events of interest, this information may need to be obtained from the primary provider.

Change 14:

Section 6.4.7 Dose Delays, Disease Progression

2nd paragraph, 4th and 5th sentence:

Added text:

If the subject is not treated with any of the prohibited anti-cancer therapies, the administration of study drug may be continued until completion of 6/12 cycles. If, in the investigator's opinion, the subject will continue to receive clinical benefit from remaining on study treatment.

Change 15:

Section 5.2.1 Withdrawal Section

5th and 6th bullets:

Old text:

- If the subject experiences any non-hematological CTCAE Grade 4 ~~toxicity~~ lasting > ~~7 days~~ despite adequate treatment

- If the subject experiences Grade 3 neutropenia or Grades 3 or 4 thrombocytopenia lasting > 2 weeks or Grade 4 neutropenia lasting > ~~7 days~~ despite adequate treatment. Blood transfusions and biologic response modifiers, such as GM-CSF or G-CSF can be used for the treatment of hematological abnormalities during the treatment period.

New text:

- If the subject experiences any non-hematological CTCAE Grade 4 adverse event lasting > 1 week despite adequate treatment regardless of causality.

- If the subject experiences Grade 3 neutropenia or Grades 3 or 4 thrombocytopenia lasting > 2 weeks or Grade 4 neutropenia lasting > 1 week despite adequate treatment regardless of causality. Blood transfusions and biologic response modifiers, such as GM-CSF or G-CSF can be used for the treatment of hematological abnormalities during the treatment period.

Section 6.4.7 Dose Delays, Myelosuppression

2nd and 3rd bullets:

Old text:

- If a subject experiences sustained CTCAE Grade 3 neutropenia or sustained CTCAE Grades 3 or 4 thrombocytopenia (see Table 6-1) lasting > 2 weeks despite adequate treatment, the subject must be discontinued from treatment with radium-223 dichloride.

- If a subject experiences sustained CTCAE Grade 4 neutropenia (see Table 6-1) lasting > 1 week despite adequate treatment, the subject must be discontinued from treatment with radium-223 dichloride.

New text:

- If a subject experiences sustained CTCAE Grade 3 neutropenia or sustained CTCAE Grades 3 or 4 thrombocytopenia (see Table 6-1) lasting > 2 weeks despite adequate treatment and regardless of causality, the subject must be discontinued from treatment with radium-223 dichloride.

- If a subject experiences sustained CTCAE Grade 4 neutropenia (see Table 6-1) lasting > 1 week despite adequate treatment and regardless of causality, the subject must be discontinued from treatment with radium-223 dichloride.

Section 6.4.7 Dose delays

1st paragraph:

Old text:

If a subject experiences any non-hematological CTCAE (version 4.03) Grade 4 toxicity lasting more than 7 days despite adequate treatment, further study drug administration must be discontinued.

New text:

If a subject experiences any non-hematological CTCAE (version 4.03) Grade 4 toxicity regardless of causality lasting more than 7 days despite adequate treatment, further study drug administration must be discontinued.

Change 16:

Section 5.1 Eligibility

2nd paragraph:

Old text:

Rescreening of screen failed subjects is only allowed once after prior approval from the Bayer-designated medical representative. Sponsor approval of rescreening for a screen failed subject will be provided by written confirmation to the site. For these subjects who underwent screening procedures (i.e., scans and laboratory work) and cannot meet eligibility within the screening period (14 ± 7 days) due to logistical circumstances, screening procedures may need to be repeated. At the time of rescreening, all expired procedures must be repeated and be within 14 ± 7 days prior to randomization. ~~A maximum window of 35 days is permitted from signing the informed consent form (ICF) to randomization.~~

New text:

Rescreening of screen failed subjects is only allowed once after prior approval from the Bayer-designated medical representative. Sponsor approval of rescreening for a screen failed subject will be provided by written confirmation to the site. For these subjects who underwent screening procedures (i.e., scans and laboratory work) and cannot meet eligibility within the screening period (14 ± 7 days) due to logistical circumstances, screening procedures may need to be repeated. At the time of rescreening, all expired procedures must be repeated and be within 14 ± 7 days prior to randomization. The maximum period allowed for screening will be 35 days (14 days screening + 7 day window + 14 days for rescreening).

Section 6.4.7 Dose delays, Logistical difficulties

1st and 3rd paragraphs:

Old text:

Screening to Dose 1: An additional 14 days will be permitted for the 14-day screening window for 'failed' quality of investigational product that requires replacement or extraordinary logistical issues. Prior written approval by the sponsor designee is required and screening assessments may need to be repeated

to be within the 14 (± 7)-day window prior to randomization. The maximum period allowed for screening will be 35 days.

Doses 2 to 6 (or Doses 2 to 12 for Treatment Arm C): An additional 28 days will be permitted for Doses 2 to 6 (or Doses 2 to 12 for Treatment Arm C) for 'failed' quality of investigational product that requires replacement or extraordinary logistical issues. Prior written approval by the sponsor designee is required.

A dose delay of more than 4 weeks (maximum of 8 weeks ~~[± 7 days]~~ between 2 injections) will lead to study drug discontinuation.

New text:

Screening to Dose 1: An additional 14 days will be permitted for the 14-day screening window for 'failed' quality of investigational product that requires replacement or extraordinary logistical issues. Prior written approval by the sponsor designee is required and screening assessments may need to be repeated to be within the 14 (± 7)-day window prior to randomization. The maximum period allowed for screening will be 35 days (14 days screening + 7-day window + 14 days for rescreening).

Doses 2 to 6 (or Doses 2 to 12 for Treatment Arm C): An additional 28 days will be permitted for Doses 2 to 6 (or Doses 2 to 12 for Treatment Arm C) for 'failed' quality of investigational product that requires replacement or extraordinary logistical issues. Prior written approval by the sponsor designee is required.

A dose delay of more than 4 weeks (maximum of 8 weeks between 2 injections) will lead to study drug discontinuation.

Change 17:

Section 7.1.2.1 Screening period

15th paragraph:

Old text:

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed within 14 ± 7 days ~~of screening~~ (i.e., during the screening period). If MRI / CT scan of the abdomen and pelvis, and chest X-ray performed within 8 weeks of randomization are available, they do not need to be repeated at baseline.

New text:

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to

confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed within 14 ± 7 days prior to randomization (i.e., during the screening period). If MRI / CT scan of the abdomen and pelvis, and chest X-ray performed within 8 weeks of randomization are available, they do not need to be repeated at baseline.

Change 18:

Section 7.1.1 Tabulated overview

Footnote h:

Old text:

Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. At all sites (in US and outside US), weight is to be taken only once for each dose. For non-US sites ~~and US sites not using the central PRD depot~~, the weight should be performed within 72 hours prior to dosing. For US sites ~~using the central PRD depot ONLY~~, subject weight for the dose day should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits. Please note this is applicable to all dosing visits.

New text:

Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. At all sites (in US and outside US), weight is to be taken only once for each dose. For non-US sites, the weight should be performed within 72 hours prior to dosing. For US sites, subject weight for the dose day should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits. Please note this is applicable to all dosing visits.

Section 7.1.2.1 Screening period, Section 7.1.2.3 Initial visit - Dose 1, Day 1 (Treatment arms A, B, C), Section 7.1.2.4 Doses 2 to 6 (Treatment arms A and B), Section 7.1.2.5 Doses 2 to 12 (Treatment arm C), and Section 7.5.3.5 Body weight

Old text:

- For non-US sites ~~and US sites not using the central PRD depot~~, the weight should be performed within 72 hours prior to dosing.

New text:

- For non-US sites, the weight should be performed within 72 hours prior to dosing.

Change 19:

Synopsis – Methodology and Section 4.1 Design Overview

3rd paragraph:

Old text:

The treatment period begins at the time of randomization. During the treatment period, study medication is administered every 28 days (± 7 days) from Dose 1 and may be delivered in an outpatient setting. At each visit, prior to receiving radium 223 dichloride, the subject will be evaluated for adverse events (AEs) and laboratory abnormalities to determine whether it is safe to continue treatment.

New text:

The treatment period <u>for efficacy purposes</u> begins at the time of randomization. During the treatment period, study medication is administered every 28 days <u>(± 7 days) from Dose 1</u> and may be delivered in an outpatient setting. At each visit, prior to receiving radium 223 dichloride, the subject will be evaluated for adverse events (AEs) and laboratory abnormalities to determine whether it is safe to continue treatment.

Section 7.1.1 Tabulated overview

Footnote l:

Old text:

l. The randomization will be permuted-block, stratified by the use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total alkaline phosphatase (< 220 U/L versus ≥ 220 U/L), and by average WPS of the BPI-SF (WPS ≤4 versus WPS > 4). ~~This assessment will occur when the second call is made to the IVRS / IWRS to order drug: ≥ 10 to 14 days prior to study treatment administration.~~

New text:

1. The randomization will be permuted-block, stratified by the use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total alkaline phosphatase (< 220 U/L versus ≥ 220 U/L), and by average WPS of the BPI-SF (WPS ≤4 versus WPS > 4). Treatment group assignment will occur when the subject is randomized via IVRS / IWRS; this randomization step at up to 28 days prior to Dose 1. Randomization steps triggers an order for study drug (durations vary based on country specific ordering lead times; US depot requires additional step).

Section 7.1.2.2 Randomization

1st paragraph:

Old text:

Subjects will be randomized to either: radium-223 dichloride 50 kBq/kg IV every 28 days for up to 6 doses or radium-223 dichloride 8~~0~~ kBq/kg IV every 28 days up to 6 doses or radium-223 dichloride 50 kBq/kg IV every 28 days up to 12 doses. The randomization will be permuted-block, stratified by the use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total ALP (< 220 U/L versus ≥ 220 U/L), and by the average of the daily WPS of the screening BPI-SF (WPS ≤4 versus WPS > 4). ~~This assessment will occur when the second call is made to the IVRS / IWRS to order drug ≥ 10 to 14 days prior to study treatment administration.~~

New text:

The treatment period for efficacy purposes begins at the time of randomization. Subjects will be randomized to either: radium-223 dichloride 50 kBq/kg (55 kBq/kg after new NIST standard implementation) IV every 28 days for up to 6 doses or radium-223 dichloride 80 kBq/kg (88 kBq/kg after implementation of NIST update) IV every 28 days up to 6 doses or radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) IV every 28 days up to 12 doses. The randomization will be permuted-block, stratified by the use of prior chemotherapy (≤ 1 regimen versus > 1 regimen), by total ALP (< 220 U/L versus ≥ 220 U/L), and by the average of the daily WPS of the screening BPI-SF (WPS ≤ 4 versus WPS > 4). Treatment group assignment will occur when the subject is randomized via IVRS / IWRS; this randomization step at up to 28 days prior to Dose 1. Randomization step triggers an order for study drug (durations vary based on country specific ordering lead times; US depot requires additional step).

Section 8.4.4 Safety Analysis

5th paragraph

Added text:

The treatment period <u>for safety purposes</u> for this study extends from the initiation of treatment until 30 days after the last administration of radium-223 dichloride. Events starting or worsening within the treatment period will be considered treatment-emergent.

Change 20:

Section 7.1.2.4 Doses 2 to 6 (Treatment Arms A and B)

Old text:

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed at ~~8 weeks and 16 weeks after the start of treatment (i.e., on Dose 3 and Dose 5 visits)~~

New text:

- Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed at <u>Week 8, Week 16, Week 24, then every 12 weeks for 2 years after the subject's last dose of radium-223 dichloride or until radiologic progression.</u>

Section 7.1.2.5 Doses 2 to 12 (Treatment Arm C)

Old text:

Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed ~~at 8 weeks, 16 weeks, 24 weeks and 36 weeks after the start of treatment (i.e., on Dose 3, 5, 7 and 10 Visits).~~

New text:

Tumor assessment by MRI / CT scan of the abdomen and pelvis, chest X-ray (in the presence of suspicious lesion[s], a chest CT scan will be performed to confirm and characterize the lesion[s]), and whole body technetium-99 bone scan will be performed <u>at Week 8, Week 16, Week 24, then every 12 weeks for 2 years after the subject's last dose of radium-223 dichloride or until radiologic progression.</u>

Change 21:

Section 7.5.1.3 Assessments and documentation of adverse events:

2nd paragraph:

Old text:

A laboratory test abnormality should be reported as an AE if it is considered clinically relevant (e.g., causing the subject to withdraw from the study), requires treatment, causes apparent clinical manifestations, or is judged as relevant by the investigator. Each event should be described in detail along with start and stop dates (onset and resolution of event), intensity, temporal and causal relationship to investigational product and / or protocol-related procedures, possibly 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 and laboratory results with grades and causality assessments must be documented and retained in the source documentation.

New text:

A laboratory test abnormality should be reported as an AE if it is considered clinically relevant (e.g., causing the subject to withdraw from the study), requires treatment, causes apparent clinical manifestations, or is judged as relevant by the investigator. Laboratory abnormalities that are not considered clinically significant do not need to be entered as an AE. Laboratory abnormalities related to the disease under study (e.g. PSA, testosterone) do not need to be recorded as AEs. Each event should be described in detail along with start and stop dates (onset and resolution of event), intensity, temporal and causal relationship to investigational product and / or protocol-related procedures, possibly 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 and laboratory results with grades and causality assessments must be documented and retained in the source documentation.

Change 22:

Section 6.2 Identity of study treatment:

2nd paragraph:

Old text:

The product is manufactured ~~for Bayer in cooperation with contract partner Algeta ASA, Norway~~. The product is produced according to Good Manufacturing Practice (GMP). The product will be delivered in a glass vial, ready-to-use with a certified activity. Radium-223 dichloride is shipped in a lead container and Type A radioactive package according to international transportation guidelines for radioactive materials.

New text:

The product is manufactured by Institute for Energy Technology (IFE), Isotope laboratories Instituttveien 18,NO-2007, Kjeller, Norway on behalf of Bayer AS, Kjelsäsveien 172 A, N0-0884 Oslo, Norway. The product is produced according to Good Manufacturing Practice (GMP). The product will be delivered in a glass vial, ready-to-use with a certified activity. Radium-223 dichloride is shipped in a lead container and Type A radioactive package according to international transportation guidelines for radioactive materials.

Change 23

Section 7.3.1 Efficacy variables

7th bullet:

Deleted text:

- ~~Change in analgesic use~~

Section 7.3.1 Efficacy variables

11th, 12th, 13th, 14th, 15th bullet points

Added text:

- Increase in analgesic use rate
- Time to increase in pain management
- Pain improvement without increase in analgesic use rate
- Time to pain progression or increase in analgesic use
- Change in last 24-hour analgesic use score

Section 7.3.4.4 Pain endpoints

4th and 5th paragraph

Old text:

~~For purposes of determining pain improvement and pain progression, a daily analgesic use score will be calculated programmatically for each subject for each day, based on the subject's complete CRF data on analgesic use. Analgesic use data will be coded using the WHO drug dictionary. Oral morphine equivalents (OMEs) will be calculated. Each day's analgesic use in OME units will be calculated using the applicable CRF-reported dates and date ranges. The AQA~~

~~will be applied to obtain a daily analgesic use score. Details will be described in the SAP.~~

Additional details on pain endpoints~~, including details on the applicable baselines, evaluability for daily analgesic use increase, calculation of daily analgesic use score(s) applicable to each baseline and post-baseline time point, and definition of baseline values and "increase" in daily analgesic use for purposes of these endpoints,~~ will be provided in the SAP.

New text:

Additional details on pain endpoints will be provided in the SAP.

Section 7.3.4.4.1 Pain improvement rate

1st paragraph

Old text:

Pain improvement is defined for each baseline in subjects evaluable for pain improvement at that baseline, i.e., subjects entering the study with a WPS of at least 4 ~~and evaluable for analgesic use increase~~ at the respective baseline assessment. Pain improvement with respect to each baseline is defined in each applicable evaluable subject at each applicable post-baseline assessment time point as a 30% and 2-point decrease in WPS over 2 consecutive measurements conducted at least 4 weeks apart~~, without an increase in analgesic use~~.

New text:

Pain improvement is defined for each baseline in subjects evaluable for pain improvement at that baseline, i.e., subjects entering the study with a WPS of at least 4 at the respective baseline assessment. Pain improvement with respect to each baseline is defined in each applicable evaluable subject at each applicable post-baseline assessment time point as a 30% and 2-point decrease in WPS over 2 consecutive measurements conducted at least 4 weeks apart.

Section 7.3.4.4.2 Time to pain progression

1st paragraph

Old text:

Pain progression is defined for each baseline in subjects evaluable for pain progression at the applicable baseline, i.e., subjects with a WPS of ≤ 7 at the respective baseline assessment. Pain assessments will occur daily for one week, beginning a week prior to each visit and including the day of the visit. An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 daily questions. Pain progression is defined as the occurrence of ~~either~~ a pain

increase ~~or an increase in pain management~~ with respect to the applicable baseline, ~~whichever occurs first~~.

New text:

Pain progression is defined for each baseline in subjects evaluable for pain progression at the applicable baseline, i.e., subjects with a WPS of ≤ 7 at the respective baseline assessment. Pain assessments will occur daily for one week, beginning a week prior to each visit and including the day of the visit. An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 daily questions. Pain progression is defined as the occurrence of a pain increase with respect to the applicable baseline.

Section 7.3.4.4.2 Time to pain progression

3rd paragraph

Deleted text:

~~An increase in pain management is defined as follows:~~

~~For patients not on opioids at the applicable baseline, initiation of short or long-acting opioid use for pain will constitute an increase in pain management. For patients being treated with ≤ 600 OME (oral morphine equivalents) of opioids at the applicable baseline, an increase by 1 point in the daily AQA score and increase ≥ 50% in daily OMEs will constitute an increase in pain management. For patients being treated at the highest AQA level (> 600 OME/day) at the applicable baseline, an increase ≥ 50% in daily OMEs from that baseline will constitute an increase in pain management.~~

Section 7.3.5.5 Exploratory pain and analgesic use endpoints

Added text:

For purposes of determining exploratory increase in analgesic use, pain improvement without an increase in analgesic use, and pain progression without an increase in analgesic use, a daily analgesic use score will be calculated programmatically for each subject for each day, based on the subject's complete CRF data on analgesic use. Analgesic use data will be coded using the WHO drug dictionary. Oral morphine equivalents (OMEs) will be calculated. Each day's analgesic use in OME units will be calculated using the applicable CRF-reported dates and date ranges. The AQA will be applied to obtain a daily analgesic use score. Details will be described in the SAP.

An increase in analgesic use is defined for each baseline in evaluable subjects, i.e. subjects with a valid AQA analgesic use score at the applicable baseline, as follows:

For subjects not on opioids at the applicable baseline, initiation of short or long-acting opioid use for pain will constitute an increase in analgesic use. For subjects

being treated with ≤ 600 OME (oral morphine equivalents) of opioids at the applicable baseline, an increase by 1 point in the daily AQA score and increase ≥ 50% in daily OMEs will constitute an increase in analgesic use. For subjects being treated at the highest AQA level (> 600 OME/day) at the applicable baseline, an increase ≥ 50% in daily OMEs from that baseline will constitute an increase in analgesic.

Additional details on analgesic use endpoints, including details on the applicable baselines, evaluability for daily analgesic use increase, calculation of daily analgesic use score(s) applicable to each baseline and post-baseline time point, and definition of baseline values and "increase" in daily analgesic use for purposes of these endpoints, will be provided in the SAP.

7.3.5.5.1 Increase in analgesic use rate

Increase in analgesic use rate is defined for each applicable baseline as the number of subjects with an increase in analgesic use from that baseline, divided by the number of subjects evaluable for analgesic use at that baseline.

7.3.5.5.2 Time to Increase in analgesic use

Time to increase in analgesic use is defined for each applicable baseline for applicable subjects as the time (in days) from the respective baseline until occurrence of the first post-baseline increase in analgesic use pain progression event. Subjects without increase in analgesic use as of the last applicable post-baseline assessment, whether or not surviving, will be censored at the last applicable post-baseline assessment. Subjects with insufficient applicable baseline assessment(s) or without adequate post-baseline assessment(s) will be censored at the applicable baseline date. Additional censoring and other details will be described in the SAP.

7.3.5.5.3 Pain improvement rate without increase in analgesic use

Pain improvement without increase in analgesic use is defined for each baseline in subjects evaluable for both pain improvement and increase in analgesic use at that baseline, as defined in Section 7.3.4.4.1 and Section 7.3.5.5.1 respectively, at the applicable baseline assessment. Pain improvement without increase in analgesic use is defined in each applicable evaluable subject at each applicable post-baseline assessment time point with respect to each baseline, as a 30% and 2-point decrease in WPS over 2 consecutive measurements conducted at least 4 weeks apart, without an increase in analgesic use.

Pain improvement without increase in analgesic use rate is defined for each baseline and applicable post-baseline assessment time point as the number of subjects with pain improvement without increase in analgesic use at the time point, divided by the total number of subjects evaluable for pain improvement without increase in analgesic use with respect to the applicable baseline.

7.3.5.5.4 Time to pain progression or increase in analgesic use

Time to pain progression is defined for each baseline in subjects evaluable for both pain progression and increase in analgesic use, as defined in Section 7.3.4.4.2 and 7.3.5.5.1 respectively, at the applicable baseline assessment,

The time to pain progression or increase in analgesic use is defined for each applicable baseline for applicable subjects as the time (in days) from the respective baseline until occurrence of the first post-baseline pain progression (pain increase) event or increase in analgesic use event, whichever occurs first. Subjects with neither pain progression nor an increase in analgesic use as of the last applicable post-baseline assessment, whether or not surviving, will be censored at the last applicable post-baseline assessment. Subjects not evaluable for both pain progression and increase in analgesic use, and subjects without adequate post-baseline assessment(s), will be censored at the applicable baseline date. Additional censoring and other details will be described in the SAP.

7.3.5.5.5 Change in the last 24-hour analgesic use score

Change in the last 24-hour analgesic use score is calculated based on the subject's analgesic use in the last 24 hours CRF data.

For each subject, each analgesic medication from analgesic use in the last 24 hour's data taken at applicable clinic visits (and in Arms A and B, at telephone contacts) will be coded using the WHO drug dictionary and OMEs will be calculated from the coded data.

For each subject and applicable visit or telephone contact, analgesic use in the last 24 hours will be scored using the AQA (see Section 14.9) based on the coded medications and corresponding OME quantities.

Details on coding and scoring will described in the SAP.

For each subject, for each applicable baseline and post-baseline time point, the subject's change in the last 24-hour analgesic use is defined as the difference between the subject's last 24 hour AQA score at the post-baseline time point and at the applicable baseline.

Change 24

Title page, Synopsis: Title, Synopsis: Study Objectives, Synopsis: Doses, Synopsis: Methodology, Synopsis: Plan for statistical analysis, Section 1.2 Study rationale, Section 2. Study objectives, Section 4.1 Design overview, Section 6.1 Treatments to be administered, Section 6.3 Treatment assignment, Section 6.4.3 Dose calculation, Section 7.1.2.2 Randomization, Section 8.1 General considerations, Section 8.4.1 Primary efficacy analysis, Section 8.4.4 Safety analyses, Section 8.6 Determination of sample size

Global Change

Old text:

50 kBq/kg

New text:

50 kBq/kg (55 kBq/kg after implementation of NIST update)

Old text:

80 kBq/kg

New text:

80 kBq/kg (88 kBq/kg after implementation of NIST update)

Section 6.2 Identity of study treatment

1st Paragraph and 3rd paragraph

Old text:

The alpha particle-emitting radiopharmaceutical, radium-223 dichloride, is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of radium-223 dichloride for IV administration. Radium-223 is an alpha particle emitter with a physical half-life of 11.4 days. The product is isotonic and has a pH of 6.0 to 8.0. The radioactive concentration at the reference date is 1,000 kBq/mL. The product has a pre-calibration of 14 days. When administered on a day other than the reference day, the volume should be corrected according to the physical decay table.

The volume per vial is 6 mL, corresponding to 6 MBq at the reference day. Radium-223 dichloride has a shelf life of 28 days from production day, when stored at ambient temperature. The shelf life has been demonstrated for temperatures from cold storage (2ºC to 8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing. For the US, study drug may be forwarded to the country depot in vials, where it will be prepared as a patient ready dose ([PRD], in a syringe) before being delivered to the site.

New text:

The alpha particle-emitting radiopharmaceutical, radium-223 dichloride, is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of radium-223 dichloride for IV administration. Radium-223 is an alpha particle emitter with a physical half-life of 11.4 days. The product is isotonic and has a pH of 6.0 to 8.0. The radioactive concentration at the reference date is 1,000 kBq/mL (1,100 kBq/ mL after implementation of NIST update). The product has a pre-calibration of 14 days. When administered on a day other than the reference day, the volume should be corrected according to the physical decay table.

The volume per vial is 6 mL, corresponding to 6 MBq (6.6 MBq after implementation of NIST update) at the reference day. Radium-223 dichloride has a shelf life of 28 days from production day, when stored at ambient temperature. The shelf life has been demonstrated for temperatures from cold storage (2ºC to 8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing. For the US, study drug may be forwarded to the country depot in vials, where it will be prepared as a patient ready dose ([PRD], in a syringe) before being delivered to the site.

Section 6.4.1 Dose calibration

3rd Paragraph:

Added text:

As of Amendment 2, NIST has established an updated standardization for radium-223 dichloride, which indicates that an approximately 10% difference existed between activity values obtained using the current standard and the updated standardization. The current NIST standard for radium-223 dichloride (NIST 2010 [31]) will remain in effect for this protocol until all Health Authorities for which Bayer holds a marketing application for radium-223 dichloride have approved the regulatory variations for Xofigo®, anticipated Q2 2016. All sites will be notified by Bayer when regulatory approvals are in place and the updated NIST standardization is to be implemented. Upon notification, and prior to the implementation, all sites will need to add a new dial-setting to their dose calibrators for the new NIST standardization for radium-223 dichloride (NIST update [32]), which should be documented on the appropriate study forms. This step will be performed so that all sites will have the new dial setting (NIST update [32]) in place at the time of implementation. The current dial setting (NIST 2010 [31]) will be used until the worldwide global implementation date anticipated for Q2 2016.

The change in the NIST radium-223 standard has no impact on subjects; subjects are receiving, and will continue to receive, the same actual dose and volume that was studied in ALSYMPCA and is associated with the proven safety and efficacy of radium-223 dichloride, though the stated nominal radiation dose received is being updated to reflect the new standard. Subjects who are on-treatment at the time the new NIST reference standard goes into effect will be notified of this change and will be required to sign a Patient Information Sheet to acknowledge that they have received information on the updated NIST standard calibration. All patients randomized after the new reference standard is in effect will sign a revised Informed Consent Form that contains the updated NIST standardization.

The formula for the calculation of the volume to be administered has to be changed respectively. See Section 6.4.3.

Section 6.4.3 Dose calculation

1st Paragraph

Old text:

$$\frac{\text{Body Weight (kg) x 50 ~~or 80~~ kBq/kg}}{\text{DK x 1,000 kBq/mL}} = \text{volume to be injected (mL)}$$

New text:

$$\frac{\text{Body Weight (kg) x 50 kBq/kg}^{a}}{\text{DK x 1,000 kBq/mL}^{b}} = \text{volume to be injected (mL)}$$

[a] 55 kBq/kg after implementation of NIST update

[b] 1100 kBq/mL after implementation of NIST update

Added text:

For high dose treatment arm:

$$\frac{\text{Body Weight (kg) x 80 kBq/kg}^{c}}{\text{DK x 1,000 kBq/mL}^{b}} = \text{volume to be injected (mL)}$$

[c] 88 kBq/kg after implementation of NIST update

[b] 1100 kBq/mL after implementation of NIST update

Section 12. Reference list

Added text:

31. Cessna JT, Zimmerman BE. Standardization of radium-223 by liquid scintillation counting. Appl Radiat Isot. 2010;68(7-8):1523-8.

32. Zimmerman BE, Bergeron DE, Cessna JT, Fitzgerald R, Pibida L. Revision of the NIST standard for ^{223}Ra: new measurements and review of 2008 data. Journal of Research of the National Institute of Standards and Technology. 2015;120:37-57 per section 12

Change 25

List of abbreviations

Added text:

CKD-EPI	Chronic kidney disease epidemiology
CRF	Complete report form
eGFR	Estimated Glomerular
IDMS	Isotope Dilution Mass Spectrometry

NIST	National Institute of Standards and Technology
SI	International System of Units
WHO	World Health Organization

Change 26

Synopsis: Study objectives, Synopsis: Methodology, Section 2. Study objectives, Section 4.1 Design overview, Section 6.4.1 Dose calibration, Section 6.4.4 Dose preparation, Section 7.2.4 Body-size descriptors, Section 7.3.4.4.2 Time to pain progression, Section 7.3.5.5 Exploratory pain and analgesic use endpoints

Global Change

Old text:

patient

New text:

subject

Change 27

7.1 Schedule of procedures

Old text:

h Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. At all sites (in US and outside US), weight is to be taken only once for each dose. For non-US sites the weight should be performed within 72 hours prior to dosing. For US sites, subject weight for the dose day should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits. Please note this is applicable to all dosing visits.

New text:

h Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. At all sites (in US and outside US), weight is to be taken only once for each dose. For non-US sites the weight should be performed within 72 hours prior to dosing. For US sites, subject weight for the dose day should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to

the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits. Please note this is applicable to all dosing visits. Body weight can be obtained at the local healthcare provider on a calibrated scale and the results sent by fax to the Principal Investigator with advanced notice and agreement from the Covance Medical Monitor for each subject. No other procedures can be done at the local healthcare provider.

Section 7.5.3.5 Body weight

2nd bullet

Old text:

- For US sites using the central PRD depot ONLY, subject weight for the dose day should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits.

New text:

- For US sites using the central PRD depot ONLY, subject weight for the dose day should be obtained at the site within 3 to 5 days prior to the dose visit. This weight must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits. Body weight can be obtained at the local healthcare provider on a calibrated scale and the results sent by fax to the Principal Investigator with advanced notice and agreement from the Covance Medical Monitor for each subject. No other procedures can be done at the local healthcare provider.

Change 28

Section 6.9.2 Concomitant medication

3rd paragraph

Deleted text:

~~Injection of these therapies should be performed at least 2 hours before or after study drug administration.~~

Change 29

Section 7.3.1 Efficacy variables

8th bullet

Deleted text:

- ~~Bone scan lesion index~~

Section 7.3.5.1.2 Bone scan lesion index

Entire section

Deleted text:

~~7.3.5.1.2 Bone scan lesion index~~

~~Bone scan lesion intensity is defined for each subject at the screening baseline and each subsequent radiological assessment time point, as the mean normalized intensity of the set of technetium-99 pixels identified as bone lesion (sum of the pixel intensities divided by the total number of bone lesion pixels) based on central review.~~

Change 30

Synopsis: Secondary objectives, 2. Study objectives

9th bullet

Deleted text:

~~To evaluate change in analgesic use as measured by the Analgesic Quantification Algorithm (AQA)~~

Synopsis: Exploratory objectives, 2. Study objectives

5th bullet

Added text:

<u>To evaluate change in analgesic use as measured by the Analgesic Quantification Algorithm (AQA)</u>

Primary / Secondary variables

10th bullet

Deleted text:

~~Change in analgesic use~~

Change 31

Section 6.4.7 Dose delays

12th paragraph

Old text:

Any other ~~toxicity~~:

If a subject experiences any non-hematological CTCAE (version 4.03) Grade 4 ~~toxicity~~ regardless of causality lasting more than 7 days despite adequate treatment, further study drug administration must be discontinued.

New text:

Any other adverse event:

If a subject experiences any non-hematological CTCAE (version 4.03) Grade 4 adverse event regardless of causality lasting more than 7 days despite adequate treatment, further study drug administration must be discontinued.

Change 32

Synopsis: Background treatment / concomitant medications / prohibited therapies, Synopsis: Diagnosis and main criteria for exclusion, Section 5.1.2 Exclusion criteria, Section 5.2.1 Withdrawal, Section 6.4.7 Dose Delays, Section 6.9.1 Prior therapy, Section 6.9.2 Concomitant medication, Section 7.1.2.4 Doses 2 to 6 (Treatment Arms A and B), Section 7.1.2.5 Doses 2 to 12 (Treatment Arm C), Section 7.1.2.7.2 Active follow-up without scheduled clinic visits

Global Change

Deleted text:

~~including standard doses of prohibited~~

Section 7.1.2.7.2 Active follow-up without scheduled clinic visits

1st paragraph

Old text:

This period starts when subjects can no longer travel to the clinic or if the subject receives further treatment with anticancer therapies during the follow-up period,

~~including standard doses of prohibited~~ cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, other systemic radioisotopes (samarium-153, strontium-89, rhenium-186, or rhenium-188), hemibody EBRT, or other investigational drugs. Subjects who cannot travel to the clinic will be contacted by telephone every 12 weeks (± 14 days) for 2 years following the last study treatment to determine the following:

New text:

This period starts when subjects can no longer travel to the clinic or if the subject receives further treatment with <u>any of the following</u> anticancer therapies during the follow-up period: cytotoxic chemotherapy for prostate cancer, including taxanes, estramustine, and mitoxantrone, other systemic radioisotopes (samarium-153, strontium-89, rhenium-186, or rhenium-188), hemibody EBRT, or other investigational drugs. Subjects who cannot travel to the clinic will be contacted by telephone every 12 weeks (± 14 days) for 2 years following the last study treatment to determine the following:

Change 33

Section 3. Investigators and other study personnel

2nd paragraph

Added text:

<u>Study Medical Expert for the study:</u>

PPD

<u>Milano V.le Certosa 210
20156 Milano – Italia
Phone:</u> PPD

Change 34

Section 5.1 Eligibility

1st paragraph

Old text:

Eligibility should be confirmed within 14 (± 7) days ~~of~~ randomization. At Dose 1, Day 1, the hematology values need to be confirmed to be within the treatment ranges (absolute neutrophil count [ANC] ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 9.0 g/dL) prior to dosing.

Rescreening is not permitted in cases in which the initial laboratory test results do not support eligibility.

New text:

Eligibility should be confirmed within 14 (± 7) days prior to randomization. At Dose 1, Day 1, the hematology values need to be confirmed to be within the treatment ranges (absolute neutrophil count [ANC] ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 9.0 g/dL) prior to dosing.

Rescreening is not permitted in cases in which the initial safety laboratory test results do not support eligibility.

Section 7.1.2.1 Screening period

16th bullet, 1st subbullet

Old text:

- If standard of care bone scan within 8 weeks of randomization is available, ~~they do~~ not need to be repeated at baseline. If ~~they are~~ not available, ~~they~~ should be performed within 14 ± 7 days ~~of~~ randomization (i.e., during the screening period).

New text:

- If standard of care bone scan within 8 weeks of randomization is available, the scan does not need to be repeated at baseline. If this scan is not available, the scan should be performed within 14 ± 7 days prior to randomization (i.e., during the screening period).

Change 35

Section 8.2 Analysis Sets

2nd paragraph

Added text:

Week 24 (W24): All ITT subjects in Arm A (standard dose) and Arm C (extended dosing) treated with radium-223 dichloride, and eligible for further treatment at W24. The Week 24 dataset will be used for the analysis of efficacy endpoints related to Comparison 2 and associated evaluations. Subjects will be included in W24 analyses according to the treatment to which they were randomized.

Change 36

Synopsis: Plan for statistical analysis

8th paragraph

Old text:

The hazard ratio (high dose / standard dose) will be computed together with 2-sided 80% and 95% confidence intervals using a stratified Cox regression model with treatment as a factor and previous chemotherapy [≤ 1 regimen versus > 1 regimen] and total ALP [< 220 U/L versus ≥ 220 U/L] as strata in the model for the ITT ~~population~~. Kaplan-Meier survival distribution tables and plots will also be produced for both Treatment Arms A and B. Additional details will be provided in the statistical analysis plan.

New text:

The hazard ratio (high dose / standard dose) will be computed together with 2-sided 80% and 95% confidence intervals using a stratified Cox regression model with treatment as a factor and previous chemotherapy [≤ 1 regimen versus > 1 regimen] and total ALP [< 220 U/L versus ≥ 220 U/L] as strata in the model for the ITT analysis set. Kaplan-Meier survival distribution tables and plots will also be produced for both Treatment Arms A and B. Additional details will be provided in the statistical analysis plan.

8.2 Analysis sets

1st and 3rd paragraph

Old text:

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

Intent-to-treat (ITT): All randomized subjects. The ITT ~~population~~ will be used in the analysis of all efficacy endpoints. Subjects will be included in all ITT analyses according to the treatment to which they were randomized.

Safety: All randomized subjects who have received at least one study drug administration. This safety ~~population~~ will be used in the analyses of all safety endpoints. Subjects will be included in the analyses according to the treatment they received.

New text:

The following 3 analysis sets will be defined:

Intent-to-treat (ITT): All randomized subjects. The ITT analysis set will be used in the analysis of all efficacy endpoints. Subjects will be included in all ITT analyses according to the treatment to which they were randomized.

Safety: All randomized subjects who have received at least one study drug administration. This safety analysis set will be used in the analyses of all safety endpoints. Subjects will be included in the analyses according to the treatment they received.

13.3 Amendment 3

Description of the amendment

Amendment 3 is an amendment to the integrated protocol version 3.0 dated 13 AUG 2015. Changes to the protocol include:

- Updated the protocol to reflect the recent Bayer AG legal entity name change.
- Updated procedures for long-term follow-up.
- Added an option for the study site to obtain information directly from the subject's primary health care professional or caregiver.
- Updated the study Global Clinical Leader and study medical expert names.
- Updated analysis for Comparison 2 from 24 weeks to the 6th dose.
- Revised the definition for consistency across the radium-223 program.
- Deleted text for central reviewer as responsible party to determine baseline values and assess radiological progression.

13.3.1 Overview of changes

Change 1:

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

Sections affected:

- Headers
- Title Page: Sponsor

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.

Change 2:

Updated procedures for long-term follow-up

Sections affected:

- Synopsis-Methodology
- 4.1 Design overview
- 5.1 Withdrawal
- 6.8 Post-study therapy
- 7.1.1 Tabulated overview
- 7.1.2.8.1 End of active follow-up with clinic visits
- 7.1.2.8.2 End of active follow-up without scheduled clinic visits
- 7.1.2.9 Long-term follow-up to 7 years following last dose
- 7.1.2.9.1 Long-term follow-up (via telephone follow-up)
- 10 Premature termination of the study

Rationale: Updated long-term assessments specified in this protocol, to be consistent with current version of the long-term follow-up Study 16996 protocol.

Change 3:

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

Section affected:

- Synopsis-Methodology
- 4.1 Design overview
- 6.8 Post-study therapy
- 7.1.1 Tabulated overview
- 7.1.2.7.1 Active follow-up with clinic visits
- 7.1.2.7.2 Active follow-up without scheduled clinic visits
- 7.1.2.8.1 End of active follow-up with clinic visits
- 7.1.2.8.2 End of active follow-up without scheduled clinic visits
- 7.1.2.9 Long-term follow-up to 7 years following last dose

- 7.1.2.9.1 Long-term follow-up (via telephone follow-up)
- 10 Premature termination of the study

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.

Change 4:

Updated the study Global Clinical Leader and study medical expert names

Sections affected:

- Title page
- Signature of the sponsor's medically responsible person
- 3. Investigators and other study personnel

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

Change 5:

Updated analysis for Comparison 2 from 24 weeks to 6th dose date

Sections affected included:

- Synopsis-Study objectives
- Synopsis-Plan for statistical analysis
- 2.0 Study objectives
- 4.4 End of study
- 7.3.2 Definition of efficacy variables
- 7.3.5.6 Additional pain and health related quality of life endpoints
- 8.2 Analysis sets
- 8.4.1 Primary efficacy analysis
- 8.4.2.2 Analyses of standard dosing and extended dosing from the 6th dose date
- 8.6 Determination of sample size

Rationale: The 'Week 24 baseline value' is defined as the last non-missing value on or before the date of the 6th injection. Ideally, this visit would be the date of the 7th injection for Arm C subjects and expected 7th injection date for Arm A subjects. However, the end of treatment visit (30±7 days from last dose) for Arm A subjects could be missing due to consent withdrawal or happen out of visit window. Hence, there is no comparable visit for Arm A subjects that could be used as the expected 7th injection date. To account for this and

achieve comparability between the two arms, the 6th injection date is used as the reference date for Comparison 2 subjects.

Change 6:

Updated text for consistency

Sections affected included:

- 7.3.5.2 Time to increase in physical symptoms of disease based on FPSI-DRS-P
- 7.3.5.3.1 Total alkaline phosphatase response rate
- 7.3.5.3.2 Time to total alkaline phosphatase progression
- 7.3.5.4.1 Prostate specific antigen response rate
- 7.3.5.4.2 Time to prostate specific antigen progression

Rationale: Revised the definition for consistency across the radium-223 program.

Change 7:

Deleted text for central reviewer as responsible party to determine baseline values and assess radiological progression.

Sections affected included:

- 7.3.4.3 Radiological progression endpoints

Rationale: Re-baselining after 6 injections was considered at study start; hence the sentence regarding the central reviewer's responsibility to determine the applicable baseline was included in the protocol. As re-baselining was never implemented in the study and was never included in the Central Review Charter, the sentence was removed from the protocol.

13.3.2 Changes to the protocol text

Change 1:

Header

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:

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

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

Change 2 and Change 3:

Synopsis – Methodology, 6.8 Post-study therapy, 7.1.2.8.1 End of active follow-up with clinic visits, 7.1.2.8.2 End of active follow-up without scheduled clinic visits, 10 Premature termination of the study

Old text:

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and serious AEs~~, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies, including leukemias and solid tumors~~, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

New Text:

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and serious AEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic anti-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone.

All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

4.1 Design Overview

Old text:

Active follow-up period *with* clinic visits:

Subjects who discontinue study treatment and who did not have an SSE will enter an active follow-up period with clinic visits. These subjects will be evaluated every 12 weeks (± 7 days) for pain endpoints, radiological progression, SSEs, survival, treatment-related AEs and serious adverse events (SAEs), and the initiation of other anti-cancer therapies. In addition, subjects who receive cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice. During this period, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs, regardless of the investigator's causality assessment.

New text:

Active follow-up period *with* clinic visits:

Subjects who discontinue study treatment and who did not have an SSE will enter an active follow-up period with clinic visits. These subjects will be evaluated every 12 weeks (± 7 days) for pain endpoints, radiological progression, SSEs, survival, treatment-related AEs and serious adverse events (SAEs), and the initiation of other anti-cancer therapies for prostate cancer, and cytotoxic chemotherapy and radiotherapy for any new malignancy. In addition, subjects who receive cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice. During this period, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs, regardless of the investigator's causality assessment.

Old text:

Active follow-up period *without* clinic visits:

Subjects from the treatment period or the active follow-up period with clinic visits who can no longer travel to the clinical site will be followed for survival, treatment-related AEs and SAEs, SSEs, pain endpoints, and the initiation of other anti-cancer therapies with a phone call every 12 weeks (± 7 days). In addition, subjects who receive cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice. During this period, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs, regardless of the investigator's causality assessment.

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported radium-223 dichloride-related AEs and SAEs, ~~hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies, including leukemias and solid tumors,~~ and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

New text:

Subjects from the treatment period or the active follow-up period with clinic visits who can no longer travel to the clinical site will be followed for survival, treatment-related AEs and SAEs, SSEs, pain endpoints, and the initiation of other anti-cancer therapies (for prostate cancer, and cytotoxic chemotherapy and radiotherapy for any new malignancy) with a phone call every 12 weeks (± 7 days). In addition, subjects who receive cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice. During this period, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs, regardless of the investigator's causality assessment.

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported radium-223 dichloride-related AEs and SAEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic anti-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

5.2.1 Withdrawal

Old text:

For any subject who prematurely discontinues study treatment, the EOT assessments must be completed. The subject will remain in the study throughout the follow-up period. In all cases, the reason for discontinuation from study treatment must be recorded in the electronic case report form (eCRF) and in the source documentation.

New text:

For any subject who prematurely discontinues study treatment, the EOT assessments must be completed. The subject will remain in the study throughout the follow-up period. Any subject who withdraws from the study procedures but does not withdraw consent should enter active follow-up without clinic visits for survival assessment (see Section 7.1.2.8.2). In all cases, the reason for discontinuation from study treatment must be recorded in the electronic case report form (eCRF) and in the source documentation.

7.1.1 Tabulated overview

Old text:

Table 7-1 Schedule of procedures (continued)

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Record radium-223 dichloride related AEs and SAEs[gg]																					X	X	X	X		
~~Record radium-223 dichloride related SAEs[hh]~~																									~~X~~	~~X~~

b. Once a separate, extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical studies, has been implemented, the study subjects surviving after the end of the 2 years of active follow-up will be transitioned to this separate, extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned.

New text:

Table 7-1 Schedule of procedures (continued)

Study Period	Screen	Treatment Arms A and B						Treatment Arm C												EOT Visit	Active Follow-up (at least 2 years after last dose)				Long-term follow-up (up to 7 years after last dose)	
Visit	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13		With clinic visits[a]		Without scheduled clinic visits[a]		Phone follow-up[b]	
Dose		1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12							
Frequency / Timing	Within 14 days prior to random[c]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 0[d]	Day 1, Week 4[d]	Day 1, Week 8[d]	Day 1, Week 12[d]	Day 1, Week 16[d]	Day 1, Week 20[d]	Day 1, Week 24[d]	Day 1, Week 28[d]	Day 1, Week 32[d]	Day 1, Week 36[d]	Day 1, Week 40[d]	Day 1, Week 44[d]	30 days post-last dose	q12 wks[e]	End of active visits	q12 wks	End of active visits	q6 months up to 7 years post-last dose	End of Long-term follow-up
Window (days)	±7		±7	±7	±7	±7	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	±14
Record chemotherapy for other malignancies																					X	X	X	X	X	X
Record radium-223 dichloride related AEs and SAEs[gg]																					X	X	X	X		

[b.] Subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. Once a separate, extended safety follow-up protocol, for the inclusion of subjects who received radium-223 dichloride in the course of Bayer sponsored clinical studies, has been implemented, the study subjects surviving after the end of the 2 years of active follow-up will be transitioned to this separate, extended safety follow-up protocol and the current study will be terminated at the time the last study subject is transitioned. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

7.1.2.7.1 Active follow-up with clinic visits

Added text:

- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy

7.1.2.7.2 Active follow-up without scheduled clinic visits

Added text:

- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy

7.1.2.8.1 End of active follow-up with clinic visits

Added text:

- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy

Old text:

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and serious AEs~~, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies, including leukemias and solid tumors~~, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

New text:

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and serious AEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic anti-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

7.1.2.8.2 End of active follow-up without scheduled clinic visits

Added text:

- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy

Old text:

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and serious AEs~~, hematologic toxicity (e.g., myelosuppression / myelofibrosis / bone marrow aplasia), new primary malignancies, including leukemias and solid tumors~~, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

New text:

All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported, radium-223 dichloride-related AEs and serious AEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic anti-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

7.1.2.9 Long-term follow-up to 7 years following last dose

Old text:

This period starts when subjects have completed the active follow-up period and ends 7 years after the last dose of radium-223 dichloride or when the subject dies. All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported radium-223 dichloride-related AEs and SAEs, ~~hematologic toxicity (e.g., myelosuppression /~~

~~myelofibrosis / bone marrow aplasia), new primary malignancies, including leukemias and solid tumors~~, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

New text:

This period starts when subjects have completed the active follow-up period and ends 7 years after the last dose of radium-223 dichloride or when the subject dies. All study subjects will be eligible for further follow-up either in this study or in a separate long-term follow-up study for up to 7 years. The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The long-term follow-up study has a specific focus on investigator reported radium-223 dichloride-related AEs and SAEs, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer or any other new primary malignancy, cancer treatment (including any systemic cytotoxic chemotherapy or radiotherapy for any malignancy; all systemic ant-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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, and survival for up to 7 years after last dose of radium-223 dichloride or until death. During long-term follow-up, subjects, their treating health care professional, or caregiver will be contacted every 6 months by telephone. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. Subject data collected at other standard-of-care visits and / or contacts may be used to satisfy study-required data.

7.1.2.9.1 Long-term follow-up (via telephone follow-up)

Old text:

Subjects will be contacted by telephone every 6 months (± 14 days) for 7 years following the last study treatment or until death to determine the following:

- Survival status
- All SAEs occurring during this period have to be documented and reported if considered to be related to study medication. Concomitant ~~medication~~ associated with these events will not be collected. If a subject is unable to provide required details for events of interest, this information ~~may~~ need to be obtained from the primary provider.
- Recording of new primary malignancies
- All occurrences of hematological conditions such as myelodysplastic syndrome, aplastic anemia, myelofibrosis, and primary bone cancer or any other new primary malignancy, such as acute myeloid leukemia, must be reported as SAEs at any time and regardless of the investigator's causality assessment.

Since this information will be collected over the telephone from the subject, 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.

New text:

Subjects, their treating health care professional, or caregiver will be contacted by telephone every 6 months (± 14 days) for 7 years following the last study treatment or until death to determine the following:

- Survival status
- Recording of prostate cancer therapies
- All radium-223 dichloride/placebo related adverse events (AEs)
- All SAEs occurring during this period have to be documented and reported if considered to be related to study medication. 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; all systemic ant-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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.
- Recording of new primary malignancies
- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy
- All occurrences of hematological conditions such as myelodysplastic syndrome, aplastic anemia, myelofibrosis, and primary bone cancer or any other new primary malignancy, such as acute myeloid leukemia, must be reported as SAEs at any time and regardless of the investigator's causality assessment
- In subjects who receive cytotoxic chemotherapy: all occurrences of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter.

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

Since this information will be collected over the telephone from the subject, their treating health care professional, or caregiver, 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.

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.

7.1.2.9.2 End of long-term follow-up

Old text:

The end of study procedures for subjects who are in the long-term follow-up period will include the following:

- Survival status
- All SAEs have to be documented and reported if considered to be related to study medication. Concomitant ~~medication~~ associated with these events will not be collected. If a subject is unable to provide required details for events of interest, this information ~~may~~ need to be obtained from the primary provider.
- Recording of new primary malignancies
- All occurrences of hematological conditions such as myelodysplastic syndrome, aplastic anemia, myelofibrosis, and primary bone cancer or any other new primary malignancy, such as acute myeloid leukemia, must be reported as SAEs at any time and regardless of the investigator's causality assessment.

Since this information will be collected over the telephone from the subject, 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.

New text:

The end of study procedures for subjects who are in the long-term follow-up period will include the following:

- Survival status
- Recording of prostate cancer therapies
- All SAEs occurring during this period have to be documented and reported if considered to be related to study medication. 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; all systemic ant-cancer therapies for prostate cancer, including androgen synthesis inhibitors / androgen-receptor antagonists, systemic radioisotopes 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.
- Recording of new primary malignancies
- Recording of cytotoxic chemotherapy and radiotherapy for any new primary malignancy
- All occurrences of hematological conditions such as myelodysplastic syndrome, aplastic anemia, myelofibrosis, and primary bone cancer or any other new primary

malignancy, such as acute myeloid leukemia, must be reported as SAEs at any time and regardless of the investigator's causality assessment

- In subjects who receive cytotoxic chemotherapy: all occurrences of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter.

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

Since this information will be collected over the telephone from the subject, their treating health care professional, or caregiver, 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.

Change 4:

Title page

Old text:

Sponsor's medical expert: PPD
PPD
~~Milano V.le Certosa 210~~
~~20156 Milano - Italia~~
~~Phone:~~ PPD

New text:

Sponsor's medical expert: PPD
PPD
Rua Domingos Jorge, 1100,
Predio 9301 2o andar
04779-900 São Paulo – SP - Brasil
Phone: PPD

Signature of the sponsor's medically responsible person

Old text:

Name: PPD Role: Global Clinical Leader, PPD

New text:

Name: PPD Role: Global Clinical Leader, PPD

3. *Investigators and other study personnel*

Old text:

PPD

Bayer HealthCare Pharmaceuticals, Inc.
100 Bayer Blvd.
PO Box 915
Whippany, New Jersey 07981
~~Tel:~~ PPD

PPD

~~Milano V.le Certosa 210~~
~~20156 Milano – Italia~~
~~Phone:~~ PPD

New text:

PPD

Bayer HealthCare Pharmaceuticals, Inc.
100 Bayer Blvd.
PO Box 915
Whippany, New Jersey 07981
Phone: PPD

PPD

Rua Domingos Jorge, 1100,
Predio 9301 2o andar
04779-900 São Paulo – SP - Brasil
Phone: PPD

Change 5

Synopsis-Plan for statistical analysis

Old text:

Both comparisons will be performed at the time of final analysis, after the latest of (1) approximately 135 SSE-FS events in subjects included in Comparison 1 as defined below; (2) approximately 75 SSE-FS events following ~~Week 24~~ in subjects included in Comparison 2 as defined below, and (3) the last subject has been followed for 30 days from last treatment. In

the event the applicable number of events is not reached, the primary endpoint analysis will mature 7 years after the last subject has received last treatment.

Comparison 2: No further radium-223 dichloride treatment versus extended dosing: SSE-FS analysis from ~~24 weeks~~ in subjects receiving standard-dose regimen

H02: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond ~~24 weeks~~ in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (extended dose) radium-223 dichloride is equal to population SSE-FS beyond ~~24 weeks~~ in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen, versus

HA2: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond ~~24 weeks~~ in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (extended dose) radium-223 dichloride is greater than population SSE-FS beyond ~~24 weeks~~ in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen.

Comparison 2 will be an analysis of SSE-FS from ~~24 weeks from randomization~~ in subjects surviving SSE-free to ~~24 weeks completing and / or not discontinued from treatment~~. It will compare subjects in Treatment Arm A with subjects in Treatment Arm C.

New text:

Both comparisons will be performed at the time of final analysis, after the latest of (1) approximately 135 SSE-FS events in subjects included in Comparison 1 as defined below; (2) approximately 75 SSE-FS events following the 6th dose in subjects included in Comparison 2 as defined below, and (3) the last subject has been followed for 30 days from last treatment. In the event the applicable number of events is not reached, the primary endpoint analysis will mature 7 years after the last subject has received last treatment.

Comparison 2: No further radium-223 dichloride treatment versus extended dosing: SSE-FS analysis from the date of the 6th dose in subjects receiving standard-dose regimen

H02: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond the 6th dose in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update)[3] (extended dose) radium-223 dichloride is equal to population SSE-FS beyond the 6th dose in subjects

receiving no further radium-223 dichloride treatment beyond the standard dose regimen, versus

HA2: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond the 6th dose in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update)[3] (extended dose) radium-223 dichloride is greater than population SSE-FS beyond the 6th dose in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen.

Comparison 2 will be an analysis of SSE-FS from the 6th dose in subjects surviving SSE-free to the completion of the 6th dose. It will compare subjects in Treatment Arm A with subjects in Treatment Arm C.

4.4 End of Study

Old text:

The primary endpoint cut-off will be reached at the later of 1) 135 SSE-FS events in subjects included in Comparison 1 as defined in Section 8,4 below, and 2) 75 SSE-FS events following ~~Week 24~~ in subjects included in Comparison 2 as defined in Section 8.4 below, and 3) the last subject has been followed for 30 days from last treatment. In the event the applicable number of events is not reached, the primary endpoint analysis will mature 7 years after the last subject has received last treatment.

New text:

The primary endpoint cut-off will be reached at the later of 1) 135 SSE-FS events in subjects included in Comparison 1 as defined in Section 8.4 below, and 2) 75 SSE-FS events following the 6th dose in subjects included in Comparison 2 as defined in Section 8.4 below, and 3) the last subject has been followed for 30 days from last treatment. In the event the applicable number of events is not reached, the primary endpoint analysis will mature 7 years after the last subject has received last treatment.

7.3.2 Definition of efficacy variables

Old text:

In this study, time-to-event endpoints are defined with respect to 2 distinct start dates, randomization date and 24 weeks. Response and progression endpoints are defined with respect to 2 corresponding baselines, the screening (or pre-treatment) baseline and 24 weeks. Details on definitions of starting points and baselines will be provided in the SAP or in the imaging charter or other central reviewer documentation.

New text:

In this study, time-to-event endpoints are defined with respect to 2 distinct start dates, randomization date and the date of the 6th dose. Response and progression endpoints are defined with respect to 2 corresponding baselines, the screening (or pre-treatment) baseline

and the 6th dose date. Details on definitions of starting points and baselines will be provided in the SAP or in the imaging charter or other central reviewer documentation.

7.3.5.6 Additional pain and health related quality of life endpoints

Old text:

Subject-reported outcome data not described above, palliative pain relief procedure data, additional BPI-SF data collected at clinic visits, and pain data collected ~~following the Week 24 assessment,~~ will be evaluated as described in the SAP.

New text:

Subject-reported outcome data not described above, palliative pain relief procedure data, additional BPI-SF data collected at clinic visits, and pain data collected will be evaluated as described in the SAP.

8.2 Analysis sets

Old text:

Week 24 (W24): All ITT subjects in Arm A (standard dose) and Arm C (extended dosing) ~~treated with radium-223 dichloride and eligible for further treatment at W 24~~. The W24 dataset will be used for the analysis of efficacy endpoints related to Comparison 2 and associated evaluations. Subjects will be included in W2~~4~~ analyses according to the treatment to which they were randomized.

New text:

Week 24 (W24): All ITT subjects in Arm A (standard dose) and Arm C (extended dosing) treated with radium-223 dichloride and eligible for further treatment at W 24 (i.e., 7th injection). Week 24 applies to subjects who received the 6th injection without any dose delays. As dose delays are allowed per protocol, 6th injection can occur after Week 24 for subjects who had dose delays. Hence, this population is defined based on the number of injections not based on the timing. The W24 dataset will be used for the analysis of efficacy endpoints related to Comparison 2 and associated evaluations. Subjects will be included in W24 analyses according to the treatment to which they were randomized.

8.4.1 Primary efficacy analysis

Old text:

Both comparisons will be performed at the time of final analysis, after the latest of (1) approximately 135 SSE-FS events in subjects included in Comparison 1 as defined below; (2) approximately 75 SSE-FS events following ~~Week 24~~ in subjects included in Comparison 2 as defined below; and (3) the last subject has been followed for 30 days from last treatment. In the event the applicable number of events is not reached, the primary endpoint analysis will mature 7 years after the last subject has received last treatment.

Comparison 2: No further radium-223 dichloride treatment versus extended dosing: SSE-FS analysis from ~~24 weeks~~ in subjects receiving standard-dose regimen

H02: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST standard update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond ~~24 weeks~~ in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (extended dose) radium-223 dichloride is equal to population SSE-FS beyond ~~24 weeks~~ in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen, versus

HA2: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond ~~24 weeks~~ in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (extended dose) radium-223 dichloride is greater than population SSE-FS beyond ~~24 weeks~~ in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen.

Comparison 2 will be an analysis of SSE-FS from 24 weeks ~~from randomization~~ in subjects surviving SSE-free to ~~24 weeks~~ completing and / or not discontinued from treatment. It will compare subjects in Treatment Arm A with subjects in Treatment Arm C.

New text:

Comparison 2: No further radium-223 dichloride treatment versus extended dosing: SSE-FS analysis from the 6th dose in subjects receiving standard-dose regimen

H02: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST standard update) (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond the 6th dose in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update) (extended dose) radium-223 dichloride is equal to population SSE-FS beyond the 6th dose in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen, versus

HA2: In a population of subjects treated with a regimen of up to 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update)[2] (standard dose) radium-223 dichloride who survived SSE-free and are eligible for further radium-223 dichloride treatment at 24 weeks, population SSE-FS beyond the 6th dose in subjects treated with a regimen of up to an additional 6 doses of 50 kBq/kg (55 kBq/kg after implementation of NIST update)[2] (extended dose) radium-223 dichloride is greater than population SSE-FS beyond the 6th dose in subjects receiving no further radium-223 dichloride treatment beyond the standard dose regimen.

Comparison 2 will be an analysis of SSE-FS from the 6th dose, in subjects surviving completion of to the 6th dose. It will compare subjects in Treatment Arm A with subjects in Treatment Arm C.

8.4.2.2 Analyses of standard dosing and extended dosing from the 6th dose date

Old text:

For the following secondary endpoint analyses, subjects will be classified into 2 treatment groups: (1) the "standard dose" treatment group, consisting of applicable ITT subjects in Treatment Arm A, and (2) the "extended dosing" treatment group, consisting of applicable ITT subjects in Treatment Arm C. For these analyses, the start date will be ~~2~~24 weeks, and the ~~2~~24 week ~~assessment~~ baseline will be used.

For secondary endpoint time-to-event analyses for these treatment groups, subjects included will have survived to the 24 week start date without having experienced the applicable event, and will have completed and / or not been discontinued from treatment. Details defining these analyses will be provided in the SAP.

New text:

For the following secondary endpoint analyses, subjects will be classified into 2 treatment groups: (1) the "standard dose" treatment group, consisting of applicable ITT subjects in Treatment Arm A, and (2) the "extended dosing" treatment group, consisting of applicable ITT subjects in Treatment Arm C. For these analyses except for rPFS, the 6th dose date will be used as the reference date. For rPFS, randomization date will be used as the reference date.

For secondary endpoint time-to-event analyses for these treatment groups, subjects included will have survived to the 6th dose date without having experienced the applicable event, and will have completed and / or not been discontinued from treatment. Details defining these analyses will be provided in the SAP.

8.6 Determination of sample size

Old text:

Comparison 2 will analyze SSE-FS from ~~24 weeks~~ in subjects surviving SSE-free to ~~24 weeks completing and / or without prior permanent discontinuation from treatment~~.(27,28) A median SSE-FS of 9 months with constant hazards is assumed for standard dose. Extended dosing is assumed to have the same SSE-FS efficacy as standard dosing for the first 24 weeks, and 65% improvement (hazard ratio 0.606) thereafter. With 240 of 360 subjects randomized to Treatment Arm A and Treatment Arm C, simulations indicated that 44.65% of randomized subjects (107.2 of 240) would have an SSE-FS event or loss to follow-up during the first 24 weeks, leaving an estimated 55.35% (132.8) surviving SSE-free and eligible for inclusion at 24 weeks. An average of 74.9 simulated events occurred for this comparison, and a 1-sided log-rank test with 0.10 significance gave approximately 80.6%[2] power to test H02 versus HA2.

New text:

Comparison 2 will analyze SSE-FS from the 6th dose, in subjects surviving SSE-free to the 6th dose.(27,28) A median SSE-FS of 9 months with constant hazards is assumed for standard dose. Extended dosing is assumed to have the same SSE-FS efficacy as standard dosing for the first 24 weeks, and 65% improvement (hazard ratio 0.606) thereafter. With

240 of 360 subjects randomized to Treatment Arm A and Treatment Arm C, simulations indicated that 44.65% of randomized subjects (107.2 of 240) would have an SSE-FS event or loss to follow-up during the first 24 weeks, leaving an estimated 55.35% (132.8) surviving SSE-free and eligible for inclusion at 24 weeks. An average of 74.9 simulated events occurred for this comparison, and a 1-sided log-rank test with 0.10 significance gave approximately 80.6% power to test H02 versus HA2.

Change 6

7.3.5.2 Time to increase in physical symptoms of disease based on FPSI-DRS-P

Old text:

~~For each applicable baseline,~~ time to increase in physical symptoms of disease based on (FPSI-DRS-P) will be calculated with respect to ~~that~~ baseline, based only on assessments through Week 48. Details, including definition of an increase, will be provided in the SAP.

New text:

Time to increase in physical symptoms of disease based on (FPSI-DRS-P) will be calculated with respect to baseline <u>value collected prior to first dosing</u>, based only on assessments through Week 48. Details, including definition of an increase, will be provided in the SAP.

7.3.5.3.1 Total alkaline phosphatase response rate

Old text:

Total ALP response is defined with respect to each applicable baseline, as a ≥ 30% reduction of the blood total-ALP level compared to the baseline value.

New text:

Total ALP response is defined with respect to each applicable baseline, as a ≥ 30% reduction of the blood total-ALP level compared to the baseline value, <u>confirmed by a second consecutive ALP value 4 or more weeks later but within 9 weeks, among evaluable subjects</u>.

7.3.5.3.2 Time to total alkaline phosphatase progression

Old text:

Total ALP progression is defined with respect to each applicable baseline, as a ≥ 25% increase ~~above the applicable nadir (lowest respective baseline or post-baseline) value~~.

New text:

≥ 25% increase from baseline value, at least 12 weeks from baseline in subjects with no ALP decline from baseline; or ≥ 25% increase <u>above the nadir value, which is confirmed by a second consecutive value obtained 3 or more weeks later but within 9 weeks in subjects with an initial ALP decline from the baseline</u>.

7.3.5.4.1 Prostate specific antigen response rate

Old text:

Prostate specific antigen response is defined in each evaluable subject with respect to each applicable baseline as a ≥ 30% reduction of the blood PSA level, compared to the baseline

value, confirmed by a second subsequent PSA value with a ≥ 30% reduction from the applicable baseline approximately 4 or more weeks later.

New text:

Prostate specific antigen response is defined in each evaluable subject with respect to each applicable baseline as a ≥ 30% reduction of the blood PSA level, compared to the baseline value, confirmed by a second subsequent PSA value with a ≥ 30% reduction from the applicable baseline approximately 4 or more weeks later but within 9 weeks.

7.3.5.4.2 Time to prostate specific antigen progression

Old text:

Prostate specific antigen progression is defined with respect to each applicable baseline, as a ≥ 25% increase ~~above the applicable nadir (lowest baseline or post-baseline) value, and an increase in absolute value of ≥ 2 ng/mL above the nadir~~.

New text:

Prostate specific antigen progression is defined with respect to each applicable baseline, as a ≥ 25% increase from baseline value and an increase in absolute value of ≥2 ng/mL, at least 12 weeks from the applicable baseline in subjects with no PSA decline from baseline; or ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir value, which is confirmed by a second consecutive value obtained 3 or more weeks later but within 9 weeks in subjects with an initial PSA decline from the baseline.

Change 7

7.3.4.3 Radiological progression endpoints

Deleted text:

~~The central reviewer will determine the applicable baseline values for and assess radiological progression with respect to each applicable baseline.~~

13.4 Amendment 4

Description of the amendment

Amendment 4 is an amendment to the integrated protocol version 4.0 dated 16 MAY 2017. Changes to the protocol include:

- Addition that radium-223 dichloride should not be given with abiraterone plus prednisone/prednisolone.
- 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 causality to study treatment.
- Based on the available data on radium-223 dichloride, initiation of BHAs during the follow-up periods, including bisphosphonates or denosumab, should be considered taking into consideration applicable guidelines.

- Updated the study GCL and study medical expert names.
- Minor clarifications

13.4.1 Overview of changes

13.4.1.1 Change 1:

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

Sections affected include:

- Synopsis - Background treatment / concomitant medications / prohibited therapies
- 6.9.2 Concomitant medication
- 7.1.1 Tabulated overview, Schedule of procedures

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 plus prednisone/prednisolone in mCRPC is considered unfavorable.

13.4.1.2 Change 2:

Bone fractures and bone associated events (e.g., osteoporosis) need to be reported as (S)AEs, including during long-term follow-up, regardless of causality to study treatment.

Sections affected include:

- Synopsis - Methodology
- 4.1 Design overview
- 6.8 Post-study therapy
- 7.1.1 Tabulated overview
- 7.1.2.7.1 Active follow-up with clinic visits
- 7.1.2.7.2 Active follow-up without scheduled clinic visits
- 7.1.2.8.1 End of active follow-up with clinic visits
- 7.1.2.8.2 End of active follow-up without scheduled clinic visits

- 7.1.2.9 Long-term follow-up to 7 years following last dose
- 7.1.2.9.1 Long-term follow-up (via telephone follow-up)
- 7.1.2.9.2 End of long-term follow-up
- 7.5.1.3 Assessments and documentation of adverse events
- 7.5.1.4 Reporting of serious adverse events
- 10 Premature termination of the study

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 these data European Health Authorities requested that all bone fractures and bone associated events (e.g., osteoporosis) occurring during study and in the follow-up period should be documented regardless of causality to study treatment.

13.4.1.3 Change 3:

The option of starting a BHA during the follow-up periods, including bisphosphonates or denosumab, should be considered taking into consideration applicable guidelines.

Sections affected include:

- Synopsis - Methodology
- 6.9.2 Concomitant medication

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.

13.4.1.4 Change 4:

Updated the study GCL and Study Medical Expert names.

Sections affected:

- Title page
- Signature of the sponsor’s medically responsible person

- 3 Investigators and other study personnel

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

13.4.1.5 Minor clarifications:

- Added the definition for Independent Data Monitoring Committee (IDMC) and bone health agent (BHA) in the list of abbreviations and in the text where appropriate.
- For Word-related technical reasons, numbered footnotes have been replaced with a summary of changes at the start of each amended section.

13.4.2 Changes to the protocol text

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

14. Appendices

14.1 Response Evaluation Criteria in Solid Tumors, version 1.1

Section modified by Amendment 2 (Section 13.2).

Soft tissue response and progression will be evaluated in this study using a modified version of the modified RECIST guidelines version 1.1.

Modification to RECIST:

- Only lymph nodes with short axis ≥ 1.5 cm can be selected as target lesions.
- Disease progression at first assessment needs to be confirmed by a second scan 6 or more weeks later as required per the PCWG2 guidance.(1) In case of unequivocal progression, a confirmatory scan is not mandatory and it will be performed at the investigator's discretion.
- Bone lesions will not be recorded as non-target lesions or assessed per modified RECIST. Radiological progression of bone lesions will be determined according to PCWG2 criteria based on whole body technetium-99 bone scans.

Measurable Disease: Note: Subjects are excluded if they have visceral metastases as assessed by abdominal and pelvic MRI / CT scan or chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 1.5 cm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.

Malignant lymph nodes situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (pathological lymph nodes with short axis ≥ 1 cm to < 1.5 cm) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural / pericardial effusions, and lymphangitic involvement of skin or lung are all non-measurable.

Target Lesions: All measurable lesions up to a maximum of 5 lesions in total, representative of all involved regions should be identified as target lesions and be recorded and measured at baseline. These 5 lesions should be selected on the basis of their size (lesions with the longest short axis), and should be suitable for reproducible repeated measurements. A sum of nodal short axes of target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression of the measurable dimension of the disease. If there are

> 5 measurable lesions, those not selected as target lesions will be considered together with non-measurable disease as non-target lesions.

Non-target Lesions: All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 5 listed as target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present," "absent," or in rare cases "unequivocal progression."

Best Response

All subjects will have their best response on study classified as outlined below:

Complete Response (CR): Disappearance of all clinical and radiological evidence of tumor (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Stable Disease: Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD; no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non-target lesions or the appearance of one or more new lesions will also constitute PD.

Table 14–1 Response for subjects with target and non-target lesions

Target lesions	Non-target lesions	New lesions	Overall response	Best response for this category also requires
CR	CR	No	CR	
CR	Non-CR / Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	Documented at least 6 weeks from start of study treatment
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 14–2 Response for subjects with non-target lesions only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR / Non-PD	No	Non-CR / non-PD[a]
Not evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease

[a] Non-CR / non-PD is preferred over "stable disease" for non-target disease.

Note: Radiological progression of bone lesions will be determined according to PCWG2 criteria based on whole body technetium-99 bone scans.

Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Chest X-ray - In the presence of suspicious lesion(s), a chest CT scan will be performed to confirm and characterize the lesion(s). However, a chest CT scan is preferable.

CT / MRI - CT scan is the best currently available and reproducible method to measure target lesions selected for response assessment. When CT scans are used, spiral CT scans should be

used in this study. The minimum size for a measurable lesion should be twice the slice thickness. An MRI is also acceptable. This applies to the chest, abdomen, and pelvis.

Ultrasound - Ultrasound is not useful in assessment of lesion size and should not be used as method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy / Laparoscopy - The utilization of these techniques for objective tumor evaluation is not advised.

Cytology / Histology - These techniques can be used to differentiate between PR and CR in rare cases.

14.2 Recommendations of the Prostate Cancer Clinical Trials Working Group for assessment of radiological progression

Section modified by Amendments 1 (Section 13.1) and 2 (Section 13.2).

Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol.* 2008;26(7):1148-59.

Table 14–3 Recommendations of the Prostate Cancer Clinical Trials Working Group 2 for assessment of radiological progression

Site	PCWG2 criteria for radiological progression
Soft tissue	The modified RECIST criteria for progression should be used, with the additional requirement that progression at the first assessment should be confirmed by a second scan 6 or more weeks later.
Bone	Defined as the appearance of ≥ 2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions The date of progression is the date of the first scan that shows the change.

Abbreviations: PCWG2 = Prostate Cancer Clinical Trials Working Group 2; RECIST = Response Evaluation Criteria in Solid Tumors

Table 14–4 Radiological progression free survival definition per modified Response Evaluation Criteria in Solid Tumors, version 1.1, or progression by bone scan as adapted by Prostate Cancer Clinical Trials Working Group 2 criteria

Site	Criteria for radiological progression
Soft tissue	Soft tissue progression is determined by modified RECIST, version 1.1: • Only lymph nodes with short axis ≥ 1.5 cm can be selected as a target lesion
Bone	Progressive disease by bone scan as adapted from PCWG2 Consensus Criteria: • < 12 weeks after randomization: ≥ 2 new bone lesions plus 2 additional at confirmation (“2+2”) • ≥ 12 weeks after randomization: ≥ 2 new bone lesions with subsequent

	confirmation
	If progression is detected by bone scan, a confirmatory bone scan is required at least 6 weeks later. A SPECT or MRI (with and without contrast media) should be obtained to confirm any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression.

Abbreviations: RECIST = Response Evaluation Criteria in Solid Tumors

14.3 Quantitative bone scan response criteria

Table 14–5 Quantitative bone scan response criteria

Time point response	Criteria
Responder	30% or greater resolution of the applicable bone scan lesion area compared to the respective baseline
Stable disease	Not meeting the criteria for responder, progressive disease, or unable to evaluate
Progressive disease	Two or more new areas of radiotracer uptake attributable to metastatic disease in regions of bone that had not previously shown radiotracer uptake or greater than 30% increase from baseline in bone scan lesion area in areas attributable to metastatic disease.
Unable to evaluate	Assigned if bone scan results cannot be interpreted due to inconsistent image acquisition parameters compared to the reference scan, incomplete imaging, or other similar technical deficiencies.

14.4 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 June 2010. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

14.5 Eastern Cooperative Oncology Group performance status

Table 14–6 Eastern Cooperative Oncology Group performance status

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

14.6 Calculation for glomerular filtration rate

Section modified as of Amendment 2 (Section 13.2).

Baseline kidney function will be assessed using the GFR as calculated using either the Chronic Kidney Disease Epidemiology Collaboration creatinine equation, or, when this method is not available, the Modification of Diet in Renal Disease (MDRD) equation.

The MDRD calculation is an established method of estimating GFR based on 4 variables: serum creatinine level, age, sex, and ethnicity. This method has historically been the National Kidney Foundation's recommended method of estimating the GFR in individuals 18 years or older.

The MDRD Study Equation:

$GFR\ (mL/min/1.73m^2) = k \times 186 \times [\text{serum creatinine}]^{-1.154} \times [\text{age}]^{-0.203}$

Where k = 1 (men) or 0.742 (women), serum creatinine is measured in mg/dL.

In an effort to improve upon the MDRD equation, the Chronic Kidney Disease Epidemiology Collaboration developed an updated calculation, the CKD-EPI creatinine equation, using the same variables as the MDRD equation. This new calculation has been validated and is considered to be more accurate than the MDRD equation. The National Kidney Foundation now recommends using the CKD-EPI Creatinine Equation for estimating GFR.

The CKD-EPI calculation is based on a serum creatinine value that was obtained through use of isotope dilution mass spectrometry (IDMS), a standardized serum creatinine assay. Therefore, the CKD-EPI equation is only valid if the laboratory used a calibration method for serum creatinine that is traceable to IDMS. The IDMS has been adopted by laboratories globally and is widely available. If it is not clear whether your laboratory uses this serum creatinine reference method, please contact the laboratory for confirmation.

CKD-EPI Equation

- Conventional Units (creatinine as mg/dL; age in years):
- GFR (mL/min/1.73m^2) = 175 x (serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)
- SI Units (creatinine as µmol/L; age in years):
- GFR (mL/min/1.73m^2) = 175 x (serum creatinine/88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

The standard MDRD calculation should be used for any serum creatinine values that are not based on the IDMS assay.

For convenience and accuracy, a GFR calculator may be used for this study at the following URL at the National Kidney Foundation's web site:
http://www.kidney.org/professionals/KDOQI/gfr_calculator

14.7 Brief Pain Inventory-Short Form

Section modified as of Amendment 1 (Section 13.1).

The severity of pain and its impact on daily functions will be self-assessed by the study subjects using the BPI-SF (29) measure.

The BPI-SF allows subjects to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function (e.g., general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). The BPI-SF is an 11-item, self-administered, clinically valid, reliable, and responsive measure developed to assess pain related to cancer. The instrument is available in validated multilingual versions; on average, it requires less than 10 minutes to complete the questionnaire.

All BPI items are scored using rating scales. Four items measure pain intensity (pain now, average pain, worst pain, and least pain) using 0 (no pain) to 10 (pain as bad as you can imagine) numeric rating scales, and 7 items measure the level of interference with function caused by pain (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) using 0 (no interference) to 10 (complete interference) rating scales. It has a 24-hour recall period. Assessment of the worst pain score (WPS) via Question 3 and average pain score via Question 5 on the BPI-SF will occur daily for 4 days immediately prior to randomization and for 7 days prior to each scheduled visit from the Dose 1, Day 1 visit through the Week 48 visit. The data will be collected and checked for completeness at each visit. In Treatment Arms A and B only, pain will also be assessed daily for 7 days prior to each telephone contact at Weeks 28, 32, 40 and 44 and the daily PRO pain input data will be reviewed for completeness at the telephone contact.

The BPI-SF will be self-administered by the subject at Dose 1, Day 1 (before the start of study treatment) through the Week 48 visit. In Treatment Arms A and B only the BPI-SF questionnaire will also be completed on the day of each telephone contact at Weeks 28, 32, 40 and 44 and checked for completion at the telephone contact.

At the beginning of each scheduled visit, before meeting with the investigator, subjects will be asked to complete the BPI-SF, with the exception of Question 2 (locating areas of pain on a diagram) and Question 7 (regarding use of pain medication). Subjects will not be asked to answer Question 2 because the information will not be used for the score. Subjects will not be asked to answer Question 7 because pain medication used is captured elsewhere in the eCRF. The items are aggregated into 2 dimensions: (1) *Pain Severity Index*, using the sum of the 4 items on pain intensity and (2) *Function Interference Index*, using the sum of the 7 pain interference items. The *Function Interference Index* is scored as the mean of the item scores multiplied by 7, given that more than 50% (or 4 of 7), of the items have been completed.

The BPI-SF should be self-administered by the subject alone during his scheduled visit at the site. The instrument should be administered at the start of the visit, before the subject sees the physician so that any interaction between the subject and physician will not influence the subject's responses to the questionnaire. The questionnaire should also be administered before the subject is asked about AEs and concurrent illnesses, again so that any discussions of health problems do not influence the subject's responses.

A quiet place should be provided for the subject to complete the BPI-SF. It is important that the subject completes the BPI-SF alone, without any advice from family members or friends who may accompany him.

How should the Questionnaire and daily PRO pain collection be introduced?

A sample script for introducing the questionnaire and daily PRO pain collection is given below.

"Your doctor would like to better understand how you feel, how well you are able to do your usual activities, and how you rate your health. To help us better understand these things about you, we will ask you to answer 2 questions related to the worst pain in the last 24 hours and the average level of pain, for 7 days prior to each scheduled treatment visit and at the end of treatment visit. We will ask you to complete this questionnaire about your health at each of these visits. Depending on which treatment you are assigned, you may also be requested to answer these 2 questions during the first 6 months of the follow up period, for 7 days prior to the visits or telephone contacts and to complete the BPI-SF questionnaire on the day of the visits or on the day of the telephone contacts.

You will be provided with written instructions on how to do this. You should read each question and then tick the appropriate number that matches your answer. Remember that this is not a test and there are no right or wrong answers. Choose the answer that best describes the way you feel. I will quickly review the questionnaire when you are done to make sure that all the questions have been answered. You should answer these questions by yourself.

Your spouse or other family members should not help you when you answer the questionnaire. I will be nearby in case you want to ask me any questions. Please let me know when you have finished the questionnaire."

What to do if the subject asks for clarification?

Some subjects may ask the meaning of specific questions. If this happens, the staff member can assist the subject by re-reading the question for them verbatim. If the subject asks what something means, do not try to explain what the question means, but tactfully suggest that the subject use his own interpretation of the question. All subjects should answer the questions based on what they think the questions mean, or the study results may be biased.

Questionnaire completion and review of worst pain score over the previous 7 days

At the beginning of each visit or at each telephone contact (Treatment Arms A and B only), please check that the subject has answered the questions related to the WPS and the average pain score, in the 7 days prior to the visit. Thank the subject once you have reviewed the responses.

When the subject has completed the questionnaire, check that all of the questions have been answered. If the questionnaire is not complete, point out to the subject that some of the questions were not answered. If the subject does not quickly volunteer to answer these items, ask him whether he had any difficulty completing the questionnaire. If the subject says that he had trouble understanding a question, ask him why he had difficulty with that item. Re-read the question for him verbatim, but do not attempt to explain or reword the question, as explained before. If the subject is still unable to answer the question, accept the questionnaire as is.

Some subjects may be confused by the response choices. They may want to respond with "I don't know" or some other response choice that is not available. If this happens, try to help the subject choose one of the response categories by saying something like: "I know that it may be difficult for you to choose an answer, but which of these answers do you think comes closest to the way that you are thinking or feeling?" If the subject still cannot select an answer, accept the questionnaire as is.

Occasionally, subjects may not report having difficulty with a question or the response choices, but still may hesitate or refuse to answer an item or items. If this happens, accept the questionnaire as is.

If a subject asks for interpretation of his responses or asks for his scores on the questionnaire, tell him that you are not trained to score or interpret the questionnaire. Emphasize that their answers will be kept confidential.

Thank the subject once he has completed the questionnaires and you have checked them for completeness.

14.8 NCCN FACT-P Symptom Index-17 (NCCN-FACT FPSI-17) Questionnaire

Section modified as of Amendment 1 (Section 13.1).

The NCCN-FACT FPSI-17 questionnaire will be completed by the subject at the specified visits, see Section 7 and Table 7–1.

NCCN-FACT FPSI-17

Below is a list of statements that other people with your illness have said are important.

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

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	P7	I have difficulty urinating	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	NCCN3	I have weakness in my legs	0	1	2	3	4
	P3	My pain keeps me from doing things I want to do	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
	P6	I have trouble moving my bowels	0	1	2	3	4
TSE	GS7	I am satisfied with my sex life	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale
English (Universal)

03 March 2010

14.9 Analgesic Quantification Algorithm

Section modified by Amendment 1 (Section 13.1).

Analgesic Quantification Algorithm Score Categories

0 No analgesic

1 Non-opioid analgesics

2 Weak opioids (i.e., meperidine, codeine, tramadol)

3 Strong opioids ≤ 75 mg OME/d

4 Strong opioids > 75-150 mg OME/d

5 Strong opioids > 150-300 mg OME/d

6 Strong opioids > 300 mg-600 mg OME/d

7 Strong opioids > 600 mg OME/d

Abbreviations: d = day; OME = oral morphine equivalents.

References for the AQA:

Chung K, Barlev A, Braun A, Qian Y, Zagari M. Development of the Analgesic Quantification Algorithm (AQA): a new scale to assess analgesic use. Poster presented at: Joint 15th Congress of the European Cancer Organization and 34th Congress of the European Society for Medical Oncology; September 20-24, 2009; Berlin, Germany.

Charles S. Cleeland PhD, Jean-Jaques Body MD PhD, Alison Stopeck MD, et al. (2013). Pain outcomes in patients with advanced breast cancer and bone metastases: Results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer, Volume 119, Issue 4, pages 832–838.