Document Type:	Study Protocol
Official Title:	A phase II randomized, double-blind, placebo-controlled trial of radium-223 dichloride versus placebo when administered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases treated with hormonal treatment background therapy
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Cover page of the integrated clinical study protocol

A phase II randomized, double-blind, placebo-controlled trial of radium-223 dichloride versus placebo when administered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases treated with hormonal treatment background therapy

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

- Original protocol, Version 1.0, dated 13 MAY 2014
- Amendment 1 (global amendment described in Section 15.1) forming integrated protocol Version 2.0, dated 16 DEC 2014
- Amendment 2 (global amendment described in Section 15.2) forming integrated protocol Version 3.0, dated 29 APR 2015
- Amendment 3 (local amendment France only) dated 29 APR 2015
- Amendment 4 (global amendment described in Section 15.3) forming integrated protocol Version 4.0, dated 29 JUL 2015.
- Amendment 5 (global amendment described in Section 15.4) forming integrated protocol Version 5.0, dated 11 MAR 2016.
- Amendment 6 (global amendment described in Section 15.5) forming integrated protocol Version 6.0, dated 11 JUL 2016.
- Amendment 7 (global amendment described in Section 15.6) forming integrated protocol Version 7.0, dated 23 MAY 2017.
- Amendment 8 (global amendment described in Section 15.7) forming current integrated protocol Version 8.0, dated 03 APR 2018

This document integrates the original protocol and all global amendments.

1. Title page

Section modified by Amendment 1 (Section 15.1), Amendment 5 (Section 15.4), and Amendment 6 (Section 15.5), and Amendment 7 (Section 15.6).

A phase II randomized, double-blind, placebo-controlled trial of radium-223 dichloride versus placebo when administered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases treated with hormonal treatment background therapy

Study of radium-223 dichloride versus placebo with hormonal treatment as background therapy in subjects with bone predominant HER2 negative hormone receptor positive metastatic breast cancer

Test drug:	BAY 88-8223 / Radium-223 dichloride / Xofigo®		
Study purpose:	Efficacy and Safety		
Clinical study phase:	2	Date:	03 APR 2018
Registration:	EudraCT: 2014-002113-39	Version no.:	8.0
Sponsor's study no.:	16298		
Sponsor:	**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
PPD
PPD
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

Section modified by Amendment 7 (Section 15.6) and Amendment 8 (Section 15.7.1.3).

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

Name: PPD Role: PPD
PPD

Date: 11 April 2018 Signature:

Signature of principal investigator

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

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

2. Synopsis

Title	**A phase II randomized, double-blind, placebo-controlled trial of radium-223 dichloride versus placebo when administered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases treated with hormonal treatment background therapy**
Short title	Study of radium-223 dichloride versus placebo with hormonal treatment as background therapy in subjects with bone predominant HER2 negative hormone receptor positive metastatic breast cancer *Short title section modified by Amendment 1.*
Clinical study phase	2
Study objectives	The objective of this study is to assess the efficacy and safety of radium-223 dichloride in subjects with human epidermal growth factor receptor 2 negative (HER2 negative), hormone receptor positive breast cancer with bone metastases treated with hormonal treatment background therapy. The **primary endpoint** is: 1. Symptomatic skeletal event-free survival (SSE-FS) The **secondary endpoints** are: 2. Overall survival 3. Time to opiate use for cancer pain 4. Time to pain progression (only in subjects with baseline worst pain score ≤8) 5. Time to cytotoxic chemotherapy 6. Radiological progression-free survival (rPFS) 7. Pain improvement rate 8. Safety, acute and long term, including new primary malignancies and hematopoietic reserve for tolerability of subsequent chemotherapy The study will also include the following **exploratory endpoints**: 9. Time to first on-study symptomatic skeletal event (SSE) 10. Time to bone alkaline phosphatase (ALP) progression

	11. Bone ALP response at Week 12 and end of treatment (EOT) 12. Bone-specific rPFS 13. Resource utilization 14. Biomarker assessments 15. Time to visceral metastases onset *Study objectives section modified by Amendment 4.*
Test drug **Name of active ingredient** **Dose** **Route of administration** **Duration of treatment**	BAY 88-8223 Radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight every 4 weeks for 6 cycles *Dose section modified by Amendment 4.* Intravenous injection (slow bolus) 6 cycles at 4-week intervals (24 weeks)
Reference drug **Name of active ingredient** **Background treatment**	Matching placebo (normal saline) Not applicable All study subjects will receive local standard of care hormonal treatment, and best supportive care
Indication	Subjects with HER2 negative, hormone receptor positive breast cancer with bone metastases treated with a single hormonal agent as background therapy

Diagnosis and main criteria for inclusion and exclusion	Subjects must meet the following criteria for inclusion in the study: 1. Have provided written informed consent. Subjects must be able to understand and be willing to sign the written informed consent. A signed informed consent form must be appropriately obtained prior to the conduct of any study-specific procedure. 2. Documentation of histological or cytological confirmation of estrogen receptor positive (ER+) and HER2 negative adenocarcinoma of the breast must be available. HER2 status should be determined by an accredited/Ministry of Health approved laboratory by immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH) or other validated in situ hybridization (ISH) assay for detection of HER2 gene expression. 3. Tumors (from either primary or metastatic sites) must be ER+ defined as ≥10% positive tumor nuclei in the analyzed sample. ER+/progesterone receptor positive (PR+) and ER+/ progesterone receptor negative (PR-) subjects are eligible whereas estrogen receptor negative (ER-)/PR+ and ER-/PR- disease will not be eligible. 4. Women (≥18 years of age) with metastatic breast cancer not amenable to curative treatment by surgery or radiotherapy. Women of reproductive potential and their male partners must agree to use adequate contraception during treatment and for 6 months following the completion of treatment with radium-223 dichloride/placebo. 5. Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible. *Note: In premenopausal subjects, ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist/antagonist is permitted for induction of ovarian suppression if the plasma/serum estradiol assay is within local laboratory postmenopausal range at screening, performed within 7 days of randomization.* • **Pre-menopausal subjects** with or without ovarian radiation or concomitant treatment with an LH-RH

	agonist/antagonist must have a negative pregnancy test at screening and agree to use an adequate method of contraception as recommended by their treating physicians • **Post-menopausal** status is defined either by: o age ≥55 years and one year or more of amenorrhea, o age <55 years and one year or more of amenorrhea with a plasma/serum estradiol assay within local laboratory postmenopausal range, performed within 7 days of randomization, o bilateral ovariectomy. 6. Subjects with bone dominant disease with at least 2 skeletal metastases identified at baseline by bone scintigraphy and confirmed by computed tomography (CT)/magnetic resonance imaging (MRI). Presence of metastases in soft tissue (skin, subcutaneous, muscle, fat, lymph nodes) and/or visceral metastases is allowed. 7. Measurable or non-measurable disease (but radiologically evaluable) according to Response Evaluation Criteria in Solid Tumors v1.1 criteria. All disease burden must be assessed at baseline by CT or MRI of chest, pelvis and abdomen and any additional fields as needed. A bone scan should also be done at baseline for all subjects. CT/MRI done as part of the standard of practice within 3 weeks prior to randomization and standard of care bone scans done within 3 weeks prior to randomization are acceptable. F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (See also Appendix 16.2). FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same

	bone imaging modality is used throughout the study. 8. Subjects must have received at least one line of hormonal therapy in the metastatic setting. *Note: A change of the hormone agent due to progression (as per the Investigator assessment) is counted as a new line of therapy. A switch of hormone therapy from one agent to another due to toxicity or other reasons (e.g., subject's preference), in absence of progressive disease at the time of the switch, will be counted as one line although 2 different agents have been administered.* 9. Subjects who are eligible for further standard of care endocrine treatment with any of the following administered as in second line or greater of hormone therapy in metastatic setting: • Selective estrogen receptors modulators such as tamoxifen and toremifene • Non-steroidal aromatase inhibitors such as anastrozole and letrozole • Steroidal aromatase inhibitors such as exemestane • Estrogen receptor down-regulators such as fulvestrant Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (before or simultaneously to the first injection of radium-223 dichloride/placebo). 10. Subjects must have experienced no more than 2 skeletal-related events (SREs) prior to study entry defined as: Need for external beam radiotherapy (EBRT) to bone, pathological bone fracture (excluding major trauma), spinal cord compression, and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted. *Note: All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization. Separate SRE events are the ones that occur at least 21 days apart from each other to ensure that linked events (e.g., surgery to repair a fracture or multiple doses of radiation during a course of treatment) are not counted as separate events. In case of bone pain*

	that occurs in several anatomical locations and requires separate EBRT sessions, it should be counted as one event if the EBRT sessions are administered within a period of 21 days. 11. Subjects must be on therapy with bisphosphonate or denosumab and are required to have been on such therapy for at least 1 month before the start of study treatment. 12. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 13. Life expectancy ≥6 months 14. Laboratory requirements: • Absolute neutrophil count ≥1.5 x 10^9/L • Platelet count ≥100 x 10^9/L without platelet transfusion within 4 weeks prior to randomization • Hemoglobin ≥9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin within 4 weeks prior to randomization • Total bilirubin ≤1.5 x institutional upper limit of normal (ULN) (except for subjects with documented Gilbert's disease) • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x institutional ULN. • Creatinine ≤1.5 x ULN o Estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease abbreviated formula (Note: please refer to local labelling for administration of full dose of bisphosphonates) o International normalized ratio of prothrombin time (INR) and partial thromboplastin time (PTT) or activated PTT ≤1.5 x ULN at study entry. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly

evaluation of INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label.

- Serum albumin >30 g/L
- Pulse oximetry O2 saturation >92% if lung metastases are present

15. Able to swallow oral medication

Exclusion criteria

Eligible subjects must not meet any of the exclusion criteria listed below:

1. HER2-positive breast cancer (IHC=3+, positive FISH/CISH/other ISH validated assay); equivocal or unknown HER2 status
   Note: Subjects with 3+ by IHC cannot be chosen regardless of their FISH/CISH/other ISH validated assay status and those with positive FISH/CISH/other ISH validated assay cannot be chosen either, regardless of the IHC findings. Subjects with 2+ by IHC will not be eligible if no negative FISH/CISH/other ISH validated assay for detection of HER2 gene expression is available.
2. Subjects considered by the treating Investigator to be appropriate candidates for treatment with everolimus as current treatment for their metastatic breast cancer
3. Subjects with inflammatory breast cancer
5. Subjects who have either received chemotherapy for metastatic disease or are considered by the treating Investigator to be appropriate candidates for chemotherapy as current treatment for metastatic breast cancer are excluded. Chemotherapy administered for adjuvant/neo-adjuvant disease is acceptable.
6. Subjects with any previous untreated or concurrent cancer that is distinct in primary site or histology from the cancer under study, except treated basal cell carcinoma or superficial bladder tumor (Ta and Tis, American Joint Committee on Cancer, 7th edition). Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before enrollment are allowed. All cancer treatments must be completed at least 3 years prior to study entry (i.e., signature date of informed consent form).

	7. Subjects with known or history of brain metastases or leptomeningeal disease: subjects with neurological symptoms must undergo a contrast CT scan or MRI of the brain within 28 days prior to randomization to exclude active brain metastasis. Imaging of the central nervous system is otherwise not required. 8. 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. 9. Prior treatment with radium-223 dichloride 10. Prior hemibody external radiotherapy. Subjects who received other types of prior external radiotherapy are allowed provided that bone marrow function is assessed and meets the protocol requirements for hemoglobin, absolute neutrophil count, and platelets. 11. Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186, or rhenium-188 12. ECOG Performance Status ≥2 13. Blood transfusions, platelet transfusions or use of erythropoietin within 4 weeks prior to randomization. 14. Use of biologic response modifiers, such as granulocyte macrophage-colony stimulating factor or granulocyte-colony stimulating factor, within 4 weeks prior to randomization. 15. Treatment with an investigational drug or with any anti-cancer treatments not permitted by the protocol, within 4 weeks prior to randomization 16. Chronic conditions associated with non-malignant abnormal bone growth (e.g., confirmed Paget's disease of bone) 17. 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 18. Previous assignment to treatment in this study 19. Breastfeeding women 20. Known hypersensitivity to the active substance or to any of the excipients of radium-223 dichloride 21. Known presence of osteonecrosis of jaw 22. Patients with immediately life-threatening visceral disease, for whom chemotherapy is the preferred treatment option. 23. Lymphangitic carcinomatosis. 24. Patients with ascites requiring paracentesis within 2 weeks prior to study entry (signature of informed consent) and during the screening period. All local label specific criteria for the standard of care hormonal treatment as well as denosumab and bisphosphonates apply. Subjects must be treated according to the local standard of care requirements. *Diagnosis and main criteria for inclusion and exclusion section modified by Amendments 1, 2, 4, 5, and 6.*
Study design	International, phase II, double-blind, randomized, placebo-controlled, parallel-group study. Randomization will be stratified by: • Geographical regions (Europe/North America [including Israel] versus Asia) • Previous lines of hormone therapy in metastatic setting (1 versus 2 or more): for the purpose of counting the number of prior lines of hormone therapy, only a change of the hormone agent due to progression is counted as a new line of therapy. Switch of hormone therapy from one agent to another due to toxicity or other reasons (e.g., subject's preference) in absence of progressive disease at the time of switch will be counted as one line, although 2 different agents have been administered. • Prior SREs (1 versus 2): for the purpose of prior SREs stratification, separate SREs are those that occur at least 21 days apart from each other. Any procedure which is related to an SRE, such as

	orthopedic surgery to treat a pathological bone fracture or multiple doses of radiation during a course of treatment, should not be counted as a separate event. In case of bone pain that occurs in several anatomical locations and requires separate EBRT sessions, it should be counted as one event if the EBRT sessions are administered within a period of 21 days. *Study design section modified by Amendment 4.*
Methodology	The study will comprise 4 periods: screening, randomization, treatment, and the follow-up period (active follow-up with clinic visits and active follow-up without clinic visits). **Screening period:** All trial related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the informed consent form. The screening period will consist of multiple evaluations that will take place within 3 weeks prior to randomization to ensure that all eligibility criteria are met. **Randomization:** After all screening assessments have been completed and the subject's eligibility has been confirmed and documented, eligible subjects will be randomized in a ratio of 1:1 to treatment with radium-223 dichloride (Arm A - investigational arm) or placebo (Arm B - control arm). All subjects receive hormonal treatment and supportive care as background treatment according to the local standard of practice. **Treatment period:** Investigational treatment consists of up to 6 cycles of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) body weight (Arm A) or placebo (Arm B) each separated by an interval of 4 weeks. All ongoing subjects at the time of study termination will finish study treatment with radium-223 dichloride or placebo as part of the study. All subjects will receive hormonal treatment with a single agent and supportive care as background treatment according to the

	local standard of practice. Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization either before or simultaneously to the first injection of radium-223 dichloride or placebo. For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride or placebo injection. These treatments will also continue after completion of radium-223 dichloride or placebo. Subjects who discontinue treatment with radium-223 dichloride/placebo prior to experiencing an SSE or radiological progression will enter the follow-up period and will be followed up for SSEs and radiological progression. In case an SSE is not defined as progression, the subject will continue to be followed as per protocol until radiological progression. All subjects will continue to receive standard of care hormonal treatment background therapy. Hormonal treatment may also be changed according to the local standard of practice, including exemestane in combination with everolimus. For the purpose of this study, only a new hormonal treatment initiated due to disease progression will be considered a new anti-cancer therapy. If radium-223 dichloride/placebo treatment is still ongoing but the hormonal treatment is no longer considered a treatment option and the subject must start cytotoxic treatment, the subject will terminate radium-223 dichloride/placebo treatment. If radium-223 dichloride/placebo treatment is still ongoing but the background treatment is no longer considered a treatment option and the subject must start another protocol permitted concomitant systemic anticancer treatment, the subject can continue radium-223 dichloride/placebo until completion or until any withdrawal criteria are met. If however, the background hormonal treatment or further standard of care protocol permitted concomitant systemic anticancer therapy are discontinued, radium-223 dichloride/placebo must also be discontinued. Subjects will continue to be followed up for SSEs and radiological progression. Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether patient starts a new anticancer therapy (i.e. chemotherapy,

	other). Subject management unless otherwise defined by this protocol will be in accordance to the local standard of practice. The radium-223 dichloride/placebo administration should be discontinued as per the withdrawal criteria described in Section 6.3.1 of the protocol (e.g., subject experiences unacceptable toxicities, delays in radium-223 dichloride/placebo > 4 weeks, subject enters the active follow-up without clinic visits as she can no longer travel to the clinical site, and if in the Investigator's opinion, continuation of the study treatment would be harmful to the subject's well-being). Subjects who experience an SSE during radium-223 dichloride/placebo treatment may continue treatment until completion or until any withdrawal criteria are met, if in the opinion of the Investigator the subject continues to derive benefit. In case an SSE is not defined as progression, the subject will continue to be followed as per protocol until radiological progression. Subjects will be assessed for efficacy and safety endpoints at each treatment visit and will be evaluated every 12 weeks for radiological progression. Subjects who did not experience either an SSE or radiological progression during the treatment period will enter, at the end of the treatment period, the Active Follow-up with clinic visits where they will continue to be followed up for these events. Subjects who experience an SSE **and** radiological progression during the protocol defined treatment period will enter, at the end of the treatment period, the active follow-up without clinic visits. Subjects who can no longer travel to the clinical site will be discontinued from the radium-223 dichloride/placebo study treatment and will enter the active follow-up without clinic visits. During this time subjects will continue to receive hormonal background treatment as per local standard of practice. Subjects who missed 2 consecutive treatment visits will be considered unable to travel to the site, will be discontinued from study treatment and will enter the active follow-up without clinic visits. The total treatment period is defined from the day of randomization of subject in the interactive voice/web response system until 4 weeks after the last administration of radium-223

	dichloride/placebo. A specific interval, depending on country specific drug order lead time between the date of randomization and the first radium-223 dichloride/placebo administration will be necessary for the study drug shipment/availability. Randomized subjects who never received treatment will not be included in the safety analysis. An end of treatment (EOT) electronic case report form should be completed for these subjects to document the reason for discontinuation. **Follow-up period:** The active follow-up has 2 distinct periods based on whether the subject can travel to the clinic site: the active follow-up with clinic visits for subjects who can travel and the active follow-up without clinic visits for subjects who cannot travel. Once a subject switches from active follow-up with clinic visits to active follow-up without clinic visits, the subject will not be allowed to switch back. All subjects, regardless of reaching a study endpoint (on-study SSE or radiological progression), will enter the follow-up period in order to collect the required long-term safety information. ***Active follow-up period with clinic visits:*** Subjects who discontinued or completed the radium-223 dichloride or placebo treatment did not experience an SSE and radiological progression during the treatment period, had an EOT visit, and can travel to the clinic will enter an active follow-up period with clinic visits. During this period, clinic visits are to occur as follows: • For subjects who have not experienced an SSE during the treatment period, visits will continue with the same frequency as during treatment (every 4 weeks ±7 days) until the subject has an SSE. After the occurrence of the SSE, the subjects will be switched to a frequency of visits every 12 weeks ±7 days at the next scheduled visit. • For subjects who experienced an SSE during the treatment or this period, visits will occur every 12 weeks ±7 days. The subjects will continue to be followed for radiological progression and long-term safety. • Subjects who miss 2 consecutive follow-up visits will be considered unable to travel to the site and will enter the active follow-up without clinic visits.

	Radiological tumor assessment will be performed every 12 weeks, independently of the frequency of the visits, until radiological disease progression is documented. Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether patient starts a new anticancer therapy (i.e. chemotherapy, other). The active follow-up period with clinic visits extends from the EOT visit until the subject can no longer travel to the clinic, experiences an SSE **and** radiological progression, 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 until study termination. These subjects will be evaluated for pain endpoints, radiological progression, SSEs, survival, treatment-related adverse events (AEs) and serious adverse events (SAEs), and 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 any additional malignancies, including acute myelocytic leukemia (AML), and hematological conditions, such as myelodysplastic syndromes (MDS), aplastic anemia, or myelofibrosis must be reported as SAEs, regardless of the Investigator's causality assessment. All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. ***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 or those who experienced an SSE **and** radiological progression will be followed for survival, treatment-related AEs and SAEs, the initiation of other anti-cancer therapies, and SSEs with phone calls as follows: • For subjects that did not experience an SSE during treatment or the previous follow-up period, the frequency of the phone calls will be every 4 weeks ±7 days until the subject has an SSE. After the occurrence of the SSE, the subjects will be switched to a frequency of phone calls every 12 weeks ±7 days at the next scheduled phone call. • For subjects who experienced an SSE during treatment or

	the previous follow-up period, the frequency of the phone calls will be every 12 weeks ±7 days. Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether patient starts a new anticancer therapy (i.e. chemotherapy, other). The active follow-up period **without** clinic visits extends from the EOT visit **or** the end of active follow-up with clinic visits until the subject 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 until study termination. 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 any additional malignancies, including AML, and hematological conditions, such as MDS, aplastic anemia or myelofibrosis must be reported as SAEs, regardless of the Investigator's causality assessment. All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. Subject treatment management will be in accordance with routine clinical practice, at the discretion of the Investigator. Survival will also be updated for all subjects in the active follow-up period at the time of final analysis of the primary endpoint. **Long-term follow-up – Extension study:** All ongoing study subjects who have completed at a minimum the EOT visit or 30 days from last study treatment dose, whichever is latest, may be transitioned into a separate long-term follow-up study (BAY 88-8223 study 16996 / NCT02312960). 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 primary objective of this study is to define the long-term safety profile of radium-223 dichloride. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. 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., death, consent withdrawn and active objection for further data collection, lost to follow-up). Until the transition to the long-term follow up study, subjects will continue to follow all the protocols required procedures and visits in the current protocol. *Methodology section modified by Amendments 1, 2, 4, and 8.*
Type of control	Placebo-control arm
Number of subjects	227 subjects in total (with 1:1 randomization)
Primary variable	Symptomatic skeletal event-free survival (SSE-FS)
Time point/frame of measurement for primary variable(s)	The primary variable/endpoint, SSE-FS, is defined as the time from randomization to the occurrence of one of the following: (1) An on-study SSE, which is defined as: a. the use of EBRT to relieve skeletal symptoms b. the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral) c. the occurrence of spinal cord compression d. a tumor related orthopedic surgical intervention. (2) Death from any cause Note: All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization.
Plan for statistical analysis	The analysis of efficacy will be performed using the intent-to-treat population, defined as all subjects who are randomized. The primary efficacy analysis of SSE-FS will be performed using a log-rank test, stratified by the same factors as the randomization factors (i.e., geographic region, prior lines of hormone therapy in metastatic setting, and prior SREs). A one-sided alpha of 0.1 will be used for the analysis of SSE-FS. Assuming a one-sided alpha of 0.1, power of 90%, a randomization ratio of 1:1 between treatments, and the median SSE-FS for the control group to be 7 months, approximately 119 events will be required to detect a 60% increase in SSE-FS for a total of 227 subjects in the 2 treatment groups combined. The secondary and exploratory time-to-event efficacy endpoints will be analyzed using a log-rank test, stratified by the same

	factors as the randomization factors. The analysis of safety will be descriptive only (no statistical test will be applied).

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List of abbreviations

Section modified by Amendment 4 (Section 15.3), Amendment 5 (Section 15.4), and Amendment 7 (Section 15.6).

AE	Adverse event
AI	Aromatase inhibitor
ALP	Alkaline phosphatase
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer
ALT	Alanine aminotransferase
AML	Acute myelocytic leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BCE	Bone collagen equivalents
BPI-SF	Brief Pain Inventory-Short Form
BUN	Blood urea nitrogen
Ca	Calcium
CI	Confidence interval
CISH	Chromogenic in situ hybridization
Cl	Chloride
CR	Complete response
CRO	Contract research organization
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events; version 4.03
Cx	Cycle x
DK	Decay correction factor
DNA	Deoxyribonucleic acid
EBRT	External beam radiotherapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
ER	Estrogen receptor
ER-	Estrogen receptor negative

ER+	Estrogen receptor positive
EU	European Union
FDA	United States Food and Drug Administration
FDG	Fluorodeoxyglucose
FISH	Fluorescence in situ hybridization
G-CSF	Granulocyte-colony stimulating factor
GCP	Good clinical practice
GFR	Glomerular filtration rate
GM-CSF	Granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
IBW	Ideal body weight
ICF	Informed consent form
ID	Identification number
IDRC	Independent Data Review Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INR	International normalized ratio of prothrombin time
IPM	Increase in pain management
IRB	Institutional Review Board
ISH	In situ hybridization
ITT	Intent-to-treat
IV	Intravenous
IXRS	Interactive voice/web response system
K	Potassium
kBq	KiloBecquerel; SI unit of radioactivity
kg	Kilogram
LDH	Lactate dehydrogenase
LH-RH	Luteinizing hormone-releasing hormone
mCi	Millicuries
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndromes

mg	Milligram
mL	Milliliter
mRECIST 1.1	Modified Response Evaluation Criteria in Solid Tumors version 1.1
MRI	Magnetic resonance imaging
Na	Sodium
NCI	National Cancer Institute
NE	Non-evaluable
NIST	National Institute of Standards and Technology
NSAI	Non-steroidal aromatase inhibitor
NTX	N-terminal telopeptide
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Progressive response
PR-	Progesterone receptor negative
PR+	Progesterone receptor positive
PRD	Patient ready dose
PS	Performance status
PSA	Prostate specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
q	Every
QoL	Quality of life
RANKL	Receptor activator of NF–κB ligand
RAVE	Medidata Rave; electronic data capture tool
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiological progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	SAS Institute Inc.
SC	Subcutaneously
SD	Stable disease
SPECT	Single photon emission tomography
SRE	Skeletal-related event

SSE	Symptomatic skeletal event
SSE-FS	Symptomatic skeletal event-free survival
SUSAR	Suspected unexpected serious adverse reaction
TBW	Total body weight
TTP	Time to progression
tx	Treatment
ULN	Upper limit of normal
US	United States
W/O	Without
WBC	White blood cell
wk	Week
WPS	Worst pain score

Definitions of terms

Radium-223 dichloride	The investigational product, a targeted 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 ($^{223}Ra^{2+}$).
Dose	Doses are given as kiloBecquerel (kBq) per kilogram body weight, with the corresponding dose given in millicurie (mCi) per kilogram in parenthesis. The term “dose” is used to describe the quantity of radioactivity from radium-223 administered.

3. Introduction

3.1 Metastatic breast cancer

Breast cancer is by far, the most common cancer among women worldwide with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers). It is the most frequent cause of cancer death in women in less developed regions (324,000 deaths, 14.3% of total) and the second cause of cancer death in more developed regions (198,000 deaths, 15.4%) after lung cancer.(1)

Despite recent progress in diagnostic and therapeutic approaches of early breast cancer, a significant proportion of patients relapse following adjuvant treatment and approximately 5% to 6% of women present with metastatic disease at the time of their initial diagnosis.

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

Depending on the extent of metastatic involvement, the prognosis is variable ranging from a median overall survival (OS) time of 26 months, in patients with bone metastases only, to 21 months, in patients with bone and visceral metastases, and 18 months, in patients with visceral metastases only.(2)

Patients with metastatic disease are unlikely to be cured with actual available therapies. As cure is unlikely in the metastatic setting, prolongation of survival, disease control, improvement/maintenance of quality of life (QoL) and palliation of cancer-related symptoms are reasonable goals of therapy.

Various therapeutic approaches are available; however, there are few widely accepted standards. Most patients will receive systemic therapies such as chemotherapy, endocrine therapy, biologic/targeted molecular therapies, bone-targeted agents, as well as supportive care. The selection of a certain type of therapy over the other depends upon factors, such as tumor/disease characteristics (hormone receptor status, human epidermal growth factor receptor 2 [HER2] status, extent of metastatic involvement, disease clinical behavior, etc.), prior therapies and disease response to prior therapies, patient characteristics (i.e., comorbidities, estimated treatment tolerability, menopausal status), availability and costs of therapeutic agents and, last but not least, patient preference.

Participation in well-designed clinical studies should always be considered in patients with metastatic breast cancer.

Patients with rapidly progressing or symptomatic or visceral disease as well as those patients with hormone receptor–negative tumors or with disease that is resistant to hormonal therapy are candidates for chemotherapy.

Patients with HER2/neu positive disease are candidates for anti-HER2-targeted agents (i.e., herceptin, lapatinib).

3.2 HER2 negative and hormone receptor-positive metastatic breast cancer

Presence of estrogen receptor (ER) and/or progesterone receptor (PR) is one of the most important prognostic/predictive factors in breast cancers. Approximately 70% to 75% of patients with invasive breast cancer have hormone receptor (ER and/or PR) positive disease at the time of diagnosis.(3)

Patients with hormone receptor positive disease and HER2-negative disease are candidates for endocrine therapy unless one of the factors described above would prompt the selection of another type of therapy (i.e., chemotherapy in a patient with an aggressive clinical course and rapid pace of progression). Endocrine therapy will very likely have a beneficial effect in these patients and fewer side effects in comparison with chemotherapy.(4,5)

Selection of the first line endocrine agent is generally based on the menopausal status, type of endocrine agent in the adjuvant setting, timing of relapse following treatment in the adjuvant setting, and tolerability. First line endocrine therapy is usually continued until the patient experiences disease progression or unacceptable toxicity.

Additional lines of therapy may include another endocrine agent (not previously administered) or another type of therapy such as cytotoxic therapy. There are no widely accepted standards/definitive recommendations for a specific treatment sequence, number of lines of endocrine therapy, and the therapeutic decision should be again based on the factors described above.

Endocrine therapy exerts its action either by reducing estrogen production or by interacting with ERs.

Various endocrine agents are currently in use including:

- Selective estrogen receptor modulators (SERMs): Tamoxifen and toremifene. SERMs act by antagonizing the action of estrogen in breast tissue. At the same time, they also mimic the action of estrogen in other tissues, such as bone and endometrium.(6)
- Third generation aromatase inhibitors (AIs) block peripheral estrogen synthesis by inhibiting aromatase, the enzyme responsible for the peripheral conversion of androgens to estrogen.(7) Currently available third generation AI are the nonsteroidal AIs (NSAIs), anastrozole and letrozole and the steroidal AI, exemestane. In the first-line setting, large phase III studies have shown that all 3, anastrozole, letrozole, and exemestane are equivalent or superior to tamoxifen in women with metastatic disease.(8,9,10,11)
- Estrogen receptor down-regulators: Fulvestrant is a competitive ER antagonist. It blocks the actions of estrogens at the level of the receptor without any known partial agonist (estrogen-like) activity. Fulvestrant has been approved by the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of hormone receptor positive metastatic breast cancer in post-

menopausal women with disease progression following prior anti-estrogen therapy based on results of published clinical studies.(12,13,14)

- Luteinizing hormone-releasing hormone (LH-RH) analogues: Goserelin, leuprorelin, triptorelin.
- Other: estrogens, progestins, anabolic steroids

Recently published data from a phase II study shows that addition of everolimus to tamoxifen in hormone receptor positive, HER2 negative patients who progressed on prior AI treatment significantly improved the clinical benefit rate, time to progression.(15)

In addition to this, data from the phase III BOLERO-2 study showed that the addition of everolimus to exemestane significantly improved progression-free survival (PFS) compared with single-agent exemestane in estrogen receptor positive (ER+), HER2 negative patients whose metastatic disease was refractory to prior treatment with letrozole or anastrozole.(16) This led to the recent marketing approval of everolimus by the FDA and EMA for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in post-menopausal women without symptomatic visceral disease after recurrence or progression following an NSAI.

3.3 Bone metastasis in HER2-negative and hormone receptor-positive metastatic breast cancer

Bone is a frequent site of metastatic spread with approximately 65% to 75% of patients with metastatic breast cancer having skeletal involvement.(17) The skeleton is the first site of distant spread in 46% to 47% of patients with breast cancer. The presence of skeletal metastases correlates significantly with ER and PR positivity.(18,19) Bone-only metastases have been reported to occur in 17% to 37% of women with metastatic breast cancer.(20,21,22)

Results of a recent meta-analysis from 41 randomized studies that compared bisphosphonates to no bisphosphonates and including data from 17,751 breast cancer patients suggests that adjuvant bisphosphonates reduce bone recurrences and improve breast cancer survival in post-menopausal women. Reductions in bone recurrence for post-menopausal women were similar independent of ER status, nodal involvement, bisphosphonate type, treatment schedule, or use of concomitant chemotherapy.(23)

Prognosis of patients with metastases confined to bone only seems to be better compared to patients with visceral involvement with median survival times from the diagnosis of metastatic disease to death between 24 to 36 months as reported per different publications.(2,21,22,24,25) Occurrence of osseous metastases interferes with normal bone homeostasis and impacts the normal remodeling process by disrupting the fine balance between new bone formation and bone resorption processes. This, finally results in loss of bone integrity and loss of function.

The most common sites of bone involvement are axial bones; however, other locations may also be encountered although with a lower frequency. Bone lesions may be of osteolytic, osteoblastic, or mixed phenotype as per the radiographic appearance of the lesions. It is well

known that bone metastases from breast cancer usually show osteolytic changes. However, interestingly, as per a retrospective study, when comparing the morphology of breast cancer bone metastases by computed tomography (CT) in the time period 1996 to 2000 versus 2001 to 2005, a higher prevalence of osteoblastic metastases was observed in the later period (1996 to 2000: osteolytic 53.7%, osteosclerotic 32.1%, mixed type 14.3%; 2001 to 2005: osteolytic 9.4%, osteosclerotic 71.9%, mixed type 18.7%). This might be due to the application of systematic bisphosphonate treatment.(26)

Due to the disrupted bone remodeling process, patients with metastatic bone lesions are at risk of increased morbidity including skeletal related events (SRE), such as bone pain requiring intervention (i.e., radiotherapy or surgery), pathologic fractures, spinal cord compression, as well as symptomatic hypercalcemia and bone marrow infiltration. These events will ultimately impair the patient's QoL and functional independence.

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

Use of systemic bone targeted agents, such bisphosphonates, as well as the newer anti-receptor activator of NF–κB ligand (RANKL) antibody, denosumab demonstrated a beneficial effect in patients with metastatic bone disease. While bisphosphonates inhibit osteoclast-mediated bone resorption, denosumab, a monoclonal antibody, inhibits key pathways in the vicious cycle of bone metastases by binding to RANKL, a mediator that stimulates increased osteoclast activity.

Several clinical studies have demonstrated the efficacy of bisphosphonates in women with bone metastases from breast cancer.(27,28,29,30)

More recently, denosumab has been found to be more effective than zoledronic acid as measured by the time to first and subsequent on-study SREs in patients with bone metastases.(31,32) The median time to the first on-study SRE was 26.4 months for zoledronic acid and was not yet reached for denosumab at time of reporting. Denosumab was approved for the treatment of patients with bone metastases from solid tumors, including breast cancer.

A recent review of 34 studies performed in this patient population provided further confirmation that the use of bisphosphonates or denosumab (in addition to their other cancer treatments) reduces the risk of developing SREs and delay the time to SREs. However, questions on the optimal timing and duration of treatment with these agents in patients with bone metastases from breast cancer remain unanswered.(33) Bone-targeted agent therapy (i.e., bisphosphonates or denosumab) is actually recommended for patients with breast cancer with evidence of bone metastases.(34)

Patients with multiple, mainly osteoblastic lesions and pain syndrome may also benefit from treatment with radionuclide therapy. Bone-seeking radionuclides have been developed for palliation of bone pain from metastases.(35)

Metastron (strontium-89) and Quadramet (samarium-153 ethylene diamine tetramethylene phosphonate) have been approved in several countries for symptom palliation in patients with bone metastases.(36) The bone-seeking nature of these agents results in direct delivery of beta radiation to the sites of disease. Due to the long range of the beta particles from these radioisotopes, the major dose-limiting factor with this treatment modality is toxicity to the bone marrow cells, limiting the use of these agents to pain palliation only as they have not demonstrated an OS benefit. This toxicity has seriously limited their clinical use.

The limited hematological toxicity resulting from the short particle range of new alpha emitter radiopharmaceutical radium-223 dichloride may allow an easier integration with background anti-cancer therapies. Beside pain palliation effect, the high absorbed dose delivered by alpha-emitting radionuclides might have a direct anti-tumor effect in bone.

Multimodality therapy such as bisphosphonate/denosumab and radiopharmaceutical agents in addition to the standard background treatment might offer superior symptom control and even prolonged PFS and OS.

3.4 Study medications

3.4.1 Radium-223 dichloride

3.4.1.1 Drug development

Radium-223 dichloride solution for injection is a novel alpha particle-emitting radiopharmaceutical. The bone targeting property of radium-223 is similar to that of other earth alkaline elements, like calcium or strontium-89. However, the radiation characteristics of an alpha particle-emitting radionuclide appear to be more advantageous than of a beta-emitting radionuclide. Radium-223, with a physical half-life of 11.4 days, emits high linear energy transfer alpha radiation, with a range limited to less than 100 micrometers. The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand deoxyribonucleic acid (DNA) breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases. The alpha particle range from radium-223 dichloride is less than 100 micrometers (less than 10 cell diameters), which limits damage to the surrounding normal tissue.

Biodistribution studies have shown that radium-223 is selectively concentrated in bone compared to soft tissues, and that radium-223 is retained in the bone matrix.(37,38) Due to increased bone metabolism in skeletal metastases, preferential uptake in these lesions compared to normal bone is observed. A significant radium-223 anti-tumor effect has been demonstrated in an experimental skeletal metastases model in nude rats.(38)

The clinical development of radium-223 dichloride was initiated in August 2001. A phase I clinical study in subjects with skeletal metastases from breast and prostate cancer was performed in order to evaluate whether the product could be administered safely at

therapeutically relevant doses. A total of 31 subjects were enrolled. Twenty-five subjects received a single intravenous (IV) injection in the dose escalating part of the study, with 5 subjects at each dose level of 46, 93, 163, 213, and 250 kBq/kg body weight radium-223 dichloride. The results of this phase I study were encouraging (low toxicity, significant pain relief, and decreased serum alkaline phosphatase [ALP]); thus, a phase II study (BC1-02 study) for castration-resistant prostate cancer (CRPC) was conducted,(37) where subjects received multiple doses of either 50 kBq/kg body weight radium-223 dichloride or saline 4 times at 4-week intervals. In both studies, the results showed modest dose-dependent reversible hematological toxicity. No significant deleterious changes in chemistry parameters were seen, and the most frequent adverse event (AE) was transient diarrhea, which responded well to medication. In terms of efficacy, the BC1-02 phase II results showed a significant improvement in serum bone markers, i.e., bone ALP (a primary efficacy endpoint) and, perhaps more importantly, a delayed time to prostate specific antigen (PSA) progression. Median OS at 2 years was 65.3 weeks for radium-223 dichloride and 46.3 weeks for placebo (hazard ratio [HR]=2.1; p=0.017 based on an intent-to-treat [ITT] population and adjusting for baseline covariates).

Following the positive results of the phase II study, the phase III, double-blind, randomized, BC1-06, ALSYMPCA (**Al**pharadin in **Sym**ptomatic **P**rostate **Ca**ncer) study was started in 2008. A total of 922 subjects with CRPC and symptomatic bone metastases were randomized to receive 6 injections of radium-223 dichloride (50 kBq/kg IV) or matching placebo every 4 weeks. Based on data of an interim analysis (n=809), the study was unblinded in June 2011, since radium-223 dichloride significantly improved OS compared to placebo (the median OS was 14.0 versus 11.2 months, respectively; HR= 0.695; p=0.00185). Symptomatic skeletal events (SSE) were lower in the radium-223 dichloride arm, and time to first SSE was significantly delayed (the median time to SSE was 13.6 months, versus 8.4 months, respectively; HR=0.610; p=0.00046). A low incidence of myelosuppression was observed, with Grade 3/4 events of neutropenia (1.8%) and thrombocytopenia (6.2%). Adverse events of any grade were described in 88% of the subjects who received radium-223 dichloride versus 94% in the placebo arm (Grade 3/4 AEs were described for 51% and 59%, respectively). The updated analysis (performed in June 2012) also showed that radium-223 dichloride significantly improved OS compared to placebo (median OS 14.9 versus 11.3 months, respectively; HR=0.695; p=0.00007).(39)

In an open-label, multicenter, single-arm, phase IIa study (BC1-09), 23 subjects with metastatic breast cancer with bone dominant disease were administered 4 injections of radium-223 dichloride (50 kBq/kg IV) every 4 weeks. Bone markers were assessed at baseline, prior to every treatment, and thereafter at each follow-up visit. The primary efficacy endpoints were the change in urine levels of N-terminal telopeptide (NTX) and bone ALP from baseline at Week 16. Median urine NTX levels were reduced by 20% (from 36 to 29 nmo1 bone collagen equivalents [BCE]/mmo1 creatinine; p=0.03) and 33% (from 36 to 23 nmo1 BCE/mmo1 creatinine; p=0.0124) at Week 8 and Week 16, respectively; 17/23 and 9/13 subjects (for whom data were available) had a decrease in urine NTX at Week 8 and Week 16, respectively. Median bone ALP levels were reduced by 33% (from 22.1 to 12.1 ng/mL; p=0.0001) at Week 8 and 42% (from 22.1 to 10.94 ng/mL; p=0.04) at Week 16. Bone ALP levels were reduced in 20/22 subjects at Week 8 and in 10/12 subjects (for whom

data were available) at Week 16. Radium-223 dichloride was found to be safe and well tolerated. Three subjects had serious AEs (SAEs), none related to study drug; 1 of them died due to disease progression.(40)

Further details can be found in the Investigator's Brochure (IB), which contains comprehensive information on the study drug.

3.4.1.2 Benefits and risks

Anticipated benefits of treatment with radium-223 dichloride include prolongation of symptomatic skeletal event-free survival (SSE-FS), OS, and radiological progression-free survival (rPFS), delay of SSEs, palliation of bone pain, and improvement in QoL.

The risk profile attributed to radium-223 dichloride is favorable compared with available products for the treatment of metastatic breast cancer. The anticipated risks attributed to radium-223 dichloride include the following AEs: gastrointestinal (constipation, transient but treatable diarrhea, nausea, and vomiting); hematological (transient reduction in neutrophil count, mild to moderate myelosuppression, low grade thrombocytopenia). Due to its radioactive nature, radium-223 dichloride has the potential of inducting long-term toxicities such as other primary cancers. Current ongoing studies have an increased follow-up of 7 years in order to assess this potential.

3.4.1.3 Dosing rationale

Section modified by Amendment 2 (Section 15.2) and Amendment 4 (Section 15.3).

The proposed dosing regimen in this phase II study is 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update) every 4 weeks for a 6-month treatment period (6 injections). In the completed phase I safety, tolerability, and pharmacokinetic clinical study (ATI-BC-1), subjects diagnosed with prostate or breast carcinoma and skeletal metastases were administered radium-223 dichloride in single doses of 46, 93, 163, 213, or 250 kBq/kg body weight (25 subjects) or multiple doses of 5 administrations of 50 kBq/kg body weight at 3-week intervals (3 subjects) or 2 administrations of 125 kBq/kg body weight at 6-week intervals (3 subjects). In the completed phase II study, 64 subjects with CRPC and painful skeletal metastases, received 4 injections of 50 kBq/kg body weight radium-223 dichloride (33 subjects) or placebo (31 subjects) at 4-week intervals to examine the effects of radium-223 dichloride on biomarkers of disease progression, SSEs, pain palliation, survival, and safety parameters. The completed phase III study, ALSYMPCA, enrolled 922 subjects diagnosed with CRPC and symptomatic bone metastases who received 6 injections of radium-223 dichloride (50 kBq/kg IV) in 4-week intervals. Endpoints included OS, time to disease-related events, time to progression (TTP) as measured by serum PSA and total ALP concentrations, pain palliation, acute and long-term safety profile, and health-related quality of life (HRQoL). The efficacy and safety data from the ALSYMPCA study support the selection of a dosing regimen of 6 doses of 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update) of radium-223 dichloride at 4-week intervals. This dose and schedule was determined to be efficacious, with only minor side effects and no indication of cumulative effect on bone marrow suppression following multiple administrations of radium-223 dichloride.

Currently, no data are available to assess if similar effects could be achieved with a dose lower than 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update).

The same dose was used in a phase II breast cancer study BC1-09 which provided preliminary evidence of the effects of radium-223 on bone markers, BPI score, and tumor metabolism assessed by serial F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging and supports further investigations to confirm effectiveness of radium-223 in treating bone metastases in patients with breast cancer and bone-dominant disease. Data were communicated at the San Antonio Breast Cancer Symposium 2011 and published in 2014.(40) The study results are presented in detail in Section 3.4.1.1.

3.4.2 Standard of care hormonal treatments

Patients with hormone receptor positive disease and HER2-negative disease are generally considered good candidates for endocrine therapy unless other factors would prompt the choice of another type of therapy (i.e., chemotherapy in a patient with an aggressive clinical course and rapid pace of progression).

Results of previous randomized studies and a meta-analysis suggest that AIs are more effective than tamoxifen for first-line therapy in post-menopausal women whose tumors have not become previously resistant to these drugs.(41) The choice of initial, first line, endocrine therapy depends on the endocrine agent used in the adjuvant setting and timing of recurrence/relapse. In first line setting, anastrozole was shown to be superior to tamoxifen for TTP but not for OS. Letrozole significantly prolonged TTP compared with tamoxifen but, again, had no significant difference in OS; exemestane had similar OS compared with tamoxifen using the log-rank test and significant improvement in PFS when using the Wilcoxon test.(42,43,44) Based on these results, NSAIs are currently considered the most effective first-line treatment of post-menopausal patients with metastatic breast cancer. However, tamoxifen remains a standard first-line agent for pre-menopausal women, as well as for post-menopausal women who have relapsed shortly following completion of adjuvant therapy with an AI (i.e., during or within 12 months).

The first line endocrine therapy is generally continued until disease progression. Responding patients, as well as those with very slowly progressing disease (i.e., no disease progression within 6 months of starting therapy), may be further treated, following progression, with several different endocrine agents that are generally tried in sequence.

There is, however, limited data from randomized clinical studies concerning the best sequence of endocrine therapies in patients with metastatic breast cancer and no definitive recommendations can be made.(41)

Examples of further line endocrine therapy in post-menopausal women include selective AIs (if not used in first line), such as anastrozole, letrozole, or exemestane; fulvestrant, megestrol acetate; estrogens; and androgens.

Side effects associated with the use of endocrine therapies include, but are not limited to, hot flashes, vaginal discharge, menstrual irregularities, sexual dysfunction, thromboembolic events, increased risk of uterine cancer (tamoxifen), decrease in bone mineral density, bone fracture, and hypercholesterolemia.

However, endocrine therapy will very likely have a beneficial effect and fewer side effects in comparison with chemotherapy.

3.5 Study rationale

The treatment options for patients with bone predominant metastasis of breast cancer are still limited.

Radium-223 dichloride has shown significant anti-tumor activity in phase II and phase III studies in subjects with bone predominant metastatic CRPC and in the phase II metastatic breast cancer study.

The safety profile and tolerability for radium-223 dichloride appear to be acceptable in this study population.

This study is blinded, randomized, and placebo controlled for radium-223 dichloride, and it is unblinded for standard of care hormonal treatment that will be received by all subjects (both arms). Best supportive care will also be received by both arms.

The mode of action differs for all involved compounds, as hormonal treatment targets the estrogens which promote the growth of hormone sensitive breast cancers. Tamoxifen and toremifene bind specifically to ERs, competitively with estradiol, and inhibit estrogen-induced stimulation of DNA synthesis and cell replication. Fulvestrant is a competitive ER antagonist with an affinity comparable to estradiol.

The NSAIs, anastrozole and letrozole, are competitive inhibitors of the aromatase enzyme system at the primary sites of estrogen synthesis, which in post-menopausal women, are peripheral tissues, whereas exemestane binds irreversibly to the active site of the enzyme aromatase, causing its inactivation. Radium-223 dichloride delivers alpha radiation to bone lesions of breast cancer. Based upon these individual effects, it is expected that radium-223 dichloride treatment will prolong symptomatic SSE-FS compared to placebo, when administered to HER2 negative, hormone receptor positive metastatic breast cancer patients with bone metastases who receive standard of care hormonal treatment as background therapy.

Primary efficacy endpoints

Symptomatic skeletal event-free survival is defined as the time from randomization to the occurrence of one of the following:

(1) An on-study SSE, which is defined as:
   a. the use of EBRT to relieve skeletal symptoms
   b. the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)
   c. the occurrence of spinal cord compression
   d. a tumor related orthopedic surgical intervention.

(2) Death from any cause

Since the definition for measuring skeletal events will not use pre-specified imaging assessments, the use of imaging to identify a fracture or spinal cord compression will be triggered by symptoms. As such, only symptomatic events will be captured; asymptomatic radiographic events are not included in this composite endpoint. A delay or a reduction of SSEs represents an immediate clinical benefit, as it will delay or reduce bone pain, functional impairment, and the need for surgical intervention.

In ALSYMPCA, treatment with radium-223 dichloride increased the time to first SSE from 9.8 to 15.6 months (HR=0.658, p=0.00037, data on file).

The median SSE-FS in ALSYMPCA was 9.0 and 6.4 months with and without radium-223 dichloride, respectively (HR=0.685, p=0.00004). An ad-hoc analysis (data on file) in subjects who did not receive docetaxel prior to radium-223 dichloride indicated that the median duration of SSE-FS is preserved in this subgroup of 395 subjects (SSE-FS was 9.5 months with and 6.7 months without radium-223 dichloride).

The occurrence of SREs in breast cancer patients with bone metastases is associated with worse functional, physical and emotional status and a decreased overall QoL.(45,46) Prevention of SREs, is therefore, an important aim in the therapeutic management of these patients. Bone-targeted agents, such as bisphosphonates and denosumab, have been reported to delay the time to SRE and reduce the risk of developing SREs. In addition, they also reduced bone pain and showed an improvement in QoL.(32, 33,46,47,48,49) As per the American Society of Clinical Oncology treatment guidelines, they are both recommended in patients with breast cancer with evidence of bone metastases.(34)

A recent study in patients with bone metastases also reported that patients rated chronic pain as their main symptom and the most relevant HRQoL issue related to their disease. This was followed by difficulty in carrying out their usual tasks and worries about loss of independence and mobility.(50)

The high incidence of bone metastases, as well as the prognostic relevance of bone involvement, definitely suggests that improvements in bone-targeted therapeutic approach could provide further patient benefit.

In conclusion, SSE-FS is an objective variable that is likely to predict clinical benefit in the proposed study population.

4. Study objectives

Section modified by Amendment 4 (Section 15.3).

The objective of this study is to assess the efficacy and safety of radium-223 dichloride in subjects with HER2 negative, hormone receptor positive breast cancer with bone metastases treated with hormonal treatment background therapy.

The **primary endpoint** is:

- SSE-FS

The **secondary endpoints** are:

- OS
- Time to opiate use for cancer pain
- Time to pain progression (only in subjects with baseline worst pain score (WPS) ≤8)
- Time to cytotoxic chemotherapy
- rPFS
- Pain improvement rate
- Safety, acute and long term, including new primary malignancies and hematopoietic reserve for tolerability of subsequent chemotherapy

The study will also include the following **exploratory endpoints**:

- Time to first on-study SSE
- Time to bone ALP progression
- Bone ALP response at Week 12 and end of treatment (EOT)
- Bone-specific rPFS
- Resource utilization
- Biomarker assessments
- Time to visceral metastases onset

5. Study design

5.1 Design overview

Section modified by Amendment 1 (Section 15.1) and Amendment 4 (Section 15.3).

This study is an international phase II, randomized, double-blind, placebo-controlled, parallel-group study of radium-223 dichloride versus placebo administered on top of the hormonal treatment and supportive care as background treatment in subjects with HER2 negative, hormone receptor positive breast cancer with bone metastases. Randomization will be stratified by:

- Geographical regions (Europe/North America [including Israel] versus Asia)
- Previous lines of hormone therapy in metastatic setting (1 versus 2 or more): for the purpose of counting the number of prior lines of hormone therapy, only a change of the hormone agent due to progression is counted as a new line of therapy. A switch of hormone therapy from one agent to another due to toxicity or other reasons (e.g., subject's preference) in absence of progressive disease (PD) at the time of switch will be counted as one line, although 2 different agents have been administered.
- Prior SREs (1 versus 2): for the purpose of prior SREs stratification, separate SREs are those that occur at least 21 days apart from each other. Any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture or

multiple doses of radiation during a course of treatment, should not be counted as a separate event. In case of bone pain that occurs in several anatomical locations and requires separate EBRT sessions, it should be counted as one event if the EBRT sessions are administered within a period of 21 days.

This study will be conducted at approximately 160 investigative study sites and approximately 227 subjects will be enrolled.

5.1.1 Study periods and duration

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), Amendment 5 (Section 15.4), Amendment 8 (Section 15.7.1.1 and Section 15.7.1.2).

The study will comprise 4 periods: screening, randomization, treatment, and the follow-up period (active follow-up with clinic visits and active follow-up without clinic visits).

Screening period:

All trial related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the informed consent form (ICF). The screening period will consist of multiple evaluations that will take place within 3 weeks prior to randomization to ensure that all eligibility criteria are met (Section 6).

Randomization:

After all screening assessments have been completed and the subject's eligibility has been confirmed and documented, eligible subjects will be randomized in a ratio of 1:1 to treatment with radium-223 dichloride (Arm A - investigational arm) or placebo (Arm B - control arm). All subjects will receive treatment with a single hormonal agent and supportive care as background treatment, as per the local/institutional standard of practice.

Treatment period:

Investigational treatment consists of up to 6 cycles of radium-223 dichloride 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update) (Arm A - investigational arm) or placebo (Arm B - control arm), each separated by an interval of 4 weeks.

All ongoing subjects at the time of study termination will finish study treatment with radium-223 dichloride or placebo as part of the study.

All subjects will receive hormonal treatment with a single agent and supportive care as background treatment according to the local standard of practice. Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (either before or simultaneously to the first injection of radium-223 dichloride or placebo). For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride or placebo injection.

These treatments will also continue after completion of radium-223 dichloride or placebo.

Subjects who discontinue treatment with radium-223 dichloride/placebo prior to experiencing an SSE or radiological progression will enter the follow-up period and will be followed up for SSEs and radiological progression.

In case an SSE is not defined as progression, the subject will continue to be followed as per protocol until radiological progression.

All subjects will continue to receive standard of care hormonal treatment background therapy. Hormonal treatment may also be changed according to the local standard of practice, including exemestane in combination with everolimus. For the purpose of this study, only a new hormonal treatment initiated due to disease progression will be considered a new anti-cancer therapy.

Radium-223 dichloride/placebo administration should be discontinued as per the withdrawal criteria described in Section 6.3.1 (e.g., subject experiences unacceptable toxicities, delays in radium-223 dichloride/placebo >4 weeks, subject enters the active follow-up without clinic visits as she can no longer travel to the clinical site, and if in the Investigator's opinion, continuation of the study treatment would be harmful to the subject's well-being).

If radium-223 dichloride/placebo treatment is still ongoing but the hormonal treatment is no longer considered a treatment option and the subject must start cytotoxic treatment, the subject will terminate radium-223 dichloride/placebo treatment.

If radium-223 dichloride/placebo treatment is still ongoing but the background treatment is no longer considered a treatment option and the subject must start another protocol permitted concomitant systemic anticancer treatment, the subject can continue radium-223 dichloride/placebo until completion or until any withdrawal criteria are met.

If however, the background hormonal treatment or further standard of care protocol permitted concomitant systemic anticancer therapy are discontinued, radium-223 dichloride/placebo must also be discontinued.

Subjects will continue to be followed up for SSEs and radiological progression.

Subject management unless otherwise defined by this protocol will be in accordance to the local standard of practice.

Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).

Subjects who experience an SSE during radium-223 dichloride/placebo treatment may continue treatment until completion or until any withdrawal criteria are met, if in the opinion of the Investigator the subject continues to derive benefit. In case an SSE is not defined as progression, the subject will continue to be followed as per protocol until radiological progression.

Subjects who did not experience either an SSE or radiological progression during the treatment period will enter, at the end of the treatment period, the active follow-up with clinic visits where they will continue to be followed up for these events.

Subjects who experience an SSE **and** radiological progression during the protocol-defined treatment period will enter, at the end of the treatment period, the active follow-up without clinic visits.

Subjects who can no longer travel to the clinical site will be discontinued from radium-223 dichloride/placebo study treatment and will enter the active follow-up without clinic visits. During this time subjects will continue to receive hormonal background treatment as per local standard of practice.

Subjects who missed 2 consecutive treatment visits will be considered unable to travel to the site, will be discontinued from study treatment and will enter the active follow-up without clinic visits.

Subjects will be assessed for efficacy and safety endpoints at each treatment visit and will be evaluated every 12 weeks for radiological progression.

The total treatment period is defined from the day of randomization of the subject in the interactive voice/web response system (IXRS) until 4 weeks after the last administration of radium-223 dichloride or placebo.

A specific interval, depending on country specific drug order lead time between the date of randomization and the first radium-223 dichloride/placebo administration will be necessary for the study drug shipment/availability. Randomized subjects who never received treatment, will not be included in the safety analysis. An end of treatment (EOT) electronic case report form (eCRF) should be completed for these subjects to document the reason for discontinuation.

Follow-up period:

The active follow-up has 2 distinct periods based on whether the subject can travel to the clinic site: the active follow-up with clinic visits for subjects who can travel and the active follow-up without clinic visits for subjects who cannot travel. Once a subject switches from active follow-up with clinic visits to active follow-up without clinic visits, the subject will not be allowed to switch back.

All subjects, regardless of reaching a study endpoint (on-study SSE or radiological progression), will enter the follow-up period in order to collect the required long-term safety information.

Active follow-up period with clinic visits:

Subjects who discontinued or completed the radium-223 dichloride or placebo treatment, did not experience an SSE **and** radiological progression during the treatment period, had an EOT visit, and can travel to the clinic will enter an active follow-up period with clinic visits. During this period, clinic visits are to occur as follows:

- For subjects who have not experienced an SSE during the treatment period, visits will continue with the same frequency as during treatment (every 4 weeks ±7 days) until the subject has an SSE. After the occurrence of the SSE, the subjects will be switched to a frequency of visits every 12 weeks ±7 days at the next scheduled visit.

- For subjects who experienced an SSE during the treatment or this period, visits will occur every 12 weeks ±7 days. The subjects will continue to be followed for radiological progression and long-term safety.
- Subjects who miss 2 consecutive follow-up visits will be considered unable to travel to the site and will enter the active follow-up without clinic visits. Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether patient starts a new anticancer therapy (i.e. chemotherapy, other).

Radiological tumor assessment will be performed every 12 weeks, independently of the frequency of the visits, until radiological disease progression is documented.

The active follow-up period with clinic visits extends from the EOT visit until the subject can no longer travel to the clinic, experiences SSE **and** radiological progression, 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 until study termination.

These subjects will be evaluated for pain endpoints, radiological progression, SSEs, survival, treatment-related AEs and SAEs, and 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 any additional malignancies, including acute myelocytic leukemia (AML), and hematological conditions, such as myelodysplastic syndromes (MDS), aplastic anemia, or myelofibrosis, must be reported as SAEs, regardless of the Investigator's causality assessment. All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

Subject treatment management will be in accordance with routine clinical practice, at the discretion of the Investigator.

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 clinic site or those who experienced an SSE **and** radiological progression will be followed for survival, treatment-related AEs and SAEs, and the initiation of other anti-cancer therapies, and SSEs, with phone calls as follows:

- For subjects who did not experience an SSE during treatment or the previous follow-up period, the frequency of the phone calls will be every 4 weeks ±7 days until the subject has an SSE. After the occurrence of the SSE, the subjects will be switched to a frequency of phone calls every 12 weeks ±7 days at the next scheduled phone call.
- For subjects who experienced an SSE during treatment or the previous follow-up period, the frequency of the phone calls will be every 12 weeks ±7 days. Symptomatic skeletal events should be recorded until end of active follow-up,

independent of whether patient starts a new anticancer therapy (i.e. chemotherapy, other).

The active follow-up period **without** clinic visits extends from the EOT visit or the end of active follow-up with clinic visits until the subject 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 until study termination.

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 any additional malignancies, including AML, and hematological conditions, such as MDS, aplastic anemia, or myelofibrosis, must be reported as SAEs, regardless of the Investigator's causality assessment. All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

Subject treatment management will be in accordance with routine clinical practice, at the discretion of the Investigator. Survival will also be updated for all subjects in the active follow-up period at the time of final analysis of the primary endpoint.

Long-term follow-up – Extension study

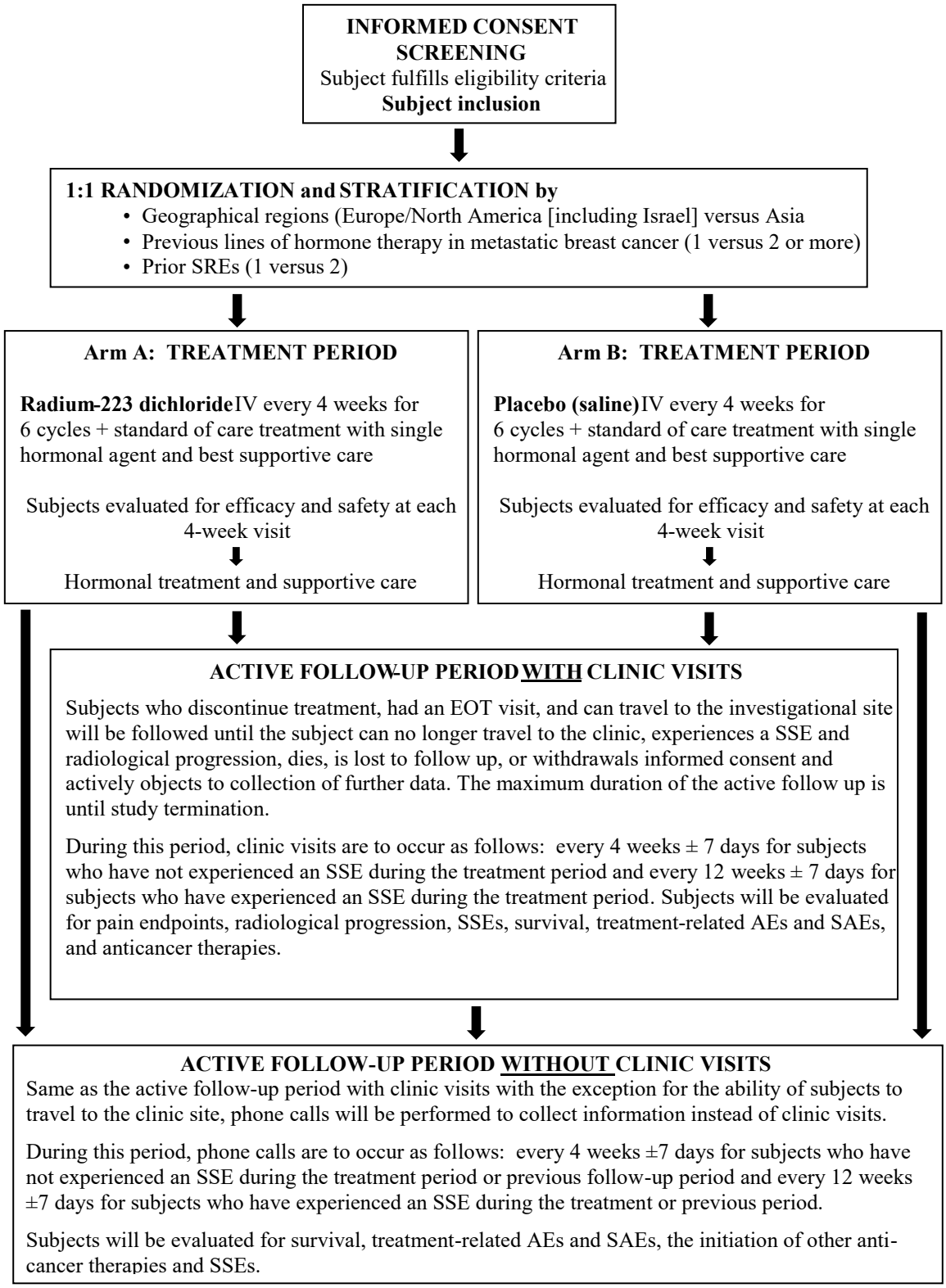
All ongoing study subjects who have completed at a minimum the EOT visit or 30 days from last study treatment dose, whichever is latest, may be transitioned into a separate long-term follow-up study (BAY 88-8223 study 16996 / NCT02312960). The separate long-term follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The primary objective of this study is to define the long-term safety profile of radium-223 dichloride.

All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

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., death, consent withdrawn and active objection for further data collection, lost to follow-up). Until the transition to the long-term follow up study, subjects will continue to follow all the protocols required procedures and visits in the current protocol.

A schematic of the study design is presented in Figure 5–1.

Figure 5–1: Study design schematic



5.1.2 Study endpoints

Section modified by Amendment 4 (Section 15.3).

Primary Endpoint: The primary endpoint is SSE-FS.

SSE-FS is defined as the time from randomization to the occurrence of one of the following:

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

a. the use of EBRT to relieve skeletal symptoms

b. the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)

c. the occurrence of spinal cord compression

d. a tumor related orthopedic surgical intervention.

(2) Death from any cause

Note: Any EBRT or orthopedic surgery related to a previous SSE but administered after signature of the ICF will not be counted as an on-study SSE.

Secondary Endpoints

- OS
- Time to opiate use for cancer pain
- Time to pain progression (only in subjects with baseline WPS ≤8)
- Time to cytotoxic chemotherapy
- rPFS
- Pain improvement rate
- Safety, acute and long term, including new primary malignancies and hematopoietic reserve for tolerability of subsequent chemotherapy

Exploratory Endpoints:

- Time to first on-study SSE
- Time to bone ALP progression
- Bone ALP response at Week 12 and EOT
- Bone-specific rPFS
- Resource utilization
- Biomarker assessments
- Time to visceral metastases onset

5.2 Primary variables

The primary variable is SSE-FS. The definition for this variable is provided in Section 5.1.2.

5.3 End of study

Section modified by Amendment 8 (Section 15.7.1.2).

All ongoing study subjects who have completed at a minimum the EOT visit or 30 days from last study treatment dose, whichever is latest, may be transitioned into a separate long-term follow-up study (BAY 88-8223 study 16996 / NCT02312960). 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 primary objective of this study is to define the long-term safety profile of radium-223 dichloride.

All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

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., death, consent withdrawn and active objection for further data collection, lost to follow-up). Until the transition to the long-term follow up study, subjects will continue to follow all the protocols required procedures and visits in the current protocol.

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 in any site has occurred.

6. Study population

Section modified by Amendment 1 (Section 15.1), Amendment 4 (Section 15.3) and Amendment 5 (Section 15.4).

Approximately 227 subjects with HER2 negative, hormone receptor positive breast cancer with bone metastases will be randomized.

Eligibility

Eligibility is confirmed at the end of the screening period. At that time, the subject is randomized and enters the treatment period. Laboratory values will be verified prior to first study drug administration as per protocol. Hematological support will be provided as needed according to the protocol guidance during the treatment period.

Rescreening

Rescreening of screen failed subjects may only be allowed after discussion with the medical monitor of the sponsor and after his/her approval. Sponsor approval of rescreening must be documented. Rescreening may be considered under the following circumstances:

- Subjects who underwent screening procedures (i.e., scans and laboratory work) that expired (are outside of the 21-day window) may need the screening procedures to be repeated in order to be within the window required prior to randomization. However,

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

- Rescreening is also permitted where the screening procedures for subject's eligibility expired due to completion of washout periods as per protocol (e.g., 4 weeks from treatment with an investigational drug), in case of expiry of investigational product that requires replacement, or for extraordinary logistical issues.

The subjects who need to repeat the screening procedures will be asked to repeat the consenting process for study participation.

6.1 Inclusion criteria

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), Amendment 5 (Section 15.4), and Amendment 6 (Section 15.5).

Subjects must meet the following criteria for inclusion in the study:

1. Have provided written informed consent. Subjects must be able to understand and be willing to sign the written informed consent. A signed ICF must be appropriately obtained prior to the conduct of any study-specific procedure.
2. Documentation of histological or cytological confirmation of ER+ and HER2 negative adenocarcinoma of the breast must be available. HER2 status should be determined by an accredited/Ministry of Health approved laboratory by immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH) or other validated in situ hybridization (ISH) assay for detection of HER2 gene expression.
3. Tumors (from either primary or metastatic sites) must be ER+ defined as ≥10% positive tumor nuclei in the analyzed sample. ER+/ progesterone receptor positive (PR+), ER+/ progesterone receptor negative (PR-) subjects are eligible whereas estrogen receptor negative (ER-)/PR+ and ER-/PR- disease will not be eligible.
4. Women (≥18 years of age) with metastatic breast cancer not amenable to curative treatment by surgery or radiotherapy. Women of reproductive potential and their male partners must agree to use adequate contraception during treatment and for 6 months following the completion of treatment with radium-223 dichloride/placebo.
5. Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible.

   Note: In premenopausal subjects, ovarian radiation or treatment with an LH-RH agonist/antagonist is permitted for induction of ovarian suppression if the plasma/serum estradiol assay is within local laboratory postmenopausal range at screening, performed within 7 days of randomization.

   - **Pre-menopausal subjects** with or without ovarian radiation or concomitant treatment with an LH-RH agonist/antagonist must have a negative pregnancy test at screening and agree to use an adequate method of

contraception as recommended by their treating physicians (please refer to Section 8.1.2)

- **Post-menopausal** status is defined either by:
  - age ≥55 years and one year or more of amenorrhea,
  - age <55 years and one year or more of amenorrhea with a plasma/serum estradiol assay within local laboratory postmenopausal range, performed within 7 days of randomization,
  - bilateral ovariectomy.

6. Subjects with bone dominant disease with at least 2 skeletal metastases identified at baseline by bone scintigraphy and confirmed by CT/magnetic resonance imaging (MRI). Presence of metastases in soft tissue (skin, subcutaneous, muscle, fat, lymph nodes) and/or visceral metastases is allowed.
7. Measurable or non-measurable disease (but radiologically evaluable) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. All disease burden must be assessed at baseline by CT or MRI of chest, pelvis, and abdomen and any additional fields as needed. A bone scan should also be done at baseline for all subjects.

   CT/MRI done as part of the standard of practice within 3 weeks prior to randomization and standard of care bone scans done within 3 weeks prior to randomization are acceptable.

   FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

   FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.
8. Subjects must have received at least one line of hormonal therapy in the metastatic setting.

   Note: A change of the hormone agent due to progression (as per the Investigator assessment) is counted as a new line of therapy. A switch of hormone therapy from one agent to another due to toxicity or other reasons (e.g., subject's preference), in absence of PD at the time of the switch, will be counted as one line although 2 different agents have been administered.

9. Subjects who are eligible for further standard of care endocrine treatment with any of the following administered as in second line or greater of hormone therapy in metastatic setting:
    - SERMs such as tamoxifen and toremifene
    - NSAIs such as anastrozole and letrozole
    - Steroidal AIs such as exemestane
    - ER down-regulators such as fulvestrant

    Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (before or simultaneously to the first injection of radium-223 dichloride/placebo).
10. Subjects must have experienced no more than 2 SREs prior to study entry defined as: Need for EBRT to bone, pathological bone fracture (excluding major trauma), spinal cord compression, and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.

    Note: All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization. Separate SRE events are the ones that occur at least 21 days apart from each other to ensure that linked events (e.g., surgery to repair a fracture or multiple doses of radiation during a course of treatment) are not counted as separate events. In case of bone pain that occurs in several anatomical locations and requires separate EBRT sessions, it should be counted as one event if the EBRT sessions are administered within a period of 21 days.
11. Subjects must be on therapy with bisphosphonate or denosumab and are required to have been on such therapy for at least 1 month before the start of study treatment.
12. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1
13. Life expectancy ≥6 months
14. Laboratory requirements:
    - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    - Platelet count ≥100 x 10^9/L without platelet transfusion within 4 weeks prior to randomization
    - Hemoglobin ≥9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin within 4 weeks prior to randomization
    - Total bilirubin level ≤1.5 x institutional upper limit of normal (ULN) (except for subjects with documented Gilbert's disease)
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x institutional ULN.
    - Creatinine ≤1.5 x ULN

- Estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula (Note: please refer to local labelling for administration of full dose of bisphosphonates)
- International normalized ratio of prothrombin time (INR) and partial thromboplastin time (PTT) or activated PTT ≤1.5 x ULN at study entry. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label.
- Serum albumin >30 g/L
- Pulse oximetry O2 saturation >92% if lung metastases are present

15. Able to swallow oral medication

6.2 Exclusion criteria

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 5 (Section 15.4), Amendment 6 (Section 15.5)

Eligible subjects must not meet any of the exclusion criteria listed below:

1. HER2-positive breast cancer (IHC=3+, positive FISH/CISH/other ISH validated assay); equivocal or unknown HER2 status
   Note: *Subjects with 3+ by IHC cannot be chosen regardless of their FISH/CISH/other ISH validated assay status and those with positive FISH/CISH/other ISH validated assay cannot be chosen either, regardless of the IHC findings. Subjects with 2+ by IHC will not be eligible if no negative FISH/CISH/other ISH validated assay for detection of HER2 gene expression is available.*
2. Subjects considered by the treating investigator to be appropriate candidates for treatment with everolimus as current treatment for their metastatic breast cancer
3. Subjects with inflammatory breast cancer
5. Subjects who have either received chemotherapy for metastatic disease or are considered by the treating Investigator to be appropriate candidates for chemotherapy as current treatment for metastatic breast cancer are excluded. Chemotherapy administered for adjuvant/neo-adjuvant disease is acceptable.
6. Subjects with any previous untreated or concurrent cancer that is distinct in primary site or histology from the cancer under study, except treated basal cell carcinoma or superficial bladder tumor (Ta and Tis, American Joint Committee on Cancer, 7th edition). Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before enrollment are allowed.

All cancer treatments must be completed at least 3 years prior to study entry (i.e., signature date of ICF).

7. Subjects with known or history of brain metastases or leptomeningeal disease: subjects with neurological symptoms must undergo a contrast CT scan or MRI of the brain within 28 days prior to randomization to exclude active brain metastasis. Imaging of the central nervous system is otherwise not required
8. 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.
9. Prior treatment with radium-223 dichloride
10. Prior hemibody external radiotherapy. Subjects who received other types of prior external radiotherapy are allowed provided that bone marrow function is assessed and meets the protocol requirements for hemoglobin, ANC, and platelets.
11. Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186, or rhenium-188
12. ECOG Performance Status ≥2
13. Blood transfusions, platelet transfusions or use of erythropoietin within 4 weeks prior to randomization.
14. 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 randomization
15. Treatment with an investigational drug or with any anti-cancer treatments not permitted by the protocol, within 4 weeks prior to randomization
16. Chronic conditions associated with non-malignant abnormal bone growth (e.g., confirmed Paget's disease of bone)
17. 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
18. Previous assignment to treatment in this study
19. Breastfeeding women
20. Known hypersensitivity to the active substance or to any of the excipients of radium-223 dichloride
21. Known presence of osteonecrosis of jaw

22. Patients with immediately life-threatening visceral disease, for whom chemotherapy is the preferred treatment option.
23. Lymphangitic carcinomatosis.
24. Patients with ascites requiring paracentesis within 2 weeks prior to study entry (signature of informed consent) and during the screening period.

All local label specific criteria for the standard of care hormonal treatment as well as denosumab and bisphosphonates apply. Subjects must be treated according to the local standard of care requirements.

6.3 Withdrawal of subjects from study

6.3.1 Withdrawal

The study will comprise the following 4 periods:

1. Screening
2. Randomization
3. Treatment period
4. Active follow-up period with or without clinic visits

Note: Study drug (radium-223 dichloride/placebo) discontinuation (i.e., discontinuation during the treatment period) does not constitute withdrawal from the study. Every effort should be made to retain subjects who discontinue the treatment period for any reason. These subjects are to be encouraged to remain on the study for follow-up of primary, secondary, and exploratory endpoints (i.e., continue in the active follow-up period with or without clinic visits).

Subjects are expected to participate in the follow-up unless they explicitly object. Withdrawal of consent should be documented in the subject's medical file. If the subject does not wish to be followed up further, she should sign the "*Declaration of Objection to the Collection of Study Data after Withdrawal of Consent" form.*

A "dropout" is defined as a subject who has been randomized and discontinues study participation prematurely for any reason.

A "screening failure" is defined as a subject who has signed informed consent and terminates the study for any reason (e.g., failure to satisfy the selection criteria) before randomization.

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

In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's medical records (consent withdrawal [due to AE or for other reason], lost to follow-up, or death).

When a subject is withdrawn from the study, i.e., is not attending follow-up visits, the EOS page in the eCRF is to be completed.

6.3.1.1 Withdrawal from treatment period (collection of follow-up data)

Section modified by Amendment 1 (Section 15.1) and Amendment 2 (Section 15.2).

The treatment period starts with the date of randomization and ends 4 weeks (±7 days) after the last administration of radium-223 dichloride/placebo.

Subjects *must* be withdrawn from the radium-223 dichloride/placebo treatment for the following reasons:

- If, in the Investigator's opinion, continuation of the radium-223 dichloride/placebo treatment would be harmful to the subject's well-being
- If the subject experiences unacceptable toxicities to radium-223 dichloride/placebo
- If a subject experiences National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 4 anemia, neutropenia, or thrombocytopenia lasting >2 weeks despite adequate supportive care treatment
- If a subject experiences any non-hematological CTCAE Grade 4 toxicity lasting >1 week despite adequate treatment
- Delay in radium-223 dichloride/placebo administration of >4 weeks (maximum of 8 weeks between 2 injections of radium-223 dichloride/placebo)
- If the subject starts treatment with a prohibited metastatic breast cancer therapy (Section 8.1)
- If background hormonal treatment or further standard of care protocol permitted concomitant systemic anti-cancer therapy are discontinued, radium-223 dichloride/placebo must also be discontinued.
- If the subject can no longer travel to the clinical site, she will be discontinued from radium-223 dichloride/placebo study treatment and will enter the active follow-up without clinic visits. Subjects who missed 2 consecutive treatment visits will be considered unable to travel to the site, will be discontinued from study treatment, and will enter the active follow-up without clinic visits. Subject treatment management will be in accordance with routine clinical practice, at the discretion of the Investigator.
- At her own request or at the request of her legally acceptable representative
- At the specific request of the sponsor and in liaison with the Investigator (e.g., obvious non-compliance, safety concerns)

Subjects who experience an SSE during study treatment may continue to receive radium-223 dichloride (or placebo) until completion or until any of the above withdrawal criteria are met, if the Investigator feels the subject will receive clinical benefit.

Subjects who experience disease progression (bone or non-bone) may continue to receive radium-223 dichloride (or placebo) until completion or until any of the above withdrawal criteria are met, if the Investigator feels the subject will receive clinical benefit. These subjects must continue to receive additional hormonal or other protocol permitted

concomitant systemic anticancer treatments according to the local standard of care. If, however, chemotherapy is required as the next line of treatment, study treatment will be permanently discontinued, as concurrent chemotherapy administration is an exclusion criterion.

Note: *Radium-223 dichloride/placebo treatment discontinuation (i.e., withdrawal from treatment period) does not constitute withdrawal from the study. Every effort should be made to retain subjects who discontinue the treatment period. These subjects are to be encouraged to remain on the study for follow-up of primary, secondary, and exploratory endpoints (i.e., continue in the active follow-up period with or without clinic visits).*

6.3.1.2 Withdrawal from treatment period and/or all follow-up (no further data collection)

Subjects *must* be withdrawn from the study treatment and/or procedures and no further data will be collected for the following reasons:

- Subject withdraws consent from study treatment and/or study procedures. A subject must be removed from the study at her own request or at the request of her legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject's rights will be protected.
- Subject is lost to follow-up
- Death

Note: *Withdrawal of consent should be documented in the subject's medical file. If the subject does not wish to be followed up further, she should sign the "Declaration of Objection to the Collection of Study Data after Withdrawal of Consent" form.*

6.3.2 Replacement

Withdrawn subjects will not be replaced.

6.4 Subject identification

A subject number (a unique identification number) will be assigned via an IXRS when a subject signs the ICF and is evaluated for inclusion into the study. When the subject is eligible for the study, the study site will send an order (using the IXRS) to the manufacturer for drug shipment based on the planned visit date of the subject. See Section 7.3.

7. Treatments

7.1 Treatments to be administered

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), and Amendment 4 (Section 15.3).

Investigational medicinal product (IMP): Radium-223 dichloride, 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update) will be administered IV as a slow bolus injection for a maximum of 6 cycles at intervals of 4 weeks.

Reference therapy: A solution of isotonic saline (0.9% sodium chloride solution for injection) will be administered IV as a slow bolus injection 6 times at intervals of 4 weeks.

Non-investigational medicinal products:

- ***Background treatment with standard of care hormonal treatment:*** Subjects will receive drugs from the following classes of agents administered as a single agent:
    - SERMs, such as tamoxifen and toremifene
    - NSAIs, such as anastrozole and letrozole
    - Steroidal AIs, such as exemestane
    - ER down-regulators such as fulvestrant

  Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (either before or simultaneously to the first injection of radium-223 dichloride or placebo). For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride/placebo injection.

  These treatments will be administered according to the local labels and in line with standard practice guidelines.

- ***Bone-targeted agents: bisphosphonates or denosumab:*** Eligible subjects are required to be on therapy with bisphosphonates or denosumab at time of study entry (for at least 1 month prior to the start of investigational study treatment, radium-223 dichloride/placebo). Subjects should be maintained on bisphosphonate or denosumab therapy throughout the study, unless, in the Investigator's opinion, these treatments need to be discontinued. Bisphosphonates or denosumab should be administered as per the local label instructions and according to local standard of care. Changes in therapy should be done as per the Investigator decision.

- ***Other therapies:*** Supportive care therapies should be administered in line with local standard of care.

Please refer to the section on prior and concomitant therapy concerning prohibited and allowed concomitant treatments during the radium-223 dichloride/placebo administration (see Section 8.1).

7.2 Identity of study treatment

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 provided by the sponsor, a system of numbering in accordance with all requirements of Good Manufacturing Practices (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance group. For all sponsor supplied study drugs, lists linking all numbering levels will be maintained by the sponsor.

7.2.1 Investigational medicinal product

7.2.1.1 Radium-223 dichloride

Section modified by Amendment 4 (Section 15.3) and Amendment 5 (Section 15.4).

The alpha particle-emitting radiopharmaceutical BAY 88-8223 is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of radium-223 dichloride for IV administration. Radium-223 dichloride 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 1000 kBq/mL (1100 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 supplied with each shipment.

The sponsor will provide radium-223 dichloride which is manufactured by Bayer HealthCare. Radium-223 dichloride is produced according to GMP and will be delivered in a glass vial, ready-to-use with a certified activity. This alpha particle-emitting radiopharmaceutical is shipped in a lead container and a 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 calibration 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 (2 to 8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing.

For study sites in the US, it is possible to have a patient ready dose (PRD) prepared by a radiopharmacy. Doses will be delivered to the sites in pre-filled syringes. Cardinal Health is the radiopharmacy that will dispense the PRD in the US.

It is important to note that, in general (unless otherwise agreed), in cases where study drug has been ordered, the time window for administration should be within 3 days of the planned treatment day. If administration must be postponed more than 3 days, replacement of the drug order is required.

7.2.1.2 Saline

Isotonic saline (0.9% sodium chloride solution for injection) will be provided by the study site. Traceability of the respective manufacturers and batches will be maintained in the respective preparation documentation and drug accountability logs.

For saline solution and background treatment which will be provided to the subjects from the study site's commercial supply it is required at minimum that the assignment, batch numbers, and expiry dates are recorded. The use of saline is to be recorded and documentation retained at the study site with a copy provided for the sponsor study file.

7.2.2 Non-investigational medicinal products

7.2.2.1 Background treatment with standard of care hormonal treatment

The background standard of care hormonal treatment will be administered according to the local labels in each of the participating countries. These treatments will be captured in the eCRFs.

Hormonal treatment as well as bisphosphonates or denosumab will be supplied by study site and administered as part of the standard of care for the subject according to the local label.

7.2.2.2 Bone-targeted agents, bisphosphonates and denosumab

Bisphosphonates (diphosphonates) are a class of drugs that prevent the loss of bone mass, used to treat osteoporosis and similar diseases including bone metastases. Whichever bisphosphonate is selected for use as background therapy should be stored and administered according to the local label.

Denosumab (Xgeva®), a RANKL inhibitor, is indicated for the prevention of SREs in subjects with bone metastases from solid tumors. It is supplied as a single-use vial at a suspension of 120 mg/1.7 mL and should be stored in a refrigerator at 2 to 8°C (36 to 46°F) in the original carton. Xgeva must not be exposed to temperatures above 25°C/77°F or direct light and must be used within 14 days, as directed in the label.

Bisphosphonates or denosumab will be supplied by the study site and administered as part of the standard of care for the subject according to the local label.

7.3 Treatment assignment

Section modified by Amendment 5 (Section 15.4).

To accomplish random assignment of radium-223 dichloride/placebo treatment, a computer-generated randomization list will be prepared by the sponsor and provided to the IXRS. The IXRS will assign each eligible subject a randomization number and the respective treatment in a ratio of 1:1 to radium-223 dichloride or placebo. In addition, randomization will be stratified by geographical regions (Europe/North America [including Israel] versus Asia), previous lines of hormone therapy in metastatic setting (1 versus 2 or more), and prior SREs (1 versus 2).

The IXRS will provide only the randomization number to the caller, i.e., blinded personnel, but not the assigned treatment. A confirmation e-mail containing randomization number will be sent to the unblinded personnel who will have to log into IXRS in order to know the treatment arm assigned to the patient. The unblinded personnel will be responsible for preparing the study drug for the subject for the first administration. For US only, if a subject is allocated to radium-223 dichloride, the unblinded personnel will fax shipment request to Cardinal Health for pre-filled syringe. The timing for the drug order should be based on the planned subject visit date. If the subject is allocated to placebo, the unblinded person at the study site will be responsible for providing saline corresponding to the IXRS treatment day. This should not be made available before to avoid unblinding the subject and blinded study personnel.

Subsequent orders for each study drug administration will be made by calling the IXRS from the study site on the date of the previous injection. If after ordering, the order needs to be cancelled or amended, the Investigator should contact their monitor immediately.

7.4 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 portion of beta and gamma radiation. For these reasons the product can be administered on an out-patient basis. To minimize the risk of contamination, the subject and her caregivers will receive oral and written instructions regarding hygiene precautions to abide by after receiving the radioactive drug according to the investigational study site radiation protection guidelines. These instructions will be given to all subjects, as neither the Principal Investigator nor subject will know the assignment to radium-223 dichloride or placebo injections.

7.4.1 Dose calibration

Section modified by Amendment 4 (Section 15.3).

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

Different clinical study sites possess dose calibrators from various suppliers; thus, the isotope calibration factor may differ from site to site. Consequently, each site must perform the radium-223 dial setting on their relevant dose calibrator(s), if no isotope calibration factor for radium-223 is being provided by the vendor of the dose calibrator. For dial setting, the clinical study site will receive a sealed vial or a prefilled syringe containing a radium-223 solution for calibration only. The vial or syringe is identical to the vials/syringes used for

study treatment. The amount of radium-223 in the vial/syringe 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.

As of Amendment 4, 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 [52]) 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 [53]), 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 [53]) in place at the time of implementation. The current dial setting (NIST 2010 [52]) 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 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.

7.4.2 Radium-223 dichloride dose handling

At least 2 unblinded personnel should be nominated at each study site (Section 7.5). The primary dedicated unblinded person (“the unblinded person”), who has the responsibility delegated from the Principal Investigator, will be responsible for the safe handling and storage of radium-223 dichloride and placebo control. The unblinded person also has the responsibility of correctly receiving and recording the delivery of radium-223 dichloride in accordance with this protocol. At least one deputy unblinded person should also be nominated. Radium-223 dichloride should be handled by individuals who are qualified by training and experience in the safe handling of radionuclides.

The radium-223 dichloride vials or PRDs must be stored inside their lead container in a secure facility. The study drug should be used within 28 days of production or prior to the expiry date specified for PRDs.

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. Since PRDs will be prepared at the country depot, relevant procedures are recorded by the country depot staff. All administrations of radium-223 dichloride will be based on the certified activity of radium-223 at the reference date. Please note that all documentation that contains unblinded information should be kept by the unblinded person(s) and not shared with the other study site personnel during the conduct of the study.

7.4.3 Radium-223 dose calculation

Section modified by Amendment 4 (Section 15.3).

The dosage of radium-223 dichloride is 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update). The total activity to be injected will be calculated volumetrically using the subject's body weight within 5 days of injection (kg), the 50 kBq/kg (55 kBq/kg after implementation of NIST update) 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 according to the recommended formula below:

$$\frac{\text{Body weight (kg)} \times 50\ \text{kBq/kg}^{a}}{\text{DK} \times 1000\ \text{kBq/mL}^{b}} = \text{volume to be injected (mL)}$$

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

[b] 1100 kBq/mL after implementation of NIST update

Site specific volume calculation methods are acceptable as well provided that the patient dose is 50 kBq/kg (55 kBq/kg after implementation of NIST update).

Data regarding activity, calculations, and volume to be injected must be recorded in the IMP preparation log and in the study electronic data capture tool (Medidata Rave; RAVE) by the unblinded person. This applies to both doses that are prepared at the study site and doses that are prepared by an off-site vendor.

For subjects in Arm B (placebo injection), the volume of saline to be injected will be provided by the IXRS based on the subject's weight. Data regarding the saline batch number and the volume to be injected should be recorded in RAVE.

7.4.4 Study drug dose preparation

Section modified by Amendment 7 (Section 15.6).

In order to keep the treating physician blinded to the assignment of study medication, the unblinded person (e.g., from the hospital pharmacy or Nuclear Medicine department) will be responsible for blinding the syringe, and responsible for calculating the required dosage. Data regarding activity and volume to be injected should be recorded in the IMP preparation log and in the appropriate eCRF, both of which will not be available to the treating physician.

Copies of the vial label and the syringe serial number are to be attached with each entry in the IMP preparation log. Additional written instructions for study drug administration, for blinded and unblinded personnel, will be provided.

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) and to reduce radiation exposure. Sites 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.

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. In some countries/study sites a third party vendor will be used to prepare the injections to be used by the study site.

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.

To maintain traceability, each subject will be assigned 1 syringe label set, with a unique serial number. The serial number will link the vial/batch received with the preparation and blinded administration of the syringe.

For subjects in the placebo arm, a syringe with isotonic saline will be prepared in the same way as for the active treatment, including the use of unique serial numbers on the syringe.

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, are to be treated as radioactive waste and should be disposed in accordance with hospital procedure for the handling of radioactive material and according to local laws. Written information about radium-223 dichloride and instructions for the handling and injection of radioactive material will be provided to study personnel.

7.4.5 Dose administration

Section modified by Amendment 1 (Section 15.1).

In this subject population, disease progression is expected. Expected symptoms in this population are: bone pain, fatigue, nausea, anorexia, depression, constipation (also secondary to opioids), hematological complication as well as additional visceral metastases.

Chemotherapy is not permitted during treatment with radium-223 dichloride/placebo. If such treatment is necessary then radium-223 dichloride/placebo treatment must be stopped. Chemotherapy treatment administered in the follow-up period should not be given before a 4-week washout period after the last administration of study drug.

Every effort will be made to administer the full dosing regimen. Single dose level adjustment of radium-223 dichloride/placebo is not permitted. Treatment delays or discontinuations of

radium-223 dichloride/placebo may be instituted for the AEs described in Section 7.4.6 and dose adjustments, treatment delays, or discontinuations of hormonal treatment may be instituted according to the local label and standard of practice.

7.4.6 Dose adjustments, delays, and treatment discontinuations

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), and Amendment 4 (Section 15.3).

Radium-223 dichloride/placebo administration may be delayed by no more than 4 weeks (maximum 8 weeks between 2 injections) for recovery of AEs. If administration is delayed for >4 weeks (maximum 8 weeks between 2 injections), radium-223 dichloride/placebo administration should be discontinued.

AEs will be reported and graded according to NCI-CTCAE version 4.03.

Myelosuppression

Changes in hematology parameters may occur after injection of study drug.

Neutropenia: In case of NCI-CTCAE Grade 3 to 4 neutropenia, study drug administration should be delayed until recovery to Grade 2 (minimum ANC 1.0 x 10^9/L) or better before the next study drug administration.

Thrombocytopenia: In case of thrombocytopenia NCI-CTCAE Grade 2 to 4, study drug administration should be delayed until recovery to CTCAE Grade 1 (minimum subjects with a platelet count 75 x 10^9/L) or better before the next study drug administration.

Anemia: In case of anemia NCI-CTCAE Grade 3 to 4, study drug administration should be delayed until recovery to CTCAE Grade 2 (minimum hemoglobin [Hb] 8.0 g/dL) or better before the next study drug administration.

If a subject experiences CTCAE Grade 3 to 4 anemia, neutropenia, or thrombocytopenia lasting >2 weeks in spite of adequate treatment, the subject must be discontinued from treatment with radium-223 dichloride/placebo.

Blood transfusion is acceptable between study drug administrations. Use of biologic response modifiers, such as G-CSF or GM-CSF and erythropoietin, is allowed in the management of acute toxicity.

Gastrointestinal events

Diarrhea: No prophylactic treatment for diarrhea is recommended. Anti-diarrheals can be used when needed. A further dose of study medication should not be given before diarrhea has recovered to CTCAE Grade ≤1.

Nausea/Vomiting: No prophylactic treatments for nausea or vomiting are recommended, but anti-emetic drugs can be used when needed. A further dose of study medication should not be given before nausea/vomiting has recovered to CTCAE Grade ≤1.

Constipation: Subjects can continue laxative as concomitant medication, but start of prophylactic treatments before study drug injection is not recommended. Laxative can be

used when needed. A further dose of study medication should not be given before constipation has recovered to CTCAE Grade ≤1.

Fatigue

In cases of NCI-CTCAE Grade 3 to 4 fatigue, study drug administration should be delayed until recovery to Grade ≤1 before the next study drug administration.

Osteonecrosis of jaw

There is no specific radium-223 dose modification guidance for patients who develop osteonecrosis of jaw during radium-223 treatment. The management plan of individual patients who develop osteonecrosis of jaw in the course of the study should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in osteonecrosis of jaw, and in accordance with the local labeling of denosumab and bisphosphonates.

Non-pathological fractures

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

If a subject experiences any non-hematological NCI-CTCAE Grade 4 toxicity lasting >1 week despite adequate treatment, the subject will have to discontinue radium-223 dichloride/placebo treatment.

If radium-223 dichloride or placebo is discontinued prior to an on-study SSE, subjects will enter the follow-up period and will be followed up for these events. During this time, the standard of care hormonal treatment background therapy will continue according to the local standard of practice. Hormonal treatment may be changed according to the local standard of practice; however, for the purpose of this study, a new hormonal treatment initiated due to disease progression will be considered a new anti-cancer therapy.

If radium-223 dichloride/placebo treatment is still ongoing but standard of care hormonal treatment is no longer considered an option, and the subject must start cytotoxic therapy, the subject will terminate radium-223 dichloride or placebo treatment. Subjects will then enter the follow-up period and will continue to be followed for SSEs and radiological progression.

Background standard of care hormonal treatment

The standard of care treatment with a single hormonal agent will be administered by each participating site according to the local label and standard of practice. Local label directions for dose modifications must be applied.

7.4.7 Supportive care guidelines

Section modified by Amendment 2 (Section 15.2).

Ancillary treatment (guidelines)

- Persistent neutropenia (neutrophils/granulocytes CTCAE Grade 4 [<0.5 x 10^9/L]) without fever: These subjects may be started on G-CSF 5 µg/kg/d subcutaneously (SC) until the neutrophil count has reached the local hospital's reference range.

- Neutropenia with fever (neutrophils/granulocytes CTCAE Grade 3 to 4 [<1 x 10^9/L]; fever >38.5°C): Blood cultures will be obtained and the subject started on empiric antibiotics for as long as clinically indicated. It is highly recommended that the subject receive G-CSF 5 µg/kg/d SC until the neutrophil count has reached the local hospital's reference range with 2 separate measurements, at least 12 hours apart.
- Severe thrombocytopenia (CTCAE Grade 4 [<25.0 x 10^9/L]) or bleeding with CTCAE Grade 3 to 4 thrombocytopenia (<50.0 x 10^9/L): multiple platelet transfusions may be required to maintain platelet count ≥75 x 10^9/L if clinically indicated to control bleeding. Epsilon aminocaproic acid may be given to subjects with mucosal bleeding and platelet count CTCAE Grade 3 to 4.
- Severe anemia (Hb CTCAE Grade 3 [<80 x10^9g/L; 8.0 g/dL; 4.9 mmol/L]): Subjects will be transfused with packed red cells to maintain an Hb value >80 g/L; 8.0 g/dL; 4.9 mmol/L if clinically indicated. Treatment with erythropoietin is allowed between study drug administrations for treatment of anemia.
- During treatment with denosumab or bisphosphonates, subjects should be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.
- All label specific instructions for the standard of care hormonal treatment will apply. Subjects must be treated according to the local standard of care requirements.

7.5 Blinding

Every effort will be made to keep the study blinded. Subjects will be randomized to receive radium-223 dichloride or placebo in a double-blind fashion. All subjects will also receive the background standard of care hormonal treatment suitable for each subject. This treatment will be locally sourced by the site and will be provided in an open-label format.

Due to the nature of radium-223 dichloride, there must be at least 2 persons in the study site's Nuclear Medicine department who are unblinded to the treatment arms assigned to subjects. One of these unblinded individuals will serve as back-up for the other. In order to maintain the study blind for the hospital personnel who provide treatment to the subject, the unblinded person at the study site will be responsible for filling the syringe with the correct amount of radium-223 dichloride or placebo (saline) and labeling it. Both radium-223 dichloride and placebo are clear solutions; thus, syringes with radium-223 dichloride and placebo cannot be distinguished from each other visually. The person performing the administration of study drug must be blinded to the treatment arm. The subject will not be told whether they have received radium-223 dichloride or placebo. All treating physicians, clinical staff, subjects, and sponsor personnel will be blinded as to the treatment to which a subject is randomized, except for named representatives who will perform the verification of the drug accountability at the study sites and drug ordering.

The background standard of practice treatment with a single hormonal agent is not blinded.

Unblinding:

In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reaction (SUSAR) (see Section 9.6.1.4), the subject's treatment code will usually be

unblinded before reporting to the health authorities and ethic committees if the SUSAR was related to the blinded treatment. Investigators may only unblind subjects under emergency unblinding rules. If a subject is unblinded by the Investigator, she must discontinue study drug(s).

Investigators should note that the occurrence of an SAE or PD should not routinely precipitate the immediate unblinding of the label.

If emergency unblinding is necessary for the treatment of a subject for an SAE, the study treatment can be unblinded via the IXRS (refer to the IXRS manual for instructions). The participating site has unrestricted and immediate access to break the treatment code in IXRS. Should the blind code be broken for a subject, the medical monitor or designee should be contacted by the Principal Investigator within one working day of unblinding to discuss the rationale for the premature unblinding.

7.6 Drug logistics and accountability

All study drugs will be stored at the investigational study site, in accordance with Good Clinical Practice (GCP) and GMP requirements, and the instructions given by the clinical supplies department of the sponsor will be inaccessible to unauthorized personnel.

In some countries/study sites, it will be required to use a third party vendor to prepare the injections to be used by the study site. 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 site. 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.

The responsible study site personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Instructions for drug handling, logistics, and accountability will be reviewed with study staff prior to the initiation of the study. Summaries of these instructions are provided below.

For radium-223 dichloride:

Radium-223 dichloride will be shipped to study site upon IXRS shipment request. Lead times differ per country but the shipment will arrive at the study site one day before the planned treatment at the latest. The responsible unblinded study site personnel will confirm receipt of sponsor-supplied study drug via IXRS.

The unblinded person at the study site is responsible for drug accountability. A dedicated unblinded person representing the sponsor will monitor the drug accountability logs. Receipt, distribution, and destruction of the study drug must be properly documented according to the sponsor's agreed and specified procedures. An unblinded monitor will review overall drug accountability and destruction per the study 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 radium-223 dichloride (received, administered to subjects, and destroyed) must be maintained

and signed and the appropriate eCRF pages completed by the unblinded person responsible for drug handling at each site.

For locally provided isotonic saline (placebo):

Isotonic saline (placebo) will be provided by the study site pharmacy. Drug accountability for saline will also be performed. At a minimum, storage conditions, dispensing, batch numbers, and expiry dates will be retained in the study site files. A log of isotonic saline (administered to subjects and destroyed) must be maintained and signed and the appropriate eCRF pages completed by the unblinded person responsible for drug handling at each site. The used vials must be stored until the drug accountability has been completed by the unblinded monitor.

For locally provided background hormone treatment:

For background treatment which will be provided to the subjects from the study site's commercial supply, it is required at minimum that the assignment, batch numbers, and expiry dates are recorded.

7.7 Treatment compliance

Subjects will receive treatment with radium-223 dichloride under supervision of a physician licensed in the administration of radioisotopes. Unblinded study personnel will check the administration volume and total radioactivity injected. The dose activity and the volume injected will be recorded in a study drug log and the eCRF pages, neither of which will be available to the treating physician or site personnel. Only the unblinded monitor will review overall drug accountability and destruction per the site documentation.

8. Non-study therapy

8.1 Prior and concomitant therapy

At baseline screening, all prior cancer-related treatments are to be recorded.

All concomitant medications taken by the subject from signing of the ICF to 4 weeks after last study drug administration must be recorded in the eCRF. Thereafter, until the end of the active follow-up period, **only** medications given to treat **any grade AEs related to the study drug,** analgesic medication, and any subsequent anti-cancer treatment medication need to be recorded in the eCRF.

The generic name and trade name of each prior or concomitant medication, its indication, dosage, and, when applicable, the start and stop dates will be recorded.

The sponsor’s representative will encode all therapy and medication according to well-recognized dictionaries of medical codes.

It is not required to report the administration of contrast media or radioactive tracer in conjunction with the protocol-specified radiological procedure (CT or bone scan) on the concomitant medications eCRF page unless there is an AE related to the administration of the contrast agent (e.g., an allergic reaction related to the administration of a contrast agent) or the tracer.

8.1.1 Prohibited concomitant therapy

Section modified by Amendment 1 (Section 15.1) and Amendment 4 (Section 15.3).

Other cancer treatment with established efficacy in breast cancer except hormonal treatments or the permissible therapies mentioned in Section 8.1.2 should not be used during the treatment period. If such treatments are considered to be the best standard of care during the treatment period, further radium-223 dichloride/placebo administrations must be discontinued and the subject should enter the active follow-up period.

All supportive care for the subject may be provided at the discretion of the Investigator.

Note that all treatments for breast cancer, including other investigational drugs taken after withdrawal from treatment with radium-223 dichloride or placebo, will be recorded in the eCRFs until the end of the active follow-up period.

Concomitant therapy during the treatment phase of the study with any of the following listed is **prohibited**:

- Chemotherapy
- Radiopharmaceuticals, such as strontium-89, samarium-153, rhenium-186, or rhenium-188
- Hemibody external radiotherapy
- Other investigational drugs
- All medications that are prohibited as per the local label instructions for the background hormonal treatment. It is the site's responsibility to ensure that hormonal background treatment is administered in line with standard practice and local label instructions. The same applies for bisphosphonates and denosumab.

8.1.2 Permitted concomitant therapy

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), and Amendment 5 (Section 15.4.1).

The following supportive care medications are considered **permissible** during the study:

- Conventional multivitamins, selenium, and soy supplements
- All subjects are expected to have been on therapy with either denosumab or bisphosphonates for at least 1 month before the start of study treatment and to continue on this therapy during the course of the study, with no change to therapy expected during the treatment phase of the study, except for toxicity reasons.
- During treatment with denosumab or bisphosphonates, the subjects should be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.
- In pre-menopausal women with ovarian suppression, treatment with LH-RH agonists or antagonists must start at least 4 weeks prior to enrollment (signature of informed

consent) and continue during the treatment period. Non-hormonal methods of contraception should be employed during therapy until menses resume.

- Subjects of child-bearing potential who are sexually active must agree to utilize, during the treatment period and for 6 months after last dose of radium-223 dichloride or placebo, 2 reliable and acceptable methods of contraception used simultaneously: a barrier method such as a) condoms (male or female) with spermicidal agent or b) diaphragm or cervical cap with spermicide, combined with a highly effective non-hormonal birth control method such as an intra-uterine device.
- Standard of care background hormone treatment with any of the following as a single agent:
    - SERMs, such as tamoxifen and toremifene
    - NSAIs, such as anastrozole and letrozole
    - Steroidal AIs, such as exemestane
    - ER down-regulators such as fulvestrant
- Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (either before or simultaneously to the first injection of radium-223 dichloride/placebo). For subject's convenience injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride or placebo injection.
- Hormonal background treatment is to be administered in line with standard practice and local label instructions.
- Following discontinuation of the single agent background hormone treatment, further lines of hormone treatment as well as exemestane in combination with everolimus, may be administered concomitantly with radium-223 dichloride/placebo, in line with the local standard of practice.
- Blood transfusions and treatment with erythropoietin stimulating agents are allowed after randomization (if required to ensure that the treatment range for Hb is met at Day 1 of each cycle) but not within 4 weeks prior to randomization. Platelet transfusions are allowed after randomization but not within 4 weeks prior to randomization.
- 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. These drugs are not allowed within 4 weeks prior to randomization.
- Analgesic use will be captured via a subject diary (analgesic consumption diary) and the eCRF (24-hour analgesics use page and regular analgesics concomitant medication page, see schedule of assessments, Table 9–1). Subjects will be asked to track their analgesic use on an analgesic consumption diary for 24 hours prior to their clinic visit. Any medication taken for pain, whether for palliation of bone pain or

relief of other type of pain, and any changes should be recorded in the eCRF at each visit. Note that EBRT treatment should be recorded in the eCRFs until end of the active follow-up period without clinic visits.

8.2 Post-study treatment therapy

Treatment with radium-223 dichloride or placebo will be halted following completion of the full assigned treatment or at early termination. The background standard of care hormonal treatment will be continued according to the local standard of practice (i.e., until the time of disease progression).

Following radium-223 dichloride/placebo treatment discontinuation, subjects will be treated and followed as per the institutional standard of care and/or according to the physician's clinical judgment.

If possible, cytotoxic chemotherapy, other systemic radioisotope, hemibody external radiotherapy, or other investigational drug should not be given before a 4-week washout period after last administration of radium-223 dichloride/placebo, provided the subject's bone marrow is not compromised.

Details of post-study anti-cancer treatment will be recorded on the appropriate eCRF page.

9. Procedures and variables

9.1 Tabular schedule of evaluations

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), Amendment 5 (Section 15.4), Amendment 6 (Section 15.5), Amendment 7 (Section 15.6), and Amendment 8 (Sections 15.7.1.1 and 15.7.1.4).

All laboratory analyses will be conducted by local laboratories.

Efficacy and safety measurements obtained during the course of the study are summarized in the schedule of assessments (Table 9–1).

Table 9–1: Schedule of assessments

Study Period	Screening[a]	Randomization	Treatment[b,c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	**0-1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		**-**	**-**	**-**	**-**
Cycle:	**-**	**-**	**1**		**2**		**3**		**4**	**5**	**6**	**-**	**-**	**-**	**-**	**-**
Timing:	**3 wk pre-random.**		**C1, Day 1**	**C1, Day 15[d]**	**C2, Day 1**	**C2, Day 15**	**C3, Day 1**	**C3, Day 15**	**C4, Day 1**	**C5, Day 1**	**C6, Day 1**	**4 wk post-last dose[e]**	**q4 wk until SSE; q12 wk after SSE[f]**	**q4 wk until SSE; q12 wk after SSE[g]**		
Window (days):				**±3**	**± 7**	**±3**	**± 7**	**±3**	**± 7**	**± 7**	**± 7**	**± 7**	**±7**	**±7**	**±7**	**±7**
Informed consent[h]	X															
Subject ID assignment	X															
Review of eligibility	X															
Demographic data	X															
Medical history	X															
Disease history	X															
Prior SRE	X															
Randomization[a]		X														
BPI-SF[i]			X		X		X		X	X	X	X	X		X	
Resource utilization questionnaire			X		X		X		X	X	X	X	X	X[j]	X	X[j]
AEs, SAEs, new 1° malignancies[k]	X		X	X	X	X	X	X	X	X	X	X	X[l]	X[j,l]	X[l]	X[j,l]
Prior and con meds[m]	X		X	X	X	X	X	X	X	X	X	X	X	X[j]	X	X[j]
Cancer-related tx[n]	X		X	X	X	X	X	X	X	X	X	X	X	X[j]	X	X[j]
Analgesic consumption diary[o]			X		X		X		X	X	X	X	X		X	
Record 24 h analgesic use[o]			X		X		X		X	X	X	X	X		X	

Table 9–1: Schedule of assessments

Study Period	Screening[a]	Randomization	Treatment[b,c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	**0-1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		**-**	**-**	**-**	**-**
Cycle:	**-**	**-**	**1**		**2**		**3**		**4**	**5**	**6**	**-**	**-**	**-**	**-**	**-**
Timing:	**3 wk pre-random.**		**C1, Day 1**	**C1, Day 15[d]**	**C2, Day 1**	**C2, Day 15**	**C3, Day 1**	**C3, Day 15**	**C4, Day 1**	**C5, Day 1**	**C6, Day 1**	**4 wk post-last dose[e]**	**q4 wk until SSE; q12 wk after SSE[f]**	**q4 wk until SSE; q12 wk after SSE[g]**		
Window (days):				**±3**	**± 7**	**±3**	**± 7**	**±3**	**± 7**	**± 7**	**± 7**	**± 7**	**±7**	**±7**	**±7**	**±7**
Record opiate use			X		X		X		X	X	X	X	X		X	
Vital signs[p]	X		X	X	X	X	X	X	X	X	X	X	X[hh]		X	
12-lead ECG	X						X			X		X				
Weight (kg)	X		X[q]	X	X[q]	X	X[q]	X	X[q]	X[q]	X[q]	X				
Height (cm)	X															
Physical examination[r]	X		X		X		X		X	X	X	X	X[hh]		X	
ECOG-PS	X		X		X		X		X	X	X	X	X		X	
Hematology[s]	X[t]		X[u]	X	X[u]	X	X[u]		X[u]	X[u]	X[u]	X	X[hh]		X	
Clinical chemistry[v]	X[t]		X[w]	X	X[w]	X	X[w]		X[w]	X[w]	X[w]	X	X[hh]		X	
Coagulation panel[x]	X[t]		X		X		X		X	X	X	X				
Pregnancy test and estradiol assay[y]	X[t]		X		X		X		X	X	X	X				
Serum, plasma, and urine biomarkers[z]			X						X			X				
Whole Blood for CTCs[ii]			X		X		X		X	X	X	X				
Technetium-99m bone scan or FDG PET/CT or NaF PET/CT, same technique for all	X	X														

Table 9–1: Schedule of assessments

Study Period	Screening[a]	Randomization	Treatment[b,c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	**0-1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		**-**	**-**	**-**	**-**
Cycle:	**-**	**-**	**1**		**2**		**3**		**4**	**5**	**6**	**-**	**-**	**-**	**-**	**-**
Timing:	**3 wk pre-random.**		**C1, Day 1**	**C1, Day 15[d]**	**C2, Day 1**	**C2, Day 15**	**C3, Day 1**	**C3, Day 15**	**C4, Day 1**	**C5, Day 1**	**C6, Day 1**	**4 wk post-last dose[e]**	**q4 wk until SSE; q12 wk after SSE[f]**	**q4 wk until SSE; q12 wk after SSE[g]**		
Window (days):				**±3**	**± 7**	**±3**	**± 7**	**±3**	**± 7**	**± 7**	**± 7**	**± 7**	**±7**	**±7**	**±7**	**±7**
assessments[aa,bb]																
Chest, abdominal and pelvic CT scan[aa,cc,dd,ee]	X						X									
SSEs			X		X		X		X	X	X	X	X	X	X	X
Drug order[ff]		X	X		X		X		X	X						
Radium-223 Cl_2 or placebo injection[gg]			X		X		X		X	X	X					
Survival status													X	X[j]	X	X[j]
Drug accountability			X		X		X		X	X	X					

Abbreviations: AE = adverse event; BPI-SF = Brief Pain Inventory-Short Form; Cl_2 = dichloride; con med = concomitant medication; CT = computed tomography; Cx = Cycle x; ECG = electrocardiogram; ECOG PS = Eastern Co-operative Oncology Group performance status; eCRF = electronic case report form; EOT = end of treatment; ID = identification number; INR = international normalized ratio of prothrombin time; IXRS = interactive voice/web response system, PRD = patient ready dose; PT = prothrombin time; PTT = partial thromboplastin time; q = every; SAE = serious adverse event; SRE = skeletal related event; SSE = symptomatic skeletal event; tx = treatment; wk = week; W/O = without.

a. All screening evaluations must be complete and reviewed prior to randomization. Screening evaluations must be complete within 3 weeks prior to randomization. If all screening data are available and the subject is eligible for the study, randomization may occur at the end of the screening visit.
b. All assessments at treatment visits should be performed before study drug administration.
c. Subjects will continue in the treatment period until the occurrence of an SSE (Section 9.4.2.1). If based on the Investigator assessment the subject continues to receive clinical benefit, administration of study drug can be continued. In case an SSE is not defined as progression, the subject will continue to be followed as per protocol until radiological progression. All subjects will continue to receive background treatment.
d. Any unscheduled visits are to be conducted in the same manner as visits described for Cycle 1, Day 15.
e. EOT follow-up visit will be conducted 4 weeks after last dose of study treatment (radium-223 dichloride or placebo) or after discontinuation from study treatment.

f. For subjects who can travel to the clinic site: every 4 weeks (±7 days) for subjects who have not experienced an SSE during the treatment period until they experience an SSE or every 12 weeks (±7 days) for subjects who have experienced an SSE during the treatment or this period. All subjects will be followed in the active follow-up with clinic visits until the subject dies, experiences an SSE **and** radiological progression, can no longer travel to the clinical site, or the study is terminated. Subjects who receive subsequent 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.
g. For subjects who cannot travel to the clinic site: Telephone follow-up every 4 weeks (±7 days) for subjects who have not experienced an SSE during the treatment or the previous period until they experience an SSE or every 12 weeks (±7 days) for subjects who have experienced an SSE during the treatment, previous period, or this period until the subject dies or the study is terminated. Subjects who receive subsequent 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.
h. Informed consent is to be collected before the initiation of any study-related procedures.
i. BPI-SF will be dispensed to the subject at the visit just before Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1; Cycle 5, Day 1; Cycle 6, Day 1; EOT; and follow-up clinic visits. Additionally, PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire.
j. It is the clinical site's responsibility to obtain and make available the source documentation for the information collected from the telephone call and to document it in the eCRF.
k. Adverse events will be collected through 30 days post the last administration of study medications. Investigator should check for occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and any new malignancy.
l. All treatment-related AEs and SAEs occurring during the active follow-up period are to be documented. Investigator should check for occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, any new malignancy. 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.
m. At baseline screening, all prior concomitant medications, including analgesics, are to be recorded. Thereafter, all concomitant medications should be collected, including analgesics, up to 4 weeks post last study drug administration. Thereafter, until the end of the active follow-up period, only collect concomitant medications used to treat any grade adverse drug reaction and analgesics should be collected only up to the end of the active follow-up visits. Analgesic use has to be recorded via the analgesic concomitant medication eCRFs.
n. Record any cancer-related treatments.
o. An individual analgesic consumption diary will be dispensed to the subject just the visit before Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1; Cycle 5, Day 1; Cycle 6, Day 1; EOT; and follow-up clinic visits. Subjects will be asked to record analgesic use in 24 hours prior to their clinic visit.
p. The measurement of vital signs will include: blood pressure, heart rate, respiratory rate, and temperature.
q. Subject's weight should be re-checked prior to each injection to calculate appropriate drug dosing. At all sites, weight is to be taken only once for each dose and it should be measured within 5 days prior to dosing. For US sites using the central PRD depot only, the subject weight for the dose day must be reported in a timely manner to the country PRD depot to allow adequate time for the 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.
r. A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems.
s. Hematocrit, hemoglobin, platelet counts, red blood cell counts, white blood cell counts, and white blood cell differential. Subjects with abnormal platelet count or white blood cell count at EOT should be followed until resolution.
t. The screening clinical chemistry and hematology values are recommended to be measured within 1 week prior to randomization and the first injection should be done as soon as possible after randomization.
u. Blood sample for hematology must be taken, analyzed, and evaluated within the 5 days prior to each study drug administration.
v. Sodium, potassium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, bone alkaline phosphatase (if testing is available and can be performed locally), serum creatinine, phosphate, blood urea nitrogen, bilirubin (total), total cholesterol, and albumin.
w. Blood sample for clinical chemistry must be taken within 5 days prior to each study drug administration, and must be evaluated prior to the administration.
x. PT, INR, and PTT: Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label. Blood sample for coagulation tests must be taken and evaluated within 5 days prior to each study drug

administration.

y. Pre-menopausal women must have a negative serum pregnancy test performed within 7 days prior to randomization, prior to each study drug administration (taken and evaluated within 5 days prior to administration), and EOT. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. A plasma/serum estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea.

z. Blood and/or urine sample for exploratory evaluation of biomarkers, prior to radium-223 dichloride or placebo administration. Serum and plasma samples will be collected within 5 days of dosing at Cycle 1, Day 1; Cycle 4, Day 1; and EOT or disease progression, whichever occurs first. Urine samples will be collected at Cycle 1, Day 1; Cycle 4, Day 1; and EOT visits (or at the time of disease progression, whichever occurs earlier).

aa. Radiological tumor evaluation must be performed 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration and every 12 weeks thereafter until PD (radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS until bone progression occurs or start of a new anticancer treatment. This schedule is to be maintained and will not be shifted because of treatment interruptions/delays. Scans will be read locally. The time window for the scans is ±7 days.

bb. A historic bone scan is acceptable if taken within 3 weeks of randomization. If one is not available, it will be required as part of the protocol procedures within the screening period. FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

cc. Chest/abdominal/pelvic magnetic resonance imaging will be accepted instead of chest/abdominal/pelvic CT. FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

dd. To maintain a consistent evaluation of each subject, the same imaging technique and procedure must be used through the assessment periods. Any unexpected abnormality must be reported by the site personnel to the treating physician or the subject's general practitioner.

ee. A historic chest/abdominal/pelvic CT is acceptable if taken within 3 weeks of randomization. If not available, a scan is required as part of the protocol within the screening period.

ff. IXRS drug (re-)supply order should be coordinated at each study visit to coincide with delivery prior to the subject's next scheduled study visit.

gg. The minimum time window between 2 injections of radium-223 dichloride or placebo must be 4 weeks.

hh. Performed every 12 weeks

ii. Details of sampling are described in the Laboratory Manual. Blood samples for analysis of circulating tumor cells will be collected within 5 days of Day 1 of Cycles 1 through 6 prior to study drug dosing, and within 5 days of the EOT visit or disease progression, whichever occurs first.

9.2 Visit description

9.2.1 Screening period (Visits 0 to 1)

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), and Amendment 5 (Section 15.4).

The screening period lasts from date of signature of informed consent until the date of subject randomization in IXRS. The screening period duration is 3 weeks.

Pre-treatment evaluations will only be performed after the subject has agreed to participate and has signed and dated the ICF. No treatment or study-related procedures will be initiated before the signed consent has been obtained.

Standard of care imaging, such as CT/MRI, as well as routine bone scans performed within 3 weeks prior to randomization will be accepted as baseline imaging if they meet protocol requirements (anatomic coverage, image acquisition as per RECIST 1.1 guidelines for CT/MRI scans). Pre-treatment evaluations will be performed according to the eligibility criteria. If the subject is eligible for the study, the parameters at the screening visit showing subject health status including blood values will be recorded in the eCRF.

The following procedures and evaluations will be performed within **3 weeks** prior to planned randomization unless otherwise specified:

- Sign informed consent
- Subject registration and subject number assignment via IXRS
- Review of inclusion and exclusion criteria and confirm eligibility
- Demographics
- Record medical history
- Record disease history: HER2 status can be determined by evaluating for HER2 over-expression using IHC and/or HER2 gene amplification using in situ hybridization, e.g., FISH or CISH. For subjects with equivocal HER2 IHC (IHC 2+), it is recommended that HER2 status be confirmed using a validated assay for HER2 gene amplification.
- Record prior SRE
- Record AEs
- Record concomitant medications/therapy, including analgesics
- Record breast cancer-related treatment (prior and current)
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- 12-lead electrocardiograms (ECG). Electrocardiograms should not be obtained when serum potassium is <3.5 mmol/L. Hypokalemia should be corrected prior to ECG collection.

- Record height (cm) and weight (kg).
- Perform full physical examination: A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems.
- ECOG performance status
- Radiological tumor assessment
    - A chest/abdominal/pelvic CT or MRI. This is not needed if standard of care chest/abdominal/pelvic CT or MRI images taken within 3 weeks prior to randomization are available.

      A bone technetium-99m scan with careful identification of all disease-related hotspots. This is not needed if standard of care bone scan performed within 3 weeks prior to planned randomization date is available and in line with protocol requirements. Confirmatory scan using single photon emission tomography (SPECT)-CT/MRI or CT/MRI (with and without contrast media) should be obtained if not performed within 3 weeks prior to randomization. The field of acquisition should include all areas where bone lesions are present.
      CT/MRI done as part of the standard of practice and standard of care bone scans done within 3 weeks prior to randomization are acceptable.
    - FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).
    - FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

The following procedures and evaluations should be performed within 1 week prior to randomization. Results must be available, reviewed, and signed and dated by the Investigator prior to randomization.

- Blood draw for clinical chemistry: sodium (Na), potassium (K), chloride (Cl), calcium (Ca), ALT, AST, lactate dehydrogenase (LDH), bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, blood urea nitrogen (BUN), total bilirubin, total cholesterol, and albumin.
- Blood draw for hematology: hematocrit, Hb, platelet counts, red blood cell (RBC) counts, white blood cell (WBC) counts, and WBC differential.
- A coagulation panel: prothrombin time (PT), PTT, and INR. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban or aspirin (e.g.

≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label.

- Pregnancy test: pre-menopausal women must have a negative serum pregnancy test performed within 7 days prior to randomization. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Estradiol assay: a plasma/serum estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea.

One week prior to randomization, the subject should be given a subject diary to be used for subject questionnaires and the analgesic consumption and should receive training in its use.

Important Note: If re-screening is indicated, it must be completed with approval from the medical monitor of the sponsor. No more than one re-screening attempt will be allowed for each subject. Please refer to Section 6 for further guidance on cases in which rescreening is allowed and the time window for rescreening.

9.2.2 Randomization

Randomization in the IXRS may occur only after the completion of the screening evaluations and confirmation of subject eligibility. Randomization may coincide with the end of a screening visit if all evaluations are complete; otherwise, randomization may be performed in a separate clinic visit.

- IXRS must be called for drug supply in preparation for the next study visit. This should be done on the day of randomization (where possible) to provide the maximum time in advance of the next scheduled subject visit date and in accordance with country-specific order lead times.

9.2.3 Treatment period

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), and Amendment 4 (Section 15.3).

The treatment period extends from the day of randomization to 4 weeks post the final injection of radium-223 dichloride/placebo.

The time between randomization and first injection should be as brief as possible in accordance with the country-specific drug order lead time.

- During the treatment period, the subject will visit the study site at regular intervals. Radium-223 dichloride or placebo will be injected at 4-week intervals for 6 cycles on an outpatient basis (Section 9.1). The minimum time window between 2 injections of radium-223 dichloride/placebo must be 4 weeks. All ongoing subjects at the time of

study termination will finish study treatment with radium-223 dichloride or placebo as part of the study.

- All subjects will receive background standard of care hormonal treatment for breast cancer. Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (either before or simultaneously to the first injection of radium-223 dichloride/placebo). For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride/placebo injection.
- It is the responsibility of the unblinded person to calculate the required volume of study drug (i.e., dose of radium-223 dichloride or saline placebo) for the subject based on the subject's body weight within 5 days of administration and the reference date of the received study medication (Section 7.4.3).

For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported to the country PRD depot in a timely manner to allow adequate time for the PRD preparation and delivery. The subject's weight measurement, order confirmation call to the IXRS, and prescription for the central PRD depot are to be performed 5 days prior to injection. 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.

Before administration of radium-223 dichloride/placebo, the subject must be well hydrated; thus, the subject should be instructed to drink *ad libitum*.

Hematology parameters requirements prior to study drug administration

The blood samples for clinical chemistry and hematology should be taken within 5 days before each study drug administration, and the hematology parameters must be evaluated before each study drug administration (within 5 days).

First radium-223 dichloride/placebo administration

Before the first administration of radium-223 dichloride/placebo (within 5 days), the ANC should be $\geq 1.5 \times 10^9$/L, the platelet count $\geq 100 \times 10^9$/L, and Hb ≥8.0 g/dL.

Blood transfusions and treatment with erythropoietin stimulating agents are allowed after randomization but not within 4 weeks prior to randomization. Platelet transfusions are allowed after randomization but not within 4 weeks prior to randomization.

Subsequent radium-223 dichloride/placebo between study drug administrations

The following hematological parameters value should be met prior to each subsequent radium-223 dichloride/placebo administration: Hb level ≥8.0 g/dL, ANC $\geq 1.0 \times 10^9$/L, and the platelet count $\geq 75 \times 10^9$/L.

If Hb levels are below 8.0 g/dL, the Hb needs to recover to 8.0 g/dL or higher before next study drug administration.

If ANC is lower than 1.0×10^9/L or platelet count is lower than 75×10^9/L, radium-223 dichloride/placebo injection should be delayed until recovery to ANC $\geq 1.0 \times 10^9$/L and platelet count $\geq 75 \times 10^9$/L.

If there is more than a 4-week delay in the next injection (i.e., more than 8 weeks between injections), the study drug should be permanently discontinued and the subject should enter the active follow-up period with clinic visits. Treatment of low Hb is acceptable between study drug administrations.

9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), and Amendment 5 (Section 15.4).

Assessments to be performed PRIOR to radium-223 dichloride or placebo ("study drug") administration:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit. Additionally PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire.
- Resource utilization questionnaire to be completed by site
- Record AEs, SAEs, and all occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy.

  Note: Specifically, for this study, relevant symptoms related to SSEs should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.
- Recording of analgesic use will be performed by:
  - Analgesic use recorded via the analgesic concomitant medication eCRF
  - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for 24 hours prior to the visit. The analgesic use for 24 hours prior to the visit will be recorded by the investigator on the eCRF.
- Record opiate use
- Record concomitant medications/therapy
- Record breast cancer-related treatment
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- 12-lead ECG (Visit 6 [Cycle 3, Day 1] and Visit 9 [Cycle 5, Day 1]). Electrocardiograms should not be obtained when serum potassium is <3.5 mmol/L. Hypokalemia should be corrected prior to ECG collection.
- Record weight (kg), within 5 days prior to dosing
- Perform full physical examination: A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory,

gastrointestinal, dermatological, musculoskeletal, and neurological systems (all abnormal findings must be reported in the AE eCRF pages).

- ECOG performance status
- Blood draw for hematology evaluation (must be taken and evaluated within 5 days before radium-223 dichloride or placebo administration): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential. Results to be assessed and documented prior to study drug treatment. The Hb values need to be confirmed to be at least 8 g/dL prior to each dose. If blood is drawn the day of the administration of radium-223 dichloride/placebo, results must be available prior to study drug administration.
- Blood draw for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin (blood sample for clinical chemistry must be taken and evaluated within 5 days prior to each study drug administration).
- A coagulation panel (blood sample to be taken and evaluated within 5 days prior to each study drug administration): PT, PTT, and INR.
- Pregnancy test: pre-menopausal women must have a negative serum pregnancy test performed and evaluated within 5 days before radium-223 dichloride or placebo administration. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Blood draw and urine sample for exploratory biomarker analysis: serum, plasma, and urine samples will be collected within 5 days of Visit 2 (Cycle 1, Day 1) and within 5 days of Visit 8 (Cycle 4, Day 1) prior to study drug dosing.
- Blood draw for analysis of circulating tumor cells (CTCs) collected within 5 days of Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6), prior to study drug dosing.
- Radiological tumor assessments: please refer to Section 9.2.6 and Appendix 16.2.
- Record 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
      Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).
- Administer radium-223 dichloride or placebo. All subjects will receive the background standard of care treatment with a single hormonal agent according to the local label and standard of care.

Assessments to be performed AFTER each injection of radium-223 dichloride or placebo:

- Perform drug accountability
- IXRS must be called for drug re-supply in preparation for the next study visit (Cycles 1 through 5 only). This should be done on the day of the current treatment visit (where possible) to provide the maximum time in advance of the next scheduled subject visit date and in accordance with country-specific order lead times.
- For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported to the country PRD depot in a timely manner to allow adequate time for the PRD preparation and delivery. The subject's weight measurement, order confirmation call to the IXRS, and prescription for the central PRD depot are to be performed 5 days prior to injection. 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.

9.2.3.2 Visits 3, 5, and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), and Amendment 5 (Section 15.4).

Radium-223 dichloride or placebo will not be administered at these visits.

- Record AEs, SAEs, and all occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy.

  Note: Specifically for this study, relevant symptoms related to SSEs should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.
- Record concomitant medications/therapy, including analgesics
- Record breast cancer-related treatment
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Record weight
- Blood draw for hematology evaluation: hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential. (Performed only at Visit 3 [Cycle 1, Day 15] and Visit 5 [Cycle 2, Day 15])
- Blood draw for clinical chemistry is only required at Visit 3 (Cycle 1, Day 15) and Visit 5 (Cycle 2, Day 15): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin.

9.2.3.3 End of treatment visit

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), and Amendment 5 (Section 15.4).

An EOT visit will be performed within 4 weeks ±7 days post discontinuation or completion of radium-223 dichloride or placebo treatment. The following procedures/evaluations should be performed at this visit:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit. Additionally PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire.
- Resource utilization questionnaire to be completed by site
- Recording of analgesic use will be performed by:
    - Analgesic use recorded via the analgesic concomitant medication eCRF
    - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for 24 hours prior to the visit. The analgesic use for 24 hours prior to the visit will be recorded by the investigator on the eCRF.
- Record opiate use
- Record AEs and SAEs for 30 days after the last treatment

  Note: Specifically for this study, relevant symptoms related to SSEs should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.
- Record all occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy
- Record concomitant medications/therapy
- Record breast cancer-related treatment
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- 12-lead ECG. Electrocardiograms should not be obtained when serum potassium is <3.5 mmol/L. Hypokalemia should be corrected prior to ECG collection.
- Record weight
- Perform full physical examination: A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems.
- ECOG performance status
- Blood draws for hematology (within 5 days of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential

- Blood draws for clinical chemistry (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin
- A coagulation panel (within 5 days of the visit): PT, PTT, and INR.
- Pregnancy test (within 5 days of the visit): pre-menopausal women must have a negative serum pregnancy test. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Blood draw and urine sample for exploratory biomarker analysis (serum, plasma, and urine samples will be collected within 5 days or at the time of disease progression, whichever occurs earlier)
- Record SSEs
  Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).
- Blood draw for analysis of CTCs (within 5 days of the visit).
- Radiological tumor assessments: please refer to Section 9.2.6 and Appendix 16.2.

If 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 all occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy, as well as any anti-cancer 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.

9.2.4 Active follow-up

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 clinic visits to active follow-up without clinic visits, the subject will not be allowed to switch back.

If a subject can no longer travel, all scans and clinic visits have to be discontinued. The subject will begin active follow-up without scheduled clinic visits (telephone follow-up).

All subjects, regardless of reaching a study endpoint (on-study SSE) will enter the follow-up period in order to collect the required long-term safety information.

9.2.4.1 Active follow-up with clinic visits

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), Amendment 5 (Section 15.4), and Amendment 8 (Section 15.7.1.1).

Subjects who discontinued or completed radium-223 dichloride/placebo, did not experience an SSE **and** radiological progression during the treatment period, had an EOT visit, and can travel to the clinic will enter an active follow-up period with clinic visits. During this period, clinic visits are to occur as follows:

- For subjects who have not experienced an SSE during the treatment period, visits will continue with the same frequency as during treatment (every 4 weeks ±7 days) until the subject has an SSE. After the occurrence of the SSE, the subjects will be switched to a frequency of visits every 12 weeks ±7 days at the next scheduled visit.
- For subjects that experienced an SSE during the treatment period, visits will occur every 12 weeks ±7 days. The subjects will continue to be followed for radiological progression and long-term safety.
- Subjects who miss 2 consecutive follow-up visits will be considered unable to travel to the site and will enter the active follow-up without clinic visits.

The active follow-up period with clinic visits extends from the EOT visit until the subject can no longer travel to the clinic, experiences SSE **and** radiological progression, 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 until study termination.

The following procedures/evaluations should be performed at these visits. (Note that vital signs measurement, full physical examination, blood draws, and radiological tumor assessment are only to be performed every 12 weeks ±7 days):

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit. Additionally PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire
- Resource utilization questionnaire to be completed by site
- Recording of analgesic use will be performed by:
    - Analgesic use recorded via the analgesic concomitant medication eCRF
    - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for 24 hours prior to visit. The analgesic use for 24 hours prior to the visit will be recorded by the investigator on the eCRF.
- Record opiate use
- All AEs and SAEs occurring during this period must be documented and reported if considered to be related to study medication or study-related procedures. Note: Specifically for this study, relevant symptoms related to an SSE should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.

- All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- All occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy must be reported as SAEs regardless of the Investigator's causality assessment. Concomitant medications 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.
- Record concomitant medications/therapy
- Record breast cancer-related treatment
- Record vital signs (every 12 weeks): blood pressure, heart rate, respiratory rate, and temperature
- Perform full physical examination (every 12 weeks): A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal and neurological systems.
- ECOG performance status
- Blood draws for hematology every 12 weeks (within 5 days of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential
- Blood draws for clinical chemistry every 12 weeks (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin
- Radiological tumor assessments: please refer to Section 9.2.6 and Appendix 16.2.
- Record SSEs
  Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).
- Record survival status

Subjects who receive subsequent cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage due to thrombocytopenia during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice.

9.2.4.2 Active follow-up without clinic visits

Section modified by Amendment 1 (Section 15.1), Amendment 7 (Section 15.6), and Amendment 8 (Section 15.7.1.1).

Subjects from the treatment period or the active follow-up period with clinic visits who can no longer travel to the clinic site or those who experienced an SSE **and** radiological progression will be followed for survival, treatment-related AEs and SAEs, the initiation of other anti-cancer therapies, and SSEs with phone calls as follows:

The active follow-up period without clinic visits extends from the EOT visit or last visit of the active follow-up with clinic visits until the subject 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 until study termination.

During this follow-up, contact with the subject will take place by telephone call as follows:

- For subjects that did not experience an SSE during treatment or the previous follow-up period, the frequency of the phone calls will be every 4 weeks ±7 days until the subject has an SSE. After the occurrence of the SSE, the subjects will be switched to a frequency of phone calls every 12 weeks ±7 days at the next scheduled phone call.
- For subjects who did experience an SSE during treatment or the previous follow-up period, the frequency of the phone calls will be every 12 weeks ±7 days.

The following data should be collected during these calls:

- All AEs and SAEs occurring during this period must be documented and reported if considered to be related to study medication or study-related procedures. Note: Specifically for this study, relevant symptoms related to an SSE should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.
- All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- All occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy must be reported as SAEs at any time regardless of the Investigator's causality assessment. 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.
- Resource utilization questionnaire to be completed by site
- Record SSEs
  Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).

- Record concomitant medications/therapy (concomitant medications used to treat any grade adverse drug reaction only)
- Record breast cancer-related treatment
- Record survival status

If possible, radiological tumor assessments, as per timepoints and guidelines specified in Section 9.2.6 and Appendix 16.2, were to be performed, as applicable.

Subjects who receive subsequent cytotoxic chemotherapy will be followed 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.

Note: As 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 documented in the eCRF.

Only subjects who withdraw consent from the study will be required to follow the procedures outlined in Section 6.3.1.2 (i.e., sign the Declaration of Objection to the Collection of Study Data after Withdrawal of Consent for the active assessment follow-up period).

9.2.4.3 End of active follow-up

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), Amendment 5 (Section 15.4), and Amendment 8 (Section 15.7.1.1).

This visit will be performed only once, either at the end of the active follow-up with clinic visits or at the end of the active follow-up without clinic visits.

The procedures for subjects who complete the **active follow-up with clinic visits** period will include:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit. Additionally PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire
- Resource utilization questionnaire to be completed by site
- Recording of analgesic use will be performed by:
    - Analgesic use recorded via the analgesic concomitant medication eCRF
    - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for 24 hours prior to the visit. The analgesic use for 24 hours prior to the visit will be recorded by the investigator on the eCRF.
- Record opiate use
- All AEs and SAEs must be documented and reported if considered to be related to study medication or study-related procedures. Note: Specifically for this study,

relevant symptoms related to an SSE should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.

- All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- All occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy must be reported as SAEs regardless of the Investigator's causality assessment. 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.
- Record concomitant medications/therapy (concomitant medications used to treat any grade adverse drug reaction only)
- Record breast cancer-related treatment
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Perform full physical examination: A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems.
- ECOG performance status
- Blood draws for hematology (within 5 days of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential
- Blood draws for clinical chemistry (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin
- Radiological tumor assessments: please refer to Section 9.2.6 and Appendix 16.2)
- Record SSEs
  Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).
- Record survival status

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

The end of active follow-up procedures for subjects who are in the **active follow-up without clinic visits** period will include:

- Resource utilization questionnaire to be completed by site

- All AEs and SAEs must be documented and reported if considered to be related to study medication or study-related procedures.
- All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- All occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy must be reported as SAEs regardless of the Investigator's causality assessment. 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.
- Record concomitant medications/therapy (concomitant medications used to treat any grade adverse drug reaction only)
- Record breast cancer-related treatment (prior and current)
- Record SSEs
  Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).
- Record survival status

Note: 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 documented in the eCRF.

9.2.5 End of Study

Section modified by Amendment 8 (Section 15.7.1.2).

All ongoing study subjects who have completed at a minimum the EOT visit or 30 days from last study treatment dose, whichever is latest, may be transitioned into a separate long-term follow-up study (BAY 88-8223 study 16996 / NCT02312960). 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 primary objective of this study is to define the long-term safety profile of radium-223 dichloride.

All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent.

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., death, consent withdrawn and active objection for further data collection, lost to follow-up). Until the transition to the long-term follow up study, subjects will continue to follow all the protocols required procedures and visits in the current protocol.

9.2.6 Radiological assessment: tumor and response evaluation

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), Amendment 5 (Section 15.4), and Amendment 7 (Section 15.6).

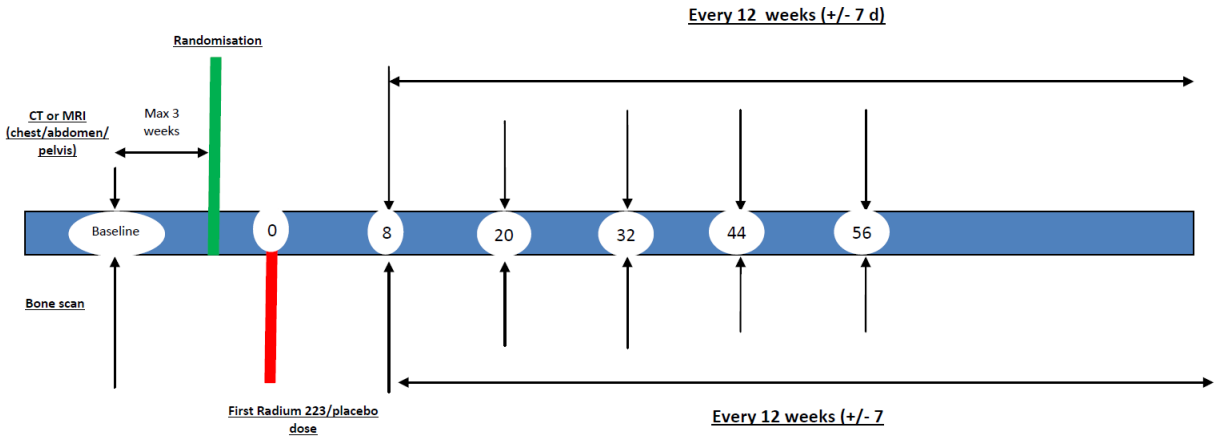
Radiological tumor evaluation, using the mRECIST 1.1 guidelines (See Section 16.2), must be performed as follows (see also Figure 9–1):

- Within 3 weeks prior to randomization,
- 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration
- Every 12 weeks (± 7 days) thereafter until PD (radiological progression) is documented.

A technetium-99m bone scan and CT or MRI (chest/abdomen/pelvis and any additional sites of disease, as applicable) should be performed at all the above mentioned timepoints.

This schedule is to be maintained and will not be shifted because of treatment interruptions/delays.

Figure 9–1: Radiological tumor evaluation schedule



If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS until bone progression occurs or start of a new anticancer treatment.

If radiologic bone progression occurs prior to occurrence of visceral metastases, MRI/CT scan of the chest, abdomen, and pelvis should continue until occurrence of visceral metastasis or start of a new anticancer treatment after the end of the current study treatment. This will allow assessment of time to visceral metastases onset.

Subjects who discontinue study treatment for reasons other than disease progression will continue to undergo tumor response evaluations until PD is documented (radiological progression).

Standard of care CT/MRI done within 3 weeks of randomization and standard of care bone scans done within 3 weeks of randomization are acceptable provided they are in line with

protocol requirements criteria (anatomic coverage chest/abdomen/pelvis and in line with RECIST 1.1/mRECIST 1.1 guidelines for image acquisition). All suspected sites of disease should be imaged.

Note: FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

A technetium-99m bone scan with careful identification of all disease-related hotspots should be performed for all patients at the above mentioned timepoints. All visible bone lesions must also be imaged with conventional anatomical imaging procedures such as CT or MRI scan. During the study a new bone lesion or progression of existing bone lesion/s initially identified on a technetium-99m bone scan must be confirmed by CT or MRI. If confirmed by CT/MRI, the date of occurrence of the new lesion or of progression of existing bone lesion/s will be the date it was initially detected (by technetium-99m bone scan) even if the confirmation by CT/MRI was done at a subsequent scan. (See also Section 16.2).

Note: FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study. The same lesions identified at baseline must be evaluated at follow-up assessments using the same technique and preferably by the same Investigator/radiologist.

For details on radiological tumor assessment please also refer to Section 16.2.

9.3 Population characteristics

9.3.1 Demographic

The following demographic characteristics will be collected:

- Date of birth
- Age at randomization
- Race and ethnicity (where it is allowed by local regulation)

9.3.2 Medical history

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 informed consent
- Considered relevant to the study

Detailed instructions on the differentiation between (i) medical history and (ii) AEs can be found in Section 9.6.1.1.

9.3.3 Other baseline characteristics

Section modified by Amendment 1 (Section 15.1) and Amendment 5 (Section 15.4).

The following other baseline characteristics will be collected:

- Date of breast cancer diagnosis
- Date of diagnosis of metastatic breast cancer
- Stage of breast cancer at diagnosis
- Treatment of breast cancer before enrollment (e.g., surgery, radiation)
- Weight (kg)
- Vital signs: blood pressure (mmHg), heart rate (bpm), respiratory rate (rpm), and temperature (°C)
- ECOG performance status
- Cancer pain assessment
- Laboratory assessments
    - Hematology: hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential
    - Clinical chemistry: Na, K, Cl, Ca, total cholesterol, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, total bilirubin, and albumin

9.4 Efficacy

9.4.1 Efficacy variables

Section modified by Amendment 4 (Section 15.3).

The primary efficacy variable is:

- SSE-FS

The secondary efficacy variables are:

- Overall survival (OS)
- Time to opiate use for cancer pain
- Time to pain progression (only in subjects with baseline WPS ≤8)
- Time to cytotoxic chemotherapy
- Radiological progression free survival (rPFS)
- Pain improvement rate

The study will also include the following **exploratory efficacy endpoints**:

- Time to first on-study SSE
- Time to bone ALP progression
- Bone ALP response at Week 12 and EOT
- Bone specific rPFS
- Time to visceral metastases onset

9.4.2 Definition of efficacy variables

9.4.2.1 Primary endpoint

Symptomatic skeletal event-free survival is defined as the time from randomization to the occurrence of one of the following:

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

a. the use of EBRT to relieve skeletal symptoms

b. the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)

c. the occurrence of spinal cord compression

d. a tumor related orthopedic surgical intervention.

(2) Death from any cause

Note: All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization.

9.4.2.2 Secondary efficacy endpoints

Section modified by Amendment 1 (Section 15.1), Amendment 2 (Section 15.2), Amendment 4 (Section 15.3), Amendment 5 (Section 15.4), and Amendment 6 (Section 15.5).

Overall survival is defined as the time (days) from the date of randomization to the date of death due to any cause. For subjects who are still alive, their OS will be censored at the last known alive date or the database cutoff date, whichever occurs first.

Time to opiate use for cancer pain is defined as the interval from the date of randomization to the date of opiate use. Subjects who have no opiate use at the time of analysis will be censored at the last assessment date of no opiate use. Subjects with no on-study assessment or no baseline assessment will be censored at the date of randomization.

Time to opiate use will be determined by analgesic use captured via different eCRF pages (24 hour analgesic use page, analgesic concomitant medication page and opiate use page, respectively, see Table 9–1 Schedule of assessments).

Time to pain progression is defined as the interval from randomization to the first date a subject experiences pain progression based on WPS and analgesics use. Time to pain

progression will be evaluated in subjects with baseline WPS ≤ 8. Pain progression is defined as an increase of 2 or more points in the "Worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥4 weeks apart

OR

an increase in pain management (IPM) with respect to baseline, whichever occurs first.

Assessments will occur on the day of the visit. An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 questions. Subjects who have not experienced pain progression at the time of analysis will be censored on the last post-baseline pain assessment date the subject was known to have not progressed. Subjects with no on-study assessment or no baseline assessment will be censored at the date of randomization.

Pain improvement is defined for subjects evaluable for pain improvement, i.e. subjects with baseline WPS ≥ 2, as a 2-point decrease or more in WPS from baseline over 2 consecutive measurements conducted at least 4 weeks apart, without an IPM.

Pain improvement rate is defined as the number of subjects with pain improvement as defined above, divided by the total number of subjects evaluable for pain improvement (i.e., subjects with baseline WPS ≥2). Pain improvement rate at week 12, EOT and any visit will be considered.

Time to cytotoxic chemotherapy is defined as the time (days) from the date of randomization to the date of the first cytotoxic chemotherapy.

Radiological progression-free survival is defined as the time (days) from the date of randomization to the date of confirmed radiological progression in either soft tissue, viscera or bone, or death (if death occurs before progression). Subjects without confirmed radiological progression or death at the time of analysis will be censored at their last date of radiological tumor assessment (See the statistical analysis plan [SAP] for detailed censoring rules). Bone scans and CT/MRIs will be read locally. All bone lesions visible on a technetium-99m bone scan will need to also be imaged using conventional anatomical imaging techniques such as SPECT-CT/MRI or CT/MRI (with or without contrast). Bone progression will be declared according to the mRECIST 1.1 criteria (see Section 16.2). If a new bone lesion or unequivocal increase in size of bone lesions is identified on bone scan, the lesion must also be confirmed by CT/MRI. If a new bone lesion or unequivocal increase in size of bone lesions is only visible on a CT/MRI and not visible on a technetium-99m bone scan, progression will be declared without further confirmation.

9.4.2.3 Exploratory efficacy endpoints

Section modified by Amendment 5 (Section 15.4) and Amendment 6 (Section 15.5).

Time to first on-study SSE is defined as the time (days) from the date of randomization to the date of the first on-study SSE.

Time to bone ALP progression is defined as the time (days) from the date of randomization to the date of first bone ALP progression. Bone ALP progression is defined as a ≥25% increase from the baseline value, at least 12 weeks from baseline in subjects with no bone

ALP decline from baseline; or a ≥25% increase above the nadir value, which is confirmed by a second value obtained 4 or more weeks later in subjects with an initial bone ALP decline from baseline.

Bone ALP response is defined as a ≥30% reduction of the blood level at Week 12 or EOT, compared to the baseline value. Confirmed bone ALP response is defined as a ≥30% reduction of the blood level, compared to the baseline value, confirmed by a second bone ALP value 4 or more weeks later.

Radiological progression free survival based on bone imaging (bone-specific rPFS) is defined as the time (days) from the date of randomization to the date of confirmed radiological progression detected by bone imaging or death (if death occurs before progression). Subjects without confirmed radiological progression or death at the time of analysis will be censored at their last date of radiological tumor assessment. (See the SAP for detailed censoring rules). Bone scans will be read locally. All bone lesions visible on a technitium-99m bone scan will need to also be imaged using conventional anatomical imaging techniques such as CT/MRI (with or without contrast). Bone progression will be declared according to the mRECIST 1.1 criteria (see Section 16.2). If a new bone lesion or unequivocal increase in size of bone lesions is identified on bone scan, the lesion must also be confirmed by CT/MRI. If a new bone lesion or unequivocal increase in size of bone lesions is only visible on a CT/MRI and not visible on a technetium-99m bone scan, progression will be declared without further confirmation.

Time to visceral metastases onset is defined as the time (days) from the date of randomization to the date of the first scan showing visceral metastatic disease. Subjects with visceral metastases at baseline will be censored at the randomization date.

9.5 Pharmacokinetics

No pharmacokinetic (PK) measurements will be performed in this study. No PK interaction is expected between radium-223 dichloride and the co-administered hormone therapy. Radium-223 is an isotope and is therefore not metabolized. There are no hints that radium is involved in any transporter process. The main portion of radioactivity is excreted with the feces. The liver seems not to be involved in the excretion of radium-223 or its decay products. They are directly excreted into the small intestine. The co-administered products are typical small molecules that are metabolized in the liver. Thus, no direct impact of radium-223 on the PK of the co-administered products is expected.

9.6 Safety

Section modified by Amendment 1 (Section 15.1).

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 9.6.1.

- Safety variables: Safety variables will include the analysis of acute and long-term effects and the appearance of new primary malignancies and hematopoietic reserve for tolerability of subsequent chemotherapy. The complete list of variables to be analyzed for this study will be provided in the SAP.
- Laboratory assessments: The following laboratory assessments with reference ranges, including Investigator determinations, will be recorded in the source documentation and the eCRF:
    - Hematology: hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential
    - Clinical chemistry: Na, K, Cl, Ca, total cholesterol, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, total bilirubin, and albumin
    - A coagulation panel: PT, PTT, and INR

All subjects who receive at least one dose of study drug will be valid for safety analysis. All AEs will be reported and graded according to NCI-CTCAE v4.03. Laboratory evaluations, vital signs, and changes in physical examination findings will also be assessed.

9.6.1 Adverse events

9.6.1.1 Definitions

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 subject 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 an AE (however, the condition for which the surgery is required may be an AE).

Adverse event versus medical history

In the following differentiation between medical history and AEs, the term “condition” may include abnormal physical examination findings, symptoms, diseases, laboratory findings, or scans.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are considered as **medical history** (e.g., seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are considered as **medical history** (e.g., allergic pollinosis).

- Symptoms that were present prior to signing of informed consent but for which the diagnosis was confirmed after signing of informed consent should be documented as **medical history**.
- Conditions that started or deteriorated after signing of informed consent will be documented as **adverse events**.

Serious adverse event

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

   The admission is pre-planned
   (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 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 any additional malignancies, including AML or hematological conditions, such as MDS, aplastic anemia, or myelofibrosis (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).

9.6.1.2 Classifications for adverse event assessment

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

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE should be documented using the NCI-CTCAE v4.03, JUN 2010; see Section 16.1.

9.6.1.2.3 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. Causal relationship of the background hormone treatment and concomitant medication of interest, bisphosphonates or denosumab will also be collected.

Possible answers are "yes" or "no"

An assessment of "no" would include:

- The existence of a clear alternative explanation, e.g., mechanical bleeding at surgical site,

  or

- 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 subject's 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 PK of the study treatment: The PK 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".

9.6.1.2.4 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 not changed
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 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

9.6.1.3 Assessments and documentation of adverse events

Section modified by Amendment 1 (Section 15.1), Amendment 5 (Section 15.4), Amendment 8 (Section 15.7.1.1).

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/placebo must be reported on the appropriate eCRF.

All SAEs that occur during the treatment period and up to 30 days after the last administration of radium-223/placebo must immediately (within 24 hours of the Investigator's awareness) be reported in the appropriate eCRF. 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 dose of study treatment must be documented and reported if considered to be related to study medication or to study-related procedures.

Subjects who receive cytotoxic chemotherapy during the follow-up period will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months after chemotherapy. Occurrence of these AEs must be documented and reported if considered to be related to the chemotherapy treatment.

However, all occurrences of additional malignancies, including AML and hematological conditions, such as MDS, aplastic anemia, and myelofibrosis, must be reported as SAEs, regardless of the Investigator's assessment.

Note: Specifically for this study, relevant symptoms related to SSEs should be captured as AEs or SAEs (if appropriate) regardless of the relationship to study drug from the date of first dose until the end of active follow-up.

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

Adverse events may be reported spontaneously by the subject or elicited through open (non-leading) questioning during each visit to the clinic and at the end of the active follow-up period without clinic visits. As far as possible, all AEs must be described by their duration (start and stop date), severity (graded according to the CTCAE v4.03), relationship to treatment, and according to the need of other specific therapy. All information will be recorded in the source documentation and AE eCRF.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment, causing apparent clinical manifestations, or judged as relevant by the Investigator should be reported as an AE. 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.

9.6.1.4 Reporting of serious adverse events

Section modified by Amendment 2 (Section 15.2) and Amendment 8 (Section 15.7.1.1).

The definition of SAEs is given in Section 9.6.1.1. 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 an SAE, 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 "alternative explanation".**

Reporting of additional malignancies

All occurrences of any additional malignancies, including AML and hematological conditions, such as MDS, aplastic anemia, or myelofibrosis, must be reported as SAEs, 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 9.6.1.3 must immediately (within 24 hours of the Investigator's awareness [or the next working day for weekends and public holidays]) be reported to the contact at the contract research organization (CRO), as detailed in the study manual. An SAE form must also be completed within 24 hours of the Investigator awareness (or the next working day for weekends and

public holidays) and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by the submission of updated reports to the designated recipient.

Additionally, all occurrences of a MDS, aplastic anemia, or any other new primary malignancy, such as AML, must be reported as SAEs at any time, and regardless of the Investigator's causality assessment (Section 9.6.1.3). All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. Grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as SAEs, 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 medical monitor.

For subjects who die >30 days after the administration of the last study treatment, submission of the AE page of the eCRF is not required. However, the SAE Complementary Form should be submitted to the applicable Bayer HealthCare Pharmacovigilance department if the death is considered related to study treatment. In addition, this death information will also be collected in the end of active follow-up page of the eCRF.

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

Notification of the independent ethics committees/institutional review boards

Notification of the independent ethics committees/institutional review boards (IECs/IRBs) about all relevant events (e.g., SAEs, 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 study site

The sponsor will inform all investigational study sites about reported relevant events (e.g., SUSARs) according to all applicable regulations. The sponsor will send SUSARs to a study site once ready to enroll and will stop sending SUSARs once the last subject EOT visit for that study site (30 days after last dose) occurs.

9.6.1.5 Expected adverse events

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

9.6.2 Pregnancies

The Investigator must report to the sponsor any pregnancy occurring in a female study subject during her participation in this study. The outcome of the pregnancy should be

followed up carefully, and any outcome of the mother and the child at delivery should be reported.

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

9.7 Other procedures and variables

Other exploratory variables in this study are resource utilization, assessment of biomarkers, and impact of baseline total body weight (TBW) and ideal body weight (IBW) on SSE-FS and AEs. Further details about these exploratory endpoints will be provided in the SAP.

9.7.1 Resource utilization

Information on healthcare resource use that is associated with the management of AEs as well as subject monitoring will be collected by questionnaire (Section 16.7).

9.7.2 Biomarker assessments

Section modified by Amendment 5 (Section 15.4).

Biomarker analyses planned within this study may include predictive, prognostic, and pharmacodynamic biomarkers analyzed from serum and urine. Serum, urine, and biomarker analyses will be dependent upon the availability of appropriate biomarker assays and may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will have no scientific value, or there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or does not reach a positive primary endpoint, completion of the biomarker assessments will be based on justification and intended utility of the data. Exploratory biomarker data including CTC analysis will be reported in a separated biomarker report.

9.7.2.1 Urine, plasma, and serum based biomarker analysis

Section modified by Amendment 1 (Section 15.1) and Amendment 4 (Section 15.3).

Blood samples will be obtained from all subjects at the following time points: (1) Cycle 1, Day 1 (Visit 2) and Cycle 4, Day 1 (Visit 8) within 5 days of the visit prior to radium-223 dichloride or placebo administration, and within 5 days of the EOT visit or disease progression, whichever occurs first. At these time points, urine samples will also be collected.

- Urine, serum, and plasma from blood samples (Cycle 1, Day 1; Cycle 4, Day 1; and EOT/disease progression) may be evaluated for expression levels of bone-related biomarkers. Elevated levels of bone biomarkers are indicative of more aggressive disease and are prognostic of worse long-term clinical outcome. In this study, levels of bone biomarkers (measured before, during, and after treatment) that are indicative of bone remodeling (e.g., bone ALP, procollagen type I N-terminal propeptide) and bone resorption (e.g., urine N-terminal telopeptide and I collagen telopeptide /serum

C-terminal telopeptide of type I collagen) may be evaluated and correlated with clinical outcomes (including SSEs, survival, and levels of other biomarkers).

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease and/or about the drug (i.e., mode of action related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing studies and/or literature data.

9.7.2.2 Collection of circulating tumor cells for biomarker analyses

Section modified by Amendment 5 (Section 15.4) and Amendment 7 (Section 15.6).

Circulating Tumor Cells (CTCs) are believed to represent a surrogate for tumor cells and can be used as surrogate to demonstrate efficacy of the drug by enumeration of CTCs, but also as source of tumor molecular characterization.

Blood samples will be obtained from all subjects at sites in France, Germany, Israel, Spain, and the United Kingdom at the following time points: (1) Cycle 1, Day 1 (Visit 2) and every subsequent cycles, Day 1 within 5 days of the visit prior to radium-223 dichloride or placebo administration, and within 5 days of the EOT visit or disease progression, whichever occurs first.

9.7.3 Analysis of the impact of body weight on SSE-FS and AEs

The impact of baseline TBW and IBW on SSE-FS and AEs will be analyzed in this study. Baseline TBW and IBW correspond to the subject's TBW and IBWs on Cycle 1, Day 1 of the study; details will be presented in the SAP.

9.8 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.

10. Statistical methods and determination of sample size

10.1 General considerations

Section modified by Amendment 4 (Section 15.3).

Subjects will be randomized to radium-223 dichloride or placebo in a 1:1 ratio. Randomization will be stratified by:

- Geographical regions (Europe/North America [including Israel] versus Asia)
- Previous lines of hormone therapy in metastatic setting (1 versus 2 or more): for the purpose of counting the number of prior lines of hormone therapy, only a change of the hormone agent due to progression is counted as a new line of therapy. A switch of hormone therapy from one agent to another due to toxicity or other reasons (e.g., subject's preference) in absence of PD at the time of switch will be counted as one line although 2 different agents have been administered.

- Prior SREs (1 versus 2): for the purpose of prior SREs stratification, separate SREs are those that occur at least 21 days apart from each other. Any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture or multiple doses of radiation during a course of treatment, should not be counted as a separate event. In case of bone pain that occurs in several anatomical locations and requires separate EBRT sessions, it should be counted as one event if the EBRT sessions are administered within a period of 21 days.

Statistical analysis will be performed using SAS Institute Inc.® (SAS); the version used will be specified in the SAP.

10.2 Analysis sets

The following 2 populations will be analyzed:

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 are randomized.

Safety: All randomized subjects who received at least one dose of any study drug. 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 receive.

10.3 Efficacy variables and planned statistical analyses

Section modified by Amendment 4 (Section 15.3).

Definition for each variable is given in Section 9.4.

The primary efficacy variable is SSE-FS.

The secondary efficacy variables are specified below:

- Overall survival (OS)
- Time to opiate use for cancer pain
- Time to pain progression (only in subjects with baseline WPS ≤8)
- Time to cytotoxic chemotherapy
- Radiological progression free survival (rPFS)
- Pain improvement rate

Exploratory efficacy variables are:

- Time to first on-study SSE
- Time to bone ALP progression
- Bone-ALP response at Week 12 and EOT
- Bone-specific radiological progression free survival

- Time to visceral metastases onset

10.3.1 Primary efficacy analysis

The overall one-sided type I error rate for the analysis of primary efficacy endpoint SSE-FS is 0.1.

The null hypothesis that both treatment groups have the same SSE-FS distribution will be tested against the alternative hypothesis that the distribution of SSE-FS time in radium-223 dichloride is different from the placebo group. The test statistic is assumed to be asymptotically normal distribution. SSE-FS will be analyzed using a stratified log-rank test with the same stratification factors as for randomization. The hazard ratio (radium-223 dichloride/placebo) will be computed together with the 2-sided 80% and 95% confidence interval (CI) using a Cox regression model stratified by the same factors. Kaplan-Meier estimates and survival curves for SSE-FS will also be presented for each treatment group.

Additional details for the analyses of the primary efficacy endpoint will be provided in the SAP.

10.3.2 Secondary efficacy analysis

Secondary efficacy endpoints are specified in Section 9.4.

The secondary efficacy time-to-event endpoints will be analyzed using a stratified log-rank test, with the factors from the randomization used for stratification. A hazard ratio with 2-sided 80% and 95% CI from a stratified Cox proportional hazards model will also be provided. Kaplan-Meier estimates and survival curves will also be presented for each treatment group.

Additional details for the analyses of secondary endpoints will be provided in the SAP.

10.3.3 Exploratory efficacy analysis

The exploratory time-to-event efficacy endpoints will be analyzed using a log-rank test, stratified by the same factors as the randomization factors.

Additional details for the analyses of exploratory endpoints will be provided in the SAP.

10.3.4 Safety analysis

Safety variables will be analyzed using frequency tables and descriptive statistics.

10.4 Determination of sample size

Section modified by Amendment 2 (Section 15.2).

Sample size is calculated based on the primary endpoint, SSE-FS. EAST 6.3 was used to calculate event number. Assuming a one-sided alpha of 0.1, power of 90%, with a median SSE-FS for the control group of 8.3 months and a randomization ratio of 1:1 between treatments, approximately 119 events will be required to detect a 60% increase in SSE-FS for a total of 227 subjects in the 2 treatment groups combined. The dropout rate is assumed to be

15%. Dropout was taken into account when calculating the sample size and study duration. The targeted improvement of 60% is not based on a bibliographical reference.

10.5 Planned interim data review

Section modified by Amendment 7 (Section 15.6).

An administrative interim data review will be performed when approximately 40 rPFS events are reached. The interim data review will be primarily focused on the rPFS, and the results will inform on future radium-223 clinical development plans in this indication. An independent unblinded data review committee will be formed.

No formal statistical testing will be performed for either SSE-FS or rPFS at the time of this interim review. Only summary statistics will be produced. There is no plan to stop the trial due to superior efficacy; therefore, no alpha adjustment is applied for this interim look at the primary endpoint of SSE-FS. The study will remain blinded after the interim data review.

Details of the interim data review will be provided in the statistical analysis plan.

11. Data handling and quality assurance

11.1 Data recording

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the study site. The study site must implement processes to ensure this happens. A source document checklist will be used at the study site to identify the source data for all data points collected and the monitor will work with the study 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 a minimum, data to be recorded in the eCRF are demographic information (subject number, date of birth/age, sex, race [if applicable] 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

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the study site prior to the start of the study to review with the study 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 study 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.

11.3 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 database or data system (e.g., TOSCA; SAS). 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., IXRS, laboratory, adjudication committees).

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used such as the Medical Dictionary for Regulatory Activities and World Health Organization Drug Dictionary.

11.4 Missing data

Every effort should be made to retain subjects who discontinue the treatment period for any reason. These subjects are to be encouraged to remain on the study for follow-up of primary, secondary, and exploratory endpoints (i.e., continue in the active follow-up period with or without clinic visits).

The method used for imputation of missing data will be described in the SAP.

11.5 Audit and inspection

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

inspections to ensure all required staff are available during the audit process. 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.

11.6 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 must notify the sponsor if the archival arrangements change (e.g., relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the Investigator/institution will contain all regulations relevant for the study site.

12. Premature termination of the study

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

- If the risk-benefit ratio becomes unacceptable owing to, for example,
    - Results of parallel clinical studies
    - Results of parallel animal studies (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 study within a reasonable time frame.

The Investigator has the right to close his/her site 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 site; head of study site) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at study site) must be returned to the sponsor or (for radium-223 dichloride samples) be destroyed at the study site in accordance with the local radioprotection regulations. 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.
- All ongoing subjects at the time of study termination will finish study treatment with radium-223 dichloride or placebo as part of the study.

Details for individual subject's withdrawal can be found in Section 6.3.1.

13. Ethical and legal aspects

13.1 Investigators and other study personnel

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 sites will be available in each site's investigator site file.

Whenever the term "Investigator" is noted in the protocol text, it may refer to either the Principal Investigator at the study site or an appropriately qualified, trained, and delegated individual of the investigational study site.

The Principal Investigator of each site must sign the protocol signature sheet before subject recruitment may start at the respective site. Likewise, all protocol amendments/integrated protocols must be signed and dated by the Principal Investigator before coming into effect at the respective site.

In addition to signing the protocol signature sheet, all ethical and legal aspects (Section 13) should be in place prior to any subject recruitment.

A complete list of all participating sites 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 page.

13.1.1 Independent data monitoring committee

Not applicable

13.1.2 Independent radiological review

Section modified by Amendment 7 (Section 15.6).

This study will have no central review.

13.1.3 Independent Data Review Committee (IDRC)

Section modified by Amendment 7 (Section 15.6).

An independent unblinded data review committee will be established.

The IDRC will conduct a one-time unblinded review of the data. IDRC review will be supported by an independent unblinded statistical analysis center, as further described in the IDRC operational plan.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

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

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and Investigator abide by GCP guidelines and 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 IEC(s)/IRBs will be obtained for all participating sites/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 site/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 study 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 12.

13.4 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 site. 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 or legal representative or proxy consenter (if the subject is under legal protection), prior to her entry into the study (i.e., before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The Investigator will also inform the subject that written approval of the IRB/IEC has been obtained.

Each subject or 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 or legal representative or proxy consenter voluntarily agrees to sign the ICF and has done so, may she enter the study. Additionally, the Investigator and other information provider (if any) will personally sign and date the form. The subject or legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the subject's note/file of the medical institution.

A summary of the consenting process, participation in the study, and date of informed consent given by the subject should be documented appropriately in the source documentation.

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

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

For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express her own will. Her refusal or the withdrawal of her consent may not be disregarded.

The ICF and any other written information provided to subjects or 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 or legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC/IRB`s approval or favorable opinion in advance of use.

A summary of any revised written ICF signed by the subject or a legal representative or a proxy should be appropriately documented by the study site within the source documents.

If at any time during the study the subject would like to withdraw consent, the Investigator must discuss with the subject the active follow-up period without the clinic visits part of the study. If the subject continues to object to having any study data collected the subject must sign the "Declaration of Objection to the Collection of Study Data after Withdrawal of Consent" form.

13.5 Publication policy and use of data

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

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

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

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

13.6 Compensation for health damage of subjects/insurance

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

13.7 Confidentiality

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

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF. 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.

14. Reference list

Section modified by Amendment 4 (Section 15.3).

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15. Protocol amendments

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version. As applicable, changes to the protocol text are highlighted as follows:

- **Addition of a whole new portion** Brief identification of the new portion
- **Removal of a whole portion** Complete display of the removed portion, formatted as ~~crossed out~~
- **Editing of an existing portion** Comparative presentation of "Old text" versus "New text," with "Old text" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "Old text." Additions are underlined in the "New text."
- **Tables / figures** The term "amended" is added to the caption.
- **Terminological changes** Brief specification of the terminological change

Correction of typos or omissions and formatting changes are not highlighted.

Starting with Amendment 8, changes to the protocol text are provided in a separate tracked changes document.

15.1 Amendment 1

Amendment 1 (dated 16 DEC 2014) is an amendment to the original protocol dated 13 MAY 2014. Changes to the protocol include:

- Clarified the inclusion criterion of menopausal status
- Changed the requirement for baseline scans to be within 3 weeks prior to randomization, not within 6 weeks of randomization
- Clarified that all prior SRE-related procedures must be administered prior to randomization
- Clarified that subjects who are considered by the treating Investigator to be appropriate candidates for treatment with everolimus as current treatment for their metastatic breast cancer would be excluded from the study
- Clarified that SSEs should be recorded until the end of active follow-up regardless of whether subjects start new anti-cancer therapies
- Clarified that permanent discontinuation of study treatment is not required for subjects who experience bone or non-bone disease progression unless chemotherapy is required
- Clarified that study treatment is radium-223 dichloride/placebo
- Changed resolution of gastrointestinal symptoms from Grade ≤2 to Grade ≤1, and added fatigue as a toxicity requiring resolution prior to administration of the next dose

- Added plasma collection to biomarker analysis
- Clarified that the timing of the on-treatment radiological assessments is Cycle 3, Day 1, Cycle 6, Day 1, and every 12 weeks thereafter until PD (radiological progression) is documented
- Added phosphate to the list of clinical chemistry tests to be evaluated
- Clarified the timing of blood and urine sample collection for biomarker analysis
- Corrected the calculation of the BPI-SF items from sums to means
- Added a requirement that all relevant symptoms related to SSEs be recorded as AEs
- Replaced the GFR formula with a link to the specific GFR calculator using the MDRD study equation
- Added an exclusion criterion for breastfeeding women
- Replaced bullets with numbering for the lists of inclusion and exclusion criteria
- Changed duration of screening period from 2 to 3 weeks to allow more time for baseline imaging.
- Changed the required duration of bisphosphonate treatment from at least 3 months prior to start of study treatment to at least 1 month prior to start of study treatment
- Clarified description of standard of care hormonal treatment background therapy
- Updated exclusion criteria to exclude only subjects with confirmed visceral metastases

15.1.1 Overview of changes to the study

Modification 1

Clarified the inclusion criterion of menopausal status based on feedback received from the sites.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 2

Changed the requirement for baseline scans to be within 3 weeks prior to randomization not within 6 weeks of randomization to ensure the time interval between baseline disease assessment and start of treatment is in line with RECIST 1.1 guidelines.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria
- Table 9-1: Schedule of assessments
- 9.2.1 Screening period (Visits 0 to 1)
- 9.2.6 Radiological assessment: tumor and response evaluation

Modification 3

Added text that all prior SRE-related procedures must be administered prior to randomization for clarification purposes.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 4

Clarified that subjects who are considered by the treating Investigator to be appropriate candidates for treatment with everolimus as current treatment for their metastatic breast cancer would be excluded from the study based on feedback from the sites.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.2 Exclusion criteria

Modification 5

Added text that SSEs should be recorded until the end of active follow-up regardless of whether subjects start new anti-cancer therapies for clarification purposes.

Sections affected include:

- Synopsis: Methods
- 5.1.1 Study periods and duration
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.2 Active follow-up without clinic visits
- 9.2.4.3 End of active follow-up

Modification 6

Clarified that permanent discontinuation of study treatment is not required for subjects who experience bone or non-bone disease progression unless chemotherapy is required. This change was made at the request of the FDA because subjects may derive clinical benefit from continuation of radium-223 treatment.

Sections affected include:

- 6.3.1.1 Withdrawal from treatment period (collection of follow-up data)

Modification 7

Clarified that study treatment is radium-223 dichloride/placebo.

Sections affected include:

- 7.4.5 Dose administration
- 7.4.6 Dose adjustments, delays, and treatment discontinuations
- 9.2.3 Treatment period

Modification 8

Reduced the maximum CTCAE grade required prior to re-dosing with radium-223 dichloride/placebo after recovery from diarrhea, nausea, vomiting, and constipation from Grade ≤2 to Grade ≤1. Fatigue was also added as a toxicity, which required recovery to Grade ≤1 prior to the next study drug administration. These changes were made at the request of the FDA.

Sections affected include:

- 7.4.6 Dose adjustments, delays, and treatment discontinuations

Modification 9

Add plasma to the serum and urine biomarker collection since biomarkers will be assessed from plasma in this study.

Sections affected include:

- Table 9-1: Schedule of assessments
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 9.7.2.1 Urine, plasma, and serum based biomarker analysis

Modification 10

Clarified that the timing of the on-treatment radiological assessments is Cycle 3, Day 1, Cycle 6, Day 1, and every 12 weeks thereafter until PD (radiological progression) is documented to ensure consistency.

Sections affected include:

- Table 9-1: Schedule of assessments
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

Modification 11

Added phosphate to the list of clinical chemistry tests to be evaluated during this study to allow a more complete evaluation of Ca2+/Phosphate metabolism as all subjects will receive concomitant bisphosphonates or denosumab based on comments received from Italian regulatory authorities.

Sections affected include:

- Table 9-1: Schedule of assessments
- 9.2.1 Screening period (Visits 0 to 1)
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.2 Visits 3, 5, and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up
- 9.3.3 Other baseline characteristics
- 9.6 Safety

Modification 12

Clarified for consistency that blood and urine samples will be collected for biomarker analysis at Cycle 1, Day 1; Cycle 4, Day 1; and EOT or disease progression, whichever occurs first.

Sections affected include:

- Table 9-1: Schedule of assessments

Modification 13

Corrected the calculation of the BPI-SF items from sums to means.

Sections affected include:

- 9.4.2.2 Secondary efficacy endpoints

Modification 14

Added a requirement that all relevant symptoms related to SSEs be recorded as AEs. SSEs refer to symptomatic skeletal events and the respective CRF (SSE form) requires the investigator to report the symptoms using a dynamic search list. To be able to select the symptoms in the SSEs form, the investigator must have completed an AE form that reports the relevant symptom(s).

Sections affected include:

- 9.6.1.3 Assessments and documentation of adverse events

Modification 15

Replaced the GFR formula with a link to the specific GFR calculator using the MDRD study equation. The MDRD formula to be used for the calculation of GFR varies depending on the method used for serum creatinine assessment (standardized/traceable to isotope dilution mass spectrometry method versus non-standardized/non-traceable to isotope dilution mass spectrometry method).

Sections affected include:

- 16.3 Calculation for glomerular filtration rate

Modification 16

Replaced bullets with numbering for the lists of inclusion and exclusion criteria for consistency with the eCRF.

Sections affected include:

- Synopsis
- 6.1 Inclusion criteria
- 6.2 Exclusion criteria

Modification 17

Added an exclusion criterion for breastfeeding women.

Sections affected include:

- Synopsis
- 6.2 Exclusion criteria

Modification 18

Changed duration of screening period from 2 to 3 weeks to allow more time for baseline imaging.

Sections affected include:

- Synopsis: Methodology
- 5.1.1 Study Periods and Durations
- 6. Study Population
- Table 9-1 Schedule of Assessments
- 9.2.1 Screening. (Visits 0 to 1)

Modification 19

Changed the required duration of bisphosphonate treatment from at least 3 months prior to start of study treatment to at least 1 month prior to start of study treatment because 1 month is sufficient to allow these treatments to have full effect on the bone function.

Sections affected include:

- Synopsis
- 6.1 Inclusion Criteria
- 7.1 Treatments to be administered
- 8.1.2 Permitted concomitant therapy

Modification 20

Clarified description of standard of care hormonal treatment background therapy per investigator feedback to allow subject to switch to local standard of treatment, which may include exemestane in combination with everolimus or 2 hormonal agents in combination (such as aromatase inhibitor and goserelin).

Sections affected include:

- Synopsis
- 5.1.1 Study periods and duration
- 8.1.1 Prohibited concomitant therapy

Modification 21

Updated exclusion criteria to exclude only subjects with confirmed visceral metastases per investigator feedback to clarify that subjects with small nodules not yet characterized and that are not considered to have confirmed visceral disease are not excluded

Sections affected include:

- Synopsis
- 6.2 Exclusion criteria

Modification 22

Updated criteria for when estradiol assay must be conducted for consistency within the protocol.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.1 Screening period (Visits 0 to 1)

15.1.2 Changes to the protocol text

Changes to the protocol text are highlighted as specified at the beginning of Section 15.

Synopsis: Diagnosis and main criteria for inclusion and exclusion

This section was changed as a result of Modifications 1 and 2. Note that for all inclusion criteria listed in the synopsis, the bulleted list has been replaced with numbering as a result of Modification 16.

Old text:

- Tumors (from either primary or metastatic sites) must be ER+ defined as ≥10% positive tumor nuclei in the analyzed sample. ER+/ progesterone positive (PR+), ER+/ progesterone receptor negative (PR-) subjects are eligible whereas estrogen receptor negative (ER-)/PR+ and ER-/PR- disease will not be eligible.
- Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible.

  Note: Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist/antagonist is permitted for induction of ovarian suppression.

  - **Pre-menopausal subjects** ~~as well as subjects~~ with ovarian radiation or concomitant treatment with an LH-RH agonist/antagonist must have a

negative pregnancy test and agree to use an adequate method of contraception as recommended by their treating physicians

- Measurable or non-measurable disease (but radiologically evaluable) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. All disease burden must be assessed at baseline by CT or MRI of chest, pelvis, and abdomen and any additional fields as needed. A bone scan should also be done at baseline for all subjects.

  CT/MRI done as part of the standard of practice within ~~6~~ weeks ~~of~~ randomization and standard of care bone scans done within ~~6~~ weeks ~~of~~ randomization are acceptable.

  ^{18}F-sodium fluoride positron emission tomography/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

New text:

2. Tumors (from either primary or metastatic sites) must be ER+ defined as ≥10% positive tumor nuclei in the analyzed sample. ER+/ progesterone receptor positive (PR+), ER+/ progesterone receptor negative (PR-) subjects are eligible whereas estrogen receptor negative (ER-)/PR+ and ER-/PR- disease will not be eligible.

5. Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible.

   Note: In premenopausal subjects, ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist/antagonist is permitted for induction of ovarian suppression. Baseline estradiol assay must be <20 pg/mL at screening.

6. **Pre-menopausal subjects** with or without ovarian radiation or concomitant treatment with an LH-RH agonist/antagonist must have a negative pregnancy test at screening and agree to use an adequate method of contraception as recommended by their treating physicians

7. Measurable or non-measurable disease (but radiologically evaluable) according to Response Evaluation Criteria in Solid Tumors v1.1 criteria. All disease burden must be assessed at baseline by CT or MRI of chest, pelvis and abdomen and any additional fields as needed. A bone scan should also be done at baseline for all subjects.

   ^{18}F-sodium fluoride positron emission tomography/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

Synopsis: Diagnosis and main criteria for inclusion and exclusion

This section was changed as a result of Modifications 3 and 19.

Old text:

- Subjects must have experienced no more than 2 skeletal-related events (SREs) prior to study entry defined as: external beam radiotherapy (EBRT) for bone pain, pathological bone fracture (excluding major trauma), spinal cord compression, and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.

  Note: For the purpose of counting prior SREs, any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture should not be counted as a separate event.

- Subjects must be on therapy with bisphosphonate or denosumab and are required to have been on such therapy for at least ~~3 months~~ before the start of study treatment.

New text:

10. Subjects must have experienced no more than 2 skeletal-related events (SREs) prior to study entry defined as: external beam radiotherapy (EBRT) for bone pain, pathological bone fracture (excluding major trauma), spinal cord compression, and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.

    Note: For the purpose of counting prior SREs, any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture, should not be counted as a separate event. All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization.

11. Subjects must be on therapy with bisphosphonate or denosumab and are required to have been on such therapy for at least 1 month before the start of study treatment.

Synopsis: Diagnosis and main criteria for inclusion and exclusion

This section was changed as a result of Modifications 4, 17, and 21. Note that for all exclusion criteria, the bulleted list has been replaced with numbering as a result of Modification 16.

Old text:

- Subjects ~~eligible~~ for treatment with everolimus
- History and/or presence of visceral metastases

New text:

2. Subjects considered by the treating physician to be appropriate candidates for treatment with everolimus as current treatment for their metastatic breast cancer

4. History and/or presence of confirmed visceral metastases

19. Breastfeeding women

Synopsis: Methodology

This section was changed as a result of Modification 18.

Old text:

Screening period:

All trial related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the informed consent form. The screening period will consist of multiple evaluations that will take place within ~~2~~ weeks prior to randomization to ensure that all eligibility criteria are met.

New text:

Screening period:

All trial related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the informed consent form. The screening period will consist of multiple evaluations that will take place within 3 weeks prior to randomization to ensure that all eligibility criteria are met.

Synopsis: Methodology

This section was changed as a result of Modifications 5 and 20.

Old text:

All subjects will continue to receive standard of care hormonal treatment background therapy. Hormonal treatment may also be changed according to the local standard of practice ~~however, only single agent hormonal treatment will be allowed~~. For the purpose of this study, only a new hormonal treatment initiated due to disease progression will be considered a new anti-cancer therapy.

If radium-223 dichloride/placebo treatment is still ongoing but the hormonal treatment is no longer considered a treatment option and the subject must start cytotoxic treatment ~~or treatment with everolimus~~, the subject will terminate radium-223 dichloride/placebo treatment. Subjects will continue to be followed up for SSEs and radiological progression.

New text:

All subjects will continue to receive standard of care hormonal treatment background therapy. Hormonal treatment may also be changed according to the local standard of practice, including exemestane in combination with everolimus. For the purpose of this study, only a new hormonal treatment initiated due to disease progression will be considered a new anti-cancer therapy.

If radium-223 dichloride/placebo treatment is still ongoing but the hormonal treatment is no longer considered a treatment option and the subject must start cytotoxic treatment, the subject will terminate radium-223 dichloride/placebo treatment. Subjects will continue to be followed up for SSEs and radiological progression. Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether patient starts a new anticancer therapy (i.e. chemotherapy, other).

Added text:

- Subjects who miss 2 consecutive follow-up visits will be considered unable to travel to the site and will enter the active follow-up without clinic visits. Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether patient starts a new anticancer therapy (i.e. chemotherapy, other).

Added text:

- For subjects who experienced an SSE during treatment or the previous follow-up period, the frequency of the phone calls will be every 12 weeks ±7 days. Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether patient starts a new anticancer therapy (i.e. chemotherapy, other).

Section 5.1.1 Study periods and duration

This section was changed as a result of Modifications 5, 18, and 20.

Added text (in 3 locations):

Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).

Old text:

All trial related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the informed consent form (ICF). The screening period will consist of multiple evaluations that will take place within ~~2~~ weeks prior to randomization to ensure that all eligibility criteria are met (Section 6).

New text:

All trial related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the informed consent form (ICF). The screening period will consist of multiple evaluations that will take place within 3 weeks prior to randomization to ensure that all eligibility criteria are met (Section 6).

Old text:

All subjects will continue to receive standard of care hormonal treatment background therapy. Hormonal treatment may also be changed according to the local standard of ~~practice however, only single agent hormonal treatment will be allowed~~. For the purpose of this

study, only a new hormonal treatment initiated due to disease progression will be considered a new anti-cancer therapy.

Radium-223 dichloride/placebo administration should be discontinued as per the withdrawal criteria described in Section 6.3.1 (e.g., subject experiences unacceptable toxicities, delays in radium-223 dichloride/placebo >4 weeks, subject enters the active follow-up without clinic visits as she can no longer travel to the clinical site, and if in the Investigator's opinion, continuation of the study treatment would be harmful to the subject's well-being).

If radium-223 dichloride/placebo treatment is still ongoing but the hormonal treatment is no longer considered a treatment option and the subject must start cytotoxic treatment ~~or treatment with everolimus~~, the subject will terminate radium-223 dichloride/placebo treatment. Subjects will continue to be followed up for SSEs and radiological progression.

New text:

All subjects will continue to receive standard of care hormonal treatment background therapy. Hormonal treatment may also be changed according to the local standard of practice, <u>including exemestane in combination with everolimus</u>. For the purpose of this study, only a new hormonal treatment initiated due to disease progression will be considered a new anti-cancer therapy.

Radium-223 dichloride/placebo administration should be discontinued as per the withdrawal criteria described in Section 6.3.1 (e.g., subject experiences unacceptable toxicities, delays in radium-223 dichloride/placebo >4 weeks, subject enters the active follow-up without clinic visits as she can no longer travel to the clinical site, and if in the Investigator's opinion, continuation of the study treatment would be harmful to the subject's well-being).

If radium-223 dichloride/placebo treatment is still ongoing but the hormonal treatment is no longer considered a treatment option and the subject must start cytotoxic treatment, the subject will terminate radium-223 dichloride/placebo treatment. Subjects will continue to be followed up for SSEs and radiological progression.

Section 6. Population Study

This section was changed as a result of Modification 18.

Old text:

- Subjects who underwent screening procedures (i.e., scans and laboratory work) that expired (are outside of the ~~14-day~~ window) may need the screening procedures to be repeated in order to be within the window required prior to randomization.

New text:

- Subjects who underwent screening procedures (i.e., scans and laboratory work) that expired (are outside of the <u>21-day</u> window) may need the screening procedures to be repeated in order to be within the window required prior to randomization

Section 6.1 Inclusion criteria

This section was changed as a result of Modifications 1, 2, 3, and 19. Note that for all inclusion criteria listed in Section 6.1, the bulleted list has been replaced with numbering as a result of Modification 16.

Old text:

- Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible.

  Note: Ovarian radiation or treatment with an LH-RH agonist/antagonist is permitted for induction of ovarian suppression.

  - **Pre-menopausal subjects** ~~as well as subjects~~ with ovarian radiation or concomitant treatment with an LH-RH agonist/antagonist must have a negative pregnancy test and agree to use an adequate method of contraception as recommended by their treating physicians

- Measurable or non-measurable disease (but radiologically evaluable) according to Response Evaluation Criteria in Solid Tumors v1.1 criteria. All disease burden must be assessed at baseline by CT or MRI of chest, pelvis, and abdomen and any additional fields as needed. A bone scan should also be done at baseline for all subjects.

  CT/MRI done as part of the standard of practice within ~~6 weeks of~~ randomization and standard of care bone scans done within ~~6 weeks of~~ randomization are acceptable.

  ^{18}F-sodium fluoride positron emission tomography/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

- Subjects must have experienced no more than 2 ~~SSEs~~ prior to study entry defined as: EBRT for bone pain, pathological bone fracture (excluding major trauma), spinal cord compression, and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.
  Note: For the purpose of counting prior SREs any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture should not be counted as a separate event.

- Subjects must be on therapy with bisphosphonate or denosumab and are required to have been on such therapy for at least ~~3 months~~ before the start of study treatment.

New text:

5. Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible.

   Note: In premenopausal subjects, ovarian radiation or treatment with an LH-RH agonist/antagonist is permitted for induction of ovarian suppression. Baseline estradiol assay must be <20 pg/mL at screening.

6. **Pre-menopausal subjects** with or without ovarian radiation or concomitant treatment with an LH-RH agonist/antagonist must have a negative pregnancy test at screening and agree to use an adequate method of contraception as recommended by their treating physicians (please refer to Section 8.1.2)
7. Measurable or non-measurable disease (but radiologically evaluable) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. All disease burden must be assessed at baseline by CT or MRI of chest, pelvis and abdomen and any additional fields as needed. A bone scan should also be done at baseline for all subjects.

   CT/MRI done as part of the standard of practice within 3 weeks prior to randomization and standard of care bone scans done within 3 weeks prior to randomization are acceptable.

   ^{18}F-sodium fluoride positron emission tomography (PET)/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.
10. Subjects must have experienced no more than 2 SREs prior to study entry defined as: EBRT for bone pain, pathological bone fracture (excluding major trauma), spinal cord compression, and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.
    Note: For the purpose of counting prior SREs, any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture, should not be counted as a separate event. All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization.
11. Subjects must be on therapy with bisphosphonate or denosumab and are required to have been on such therapy for at least 1 month before the start of study treatment.

Section 6.2 Exclusion criteria

This section was changed as a result of Modifications 4 and 21. Note that for all exclusion criteria listed in Section 6.2 the bulleted list has been replaced with numbering as a result of Modification 16.

Old text:

Subjects ~~eligible~~ for treatment with everolimus

History and/or presence of visceral metastases

New text:

2. Subjects considered by the treating physician to be appropriate candidates for treatment with everolimus as current treatment for their metastatic breast cancer

4. History and/or presence of confirmed visceral metastases

Section 6.3.1.1 Withdrawal from treatment period (collection of follow-up data)

This section was changed as a result of Modification 6.

Added text:

Subjects who experience disease progression (bone or non-bone) may continue to receive radium-223 dichloride (or placebo) until completion if the Investigator feels the subject will receive clinical benefit. These subjects may continue to receive additional hormonal treatments according to the local standard of care. If, however, chemotherapy is required as the next line of treatment, study treatment will be permanently discontinued, as concurrent chemotherapy administration is an exclusion criterion.

Section 7.1 Treatments to be administered

This section was changed as a result of Modification 19.

Old text:

- Bone-targeted agents: bisphosphonates or denosumab: Eligible subjects are required to be on therapy with bisphosphonates or denosumab at time of study entry (for at least ~~3 months~~ prior to the start of investigational study treatment, radium-223 dichloride/placebo).

New text:

- Bone-targeted agents: bisphosphonates or denosumab: Eligible subjects are required to be on therapy with bisphosphonates or denosumab at time of study entry (for at least 1 month prior to the start of investigational study treatment, radium-223 dichloride/placebo).

Section 7.4.5 Dose administration

This section was changed as a result of Modification 7.

Old text:

Every effort will be made to administer the full dosing regimen. Single dose level adjustment of radium-223 dichloride is not permitted. Treatment delays or discontinuations of radium-223 dichloride may be instituted for the AEs described in Section 7.4.6 and dose adjustments, treatment delays, or discontinuations of hormonal treatment may be instituted according to the local label and standard of practice.

New text:

Every effort will be made to administer the full dosing regimen. Single dose level adjustment of radium-223 dichloride/placebo is not permitted. Treatment delays or discontinuations of radium-223 dichloride/placebo may be instituted for the AEs described in Section 7.4.6 and dose adjustments, treatment delays, or discontinuations of hormonal treatment may be instituted according to the local label and standard of practice.

Section 7.4.6 Dose adjustments, delays, and treatment discontinuations

This section was changed as a result of Modifications 7 and 8.

Old text:

If a subject experiences CTCAE Grade 3 to 4 anemia, neutropenia, or thrombocytopenia lasting >2 weeks in spite of adequate treatment, the subject must be discontinued from treatment with radium-223 dichloride.

Diarrhea: No prophylactic treatment for diarrhea is recommended. Anti-diarrheals can be used when needed. A further dose of study medication should not be given before diarrhea has recovered to CTCAE Grade ≤~~2~~.

Nausea/Vomiting: No prophylactic treatments for nausea or vomiting are recommended, but anti-emetic drugs can be used when needed. A further dose of study medication should not be given before nausea/vomiting has recovered to CTCAE Grade ≤~~2~~.

Constipation: Subjects can continue laxative as concomitant medication, but start of prophylactic treatments before study drug injection are not recommended. Laxative can be used when needed. A further dose of study medication should not be given before constipation has recovered to CTCAE Grade ≤~~2~~.

If radium-223 dichloride treatment is still ongoing but standard of care hormonal treatment is no longer considered an option, and the subject must start cytotoxic therapy, the subject will terminate radium-223 dichloride or placebo treatment. Subjects will then enter the follow-up period and will continue to be followed for SSEs and radiological progression.

New text:

If a subject experiences CTCAE Grade 3 to 4 anemia, neutropenia, or thrombocytopenia lasting >2 weeks in spite of adequate treatment, the subject must be discontinued from treatment with radium-223 dichloride/placebo.

Diarrhea: No prophylactic treatment for diarrhea is recommended. Anti-diarrheals can be used when needed. A further dose of study medication should not be given before diarrhea has recovered to CTCAE Grade ≤1.

Nausea/Vomiting: No prophylactic treatments for nausea or vomiting are recommended, but anti-emetic drugs can be used when needed. A further dose of study medication should not be given before nausea/vomiting has recovered to CTCAE Grade ≤1.

Constipation: Subjects can continue laxative as concomitant medication, but start of prophylactic treatments before study drug injection is not recommended. Laxative can be used when needed. A further dose of study medication should not be given before constipation has recovered to CTCAE Grade ≤1.

Fatigue

In cases of NCI-CTCAE Grade 3 to 4 fatigue, study drug administration should be delayed until recovery to Grade ≤1 before the next study drug administration.

If radium-223 dichloride/placebo treatment is still ongoing but standard of care hormonal treatment is no longer considered an option, and the subject must start cytotoxic therapy, the subject will terminate radium-223 dichloride or placebo treatment. Subjects will then enter the follow-up period and will continue to be followed for SSEs and radiological progression.

Section 8.1.1 Prohibited concomitant therapy

This section was changed as a result of Modification 20.

Old text:

Concomitant therapy during the treatment phase of the study with any of the following listed is **prohibited**:

- Chemotherapy
- Radiopharmaceuticals, such as strontium-89, samarium-153, rhenium-186, or rhenium-188
- ~~Everolimus~~
- Hemibody external radiotherapy
- Other investigational drugs
- ~~Combination hormonal treatment~~
- All medications that are prohibited as per the local label instructions for the background hormonal treatment. It is the site's responsibility to ensure that hormonal background treatment is administered in line with standard practice and local label instructions. The same applies for bisphosphonates and denosumab.

New text:

Concomitant therapy during the treatment phase of the study with any of the following listed is **prohibited**:

- Chemotherapy
- Radiopharmaceuticals, such as strontium-89, samarium-153, rhenium-186, or rhenium-188
- Hemibody external radiotherapy
- Other investigational drugs
- All medications that are prohibited as per the local label instructions for the background hormonal treatment. It is the site's responsibility to ensure that hormonal

background treatment is administered in line with standard practice and local label instructions. The same applies for bisphosphonates and denosumab.

Section 8.1.2 Permitted concomitant therapy

This section was changed as a result of Modification 19.

Old text:

- All subjects are expected to have been on therapy with either denosumab or bisphosphonates for at least ~~3 months~~ before the start of study treatment and to continue on this therapy during the course of the study, with no change to therapy expected during the treatment phase of the study, except for toxicity reasons.

New text:

- All subjects are expected to have been on therapy with either denosumab or bisphosphonates for at least 1 month before the start of study treatment and to continue on this therapy during the course of the study, with no change to therapy expected during the treatment phase of the study, except for toxicity reasons.

Table 9-1: Schedule of assessments

This section was changed as a result of Modifications 2, 9, 10, and 18.

Old text:

Table 9-1: Schedule of assessments (continued)

Study Period	Screening[a]	Randomization	Treatment[b,c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	0-1	-	2	3	4	5	6	7	8	9	10		-	-	-	-
Cycle:	-	-	1		2		3		4	5	6	-	-	-	-	-
Timing:	≥ 2 wk pre-random.	1 to 3 wk pre-Dose 1	C1, Day 1	C1, Day 15[d]	C2, Day 1	C2, Day 15	C3, Day 1	C3, Day 15	C4, Day 1	C5, Day 1	C6, Day 1	4 wk post-last dose[e]	q4 wk until SSE; q12 wk after SSE[f]	q4 wk until SSE; q12 wk after SSE[g]		
Window (days):			±7	±3	± 7	±3	± 7	±3	± 7	± 7	± 7	± 7	±7	±7	±7	±7
Serum and urine biomarkers[z]			X						X			X				
Technetium-99m bone scan[aa]							~~X~~[aa]									
Chest, abdominal and pelvic CT scan[aa,cc,d]							~~X~~[aa]									
Progression			X	X	X	X	X	X	X	X	X	X	X		X	
SSEs			X		X		X		X	X	X	X	X	X	X	X
Drug order[ff]		X	X		X		X		X	X						
Radium-223 Cl_2 or placebo injection[gg]			X		X		X		X	X	X					
Survival status													X	X[j]	X	X[j]
Drug accountability			X		X		X		X	X	X					

New text:

Table 9-1: Schedule of assessments (continued)

Study Period	Screening[a]	Randomization	Treatment[b, c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	0-1	-	2	3	4	5	6	7	8	9	10		-	-	-	-
Cycle:	-	-	1		2		3		4	5	6	-	-	-	-	-
Timing:	3 wk pre-random.	1 to 3 wk pre-Dose 1	C1, Day 1	C1, Day 15[d]	C2, Day 1	C2, Day 15	C3, Day 1	C3, Day 15	C4, Day 1	C5, Day 1	C6, Day 1	4 wk post-last dose[e]	q4 wk until SSE; q12 wk after SSE[f]	q4 wk until SSE; q12 wk after SSE[g]		
Window (days):			±7	±3	± 7	±3	± 7	±3	± 7	± 7	± 7	± 7	±7	±7	±7	±7
Serum, plasma, and urine biomarkers[z]			X						X			X				
Technetium-99m bone scan[aa]	X[bb]							X[aa]			X[aa]	X[aa]	X[aa]		X[aa]	
Chest, abdominal and pelvic CT scan[aa, cc, dd]	X								X[aa]		X[aa]	X[aa]	X[aa]		X[aa]	
Progression			X	X	X	X	X	X	X	X	X	X	X		X	
SSEs			X		X		X		X	X	X	X	X	X	X	X
Drug order[ee]		X	X		X		X		X	X						
Radium-223 Cl_2 or placebo injection[ff]			X		X		X		X	X	X					
Survival status													X	X[j]	X	X[j]
Drug accountability			X		X		X		X	X	X					

Table 9-1: Schedule of assessments

This section was changed as a result of Modifications 2, 9 to 12, and 22.

Old text:

a. All screening evaluations must be complete and reviewed prior to randomization. Screening evaluations must be complete within ~~2~~ weeks prior to randomization. If all screening data are available and the subject is eligible for the study, randomization may occur at the end of the screening visit.

v. Sodium, potassium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, bone alkaline phosphatase, serum creatinine, blood urea nitrogen, bilirubin (total), total cholesterol, and albumin.

y. Pre-menopausal women must have a negative serum pregnancy test performed within 7 days prior to randomization, prior to each study drug administration, and EOT. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. An estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea ~~and no ovarian suppression.~~

z. Blood and/or urine sample for exploratory evaluation of biomarkers, prior to radium-223 dichloride or placebo administration. Serum samples will be collected at Cycle 1, Day 1; Cycle 4, Day 1; and EOT. Urine samples will be collected at Cycle, Day 1; Cycle 4, Day 1; and EOT visits (or at the time of disease progression, whichever occurs earlier).

aa. ~~Scans to be scheduled for Cycle 3, Day 1; EOT; and then every 12 weeks during the active follow-up periods~~. Scans will be read locally. The time window for the scans is ±7 days.

bb. A historic bone scan is acceptable if taken within ~~6~~ weeks of randomization. If one is not available, it will be required as part of the protocol procedures within the screening period. ^{18}F-sodium fluoride positron emission tomography/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

ee. A historic chest/abdominal/pelvic CT is acceptable if taken within ~~6~~ weeks of randomization. If not available, a scan is required as part of the protocol within the screening period.

New text:

a. All screening evaluations must be complete and reviewed prior to randomization. Screening evaluations must be complete within 3 weeks prior to randomization. If all screening data are available and the subject is eligible for the study, randomization may occur at the end of the screening visit.

v. Sodium, potassium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, bone alkaline phosphatase, serum creatinine, phosphate, blood urea nitrogen, bilirubin (total), total cholesterol, and albumin.

y. Pre-menopausal women must have a negative serum pregnancy test performed within 7 days prior to randomization, prior to each study drug administration, and EOT. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. An estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea.

z. Blood and/or urine sample for exploratory evaluation of biomarkers, prior to radium-223 dichloride or placebo administration. Serum and plasma samples will be collected at Cycle 1, Day 1; Cycle 4, Day 1; and EOT or disease progression, whichever occurs first. Urine samples will be collected at Cycle 1, Day 1; Cycle 4, Day 1; and EOT visits (or at the time of disease progression, whichever occurs earlier).

aa. Radiological tumor evaluation must be performed 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration and every 12 weeks thereafter until PD (radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS. This schedule is to be maintained and will not be shifted because of treatment interruptions/delays. Scans will be read locally. The time window for the scans is ±7 days.

bb. A historic bone scan is acceptable if taken within 3 weeks of randomization. If one is not available, it will be required as part of the protocol procedures within the screening period. ^{18}F-sodium fluoride positron emission tomography/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

ee. A historic chest/abdominal/pelvic CT is acceptable if taken within 3 weeks of randomization. If not available, a scan is required as part of the protocol within the screening period.

Section 9.2.1 Screening period (Visits 0 to 1)

This section was changed as a result of Modifications 2, 11, 18, and 22.

Old text:

The screening period lasts from date of signature of informed consent until the date of subject randomization in IXRS. The screening period duration is ~~2 weeks~~.

Standard of care imaging, such as CT/MRI, as well as routine bone scans performed within ~~6~~ weeks prior to randomization will be accepted as baseline imaging if they meet protocol requirements (anatomic coverage, image acquisition as per RECIST 1.1 guidelines for CT/MRI scans). Pre-treatment evaluations will be performed according to the eligibility criteria. If the subject is eligible for the study, the parameters at the screening visit showing subject health status including blood values will be recorded in the eCRF.

The following procedures and evaluations will be performed within ~~2 weeks~~ prior to planned randomization unless otherwise specified:

- Radiological tumor assessment
  - A chest/abdominal/pelvic CT or MRI. This is not needed if standard of care chest/abdominal/pelvic CT or MRI images taken within ~~6~~ weeks prior to randomization are available.
  - A bone technetium-99m scan with careful identification of all disease-related hotspots. This is not needed if standard of care bone scan performed within ~~6~~ weeks prior to planned randomization date is available and in line with protocol requirements. Confirmatory scan using single photon emission tomography (SPECT)-CT/MRI or CT/MRI (with and without contrast media) should be obtained if not performed within ~~6~~ weeks of randomization. The field of acquisition should include all areas where bone lesions are present.

    ^{18}F-sodium fluoride PET/CT scan is acceptable as an alternative to technetium-99m

bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

CT/MRI done as part of the standard of practice and standard of care bone scans done within ~~6 weeks of randomization~~ are acceptable.

The following procedures and evaluations should be performed within 1 week prior to randomization. Results must be available, reviewed, and signed and dated by the Investigator prior to randomization.

- Blood draw for clinical chemistry: sodium (Na), potassium (K), chloride (Cl), calcium (Ca), ALT, AST, lactate dehydrogenase (LDH), bone ALP, serum creatinine, blood urea nitrogen (BUN), total bilirubin, total cholesterol, and albumin.
- Estradiol assay: an estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea ~~and no ovarian suppression~~.

New text:

The screening period lasts from date of signature of informed consent until the date of subject randomization in IXRS. The screening period duration is 3 weeks.

Standard of care imaging, such as CT/MRI, as well as routine bone scans performed within 3 weeks prior to randomization will be accepted as baseline imaging if they meet protocol requirements (anatomic coverage, image acquisition as per RECIST 1.1 guidelines for CT/MRI scans). Pre-treatment evaluations will be performed according to the eligibility criteria. If the subject is eligible for the study, the parameters at the screening visit showing subject health status including blood values will be recorded in the eCRF.

The following procedures and evaluations will be performed within 3 weeks prior to planned randomization unless otherwise specified:

- Radiological tumor assessment
  - A chest/abdominal/pelvic CT or MRI. This is not needed if standard of care chest/abdominal/pelvic CT or MRI images taken within 3 weeks prior to randomization are available.
    - A bone technetium-99m scan with careful identification of all disease-related hotspots. This is not needed if standard of care bone scan performed within 3 weeks prior to planned randomization date is available and in line with protocol requirements. Confirmatory scan using single photon emission tomography (SPECT)-CT/MRI or CT/MRI (with and without contrast media) should be obtained if not performed within 3 weeks prior to randomization. The field of acquisition should include all areas where bone lesions are present.

^{18}F-sodium fluoride PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

CT/MRI done as part of the standard of practice and standard of care bone scans done within 3 weeks prior to randomization are acceptable

The following procedures and evaluations should be performed within 1 week prior to randomization. Results must be available, reviewed, and signed and dated by the Investigator prior to randomization.

- Blood draw for clinical chemistry: sodium (Na), potassium (K), chloride (Cl), calcium (Ca), ALT, AST, lactate dehydrogenase (LDH), bone ALP, serum creatinine, phosphate, blood urea nitrogen (BUN), total bilirubin, total cholesterol, and albumin.
- Estradiol assay: an estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea.

Section 9.2.3 Treatment period

This section was changed as a result of Modification 7.

Old text:

Before administration of radium-223 dichloride, the subject must be well hydrated; thus, the subject should be instructed to drink ad libitum.

Before the first administration of radium-223 dichloride (within 3 days), the ANC should be ≥1.5 x 10^9/L, the platelet count ≥100 x 10^9/L, and Hb ≥9 g/dL.

New text:

Before administration of radium-223 dichloride/placebo, the subject must be well hydrated; thus, the subject should be instructed to drink ad libitum.

Before the first administration of radium-223 dichloride/placebo (within 3 days), the ANC should be ≥1.5 x 10^9/L, the platelet count ≥100 x 10^9/L, and Hb ≥9 g/dL.

Section 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

This section was changed as a result of Modifications 9 to 11.

Old text:

- Blood draw for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, BUN, bilirubin (total), total cholesterol, and albumin (blood sample for clinical chemistry must be taken within 72 hours prior to each study drug administration).

- Blood draw and urine sample for exploratory biomarker analysis: Serum and urine samples will be collected at Visit 2 (Cycle 1, Day 1) and Visit 8 (Cycle 4, Day 1).
- At Visit 6 (Cycle 3, Day 1) only:

New text:

- Blood draw for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin (blood sample for clinical chemistry must be taken within 72 hours prior to each study drug administration).

- Blood draw and urine sample for exploratory biomarker analysis: Serum, plasma, and urine samples will be collected at Visit 2 (Cycle 1, Day 1) and Visit 8 (Cycle 4, Day 1).
- At Visit 6 and Visit 10 (Cycle 3, Day 1 and Cycle 6, Day 1) only (see also Section 9.2.6):

Added text:

- Spinal cord compression
  Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).

Section 9.2.3.2 Visits 3, 5, and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits

This section was changed as a result of Modification 11.

Old text:

- Blood draw for clinical chemistry is only required at Visit 3 (Cycle 1, Day 15) and Visit 5 (Cycle 2, Day 15): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, BUN, bilirubin (total), total cholesterol, and albumin.

New text:

- Blood draw for clinical chemistry is only required at Visit 3 (Cycle 1, Day 15) and Visit 5 (Cycle 2, Day 15): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin.

Section 9.2.3.3 End of treatment visit, Section 9.2.4.1 Active follow-up with clinic visits, Section 9.2.4.3 End of active follow-up

This section was changed as a result of Modification 11.

Old text:

- Blood draws for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, BUN, bilirubin (total), total cholesterol, and albumin.

New text:

- Blood draws for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin.

Section 9.2.3.3 End of treatment visit

This section was changed as a result of Modification 9.

Old text:

- Blood draw and urine sample for exploratory biomarker analysis (serum and urine samples will be collected at the EOT or at the time of disease progression, whichever occurs earlier)

New text:

- Blood draw and urine sample for exploratory biomarker analysis (serum, plasma, and urine samples will be collected at the EOT or at the time of disease progression, whichever occurs earlier)

Section 9.2.3.3 End of treatment visit, Section 9.2.4.1 Active follow-up with clinic visits, Section 9.2.4.2 Active follow-up without clinic visits, Section 9.2.4.3 End of active follow-up

This section was changed as a result of Modification 5.

Added text:

- Record SSEs
  Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).

- All AEs and SAEs occurring during this period must be documented and reported if considered to be related to study medication or study-related procedures. Note: Specifically for this study, relevant symptoms related to an SSE should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.

Section 9.2.6 Radiological assessment: tumor and response evaluation

This section was changed as a result of Modification 2.

Old text:

Radiological tumor evaluation, using the mRECIST 1.1 guidelines (See Section 16.2), must be performed at baseline ~~and every 12 weeks~~ (±7 days) after the first radium-223 dichloride/placebo administration, until PD (radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS.

Standard of care CT/MRI and standard of care bone scans done within ~~6~~ weeks prior to randomization are acceptable provided they are in line with protocol requirements criteria (anatomic coverage chest/abdomen/pelvis and in line with RECIST 1.1/mRECIST 1.1 guidelines for image acquisition). All suspected sites of disease should be imaged.

New text:

Radiological tumor evaluation, using the mRECIST 1.1 guidelines (See Section 16.2), must be performed at baseline (within 3 weeks prior to randomization), 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration and every 12 weeks thereafter until PD (radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS.

Standard of care CT/MRI and standard of care bone scans done within 3 weeks prior to randomization are acceptable provided they are in line with protocol requirements criteria (anatomic coverage chest/abdomen/pelvis and in line with RECIST 1.1/mRECIST 1.1 guidelines for image acquisition). All suspected sites of disease should be imaged.

Section 9.3.3 Other baseline characteristics

This section was changed as a result of Modification 11.

Old text:

- Clinical chemistry: Na, K, Cl, Ca, total cholesterol, ALT, AST, LDH, bone ALP, serum creatinine, BUN, total bilirubin, and albumin

New text:

- Clinical chemistry: Na, K, Cl, Ca, total cholesterol, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, total bilirubin, and albumin

Section 9.4.2.2 Secondary efficacy endpoints

This section was changed as a result of Modification 13.

Old text:

The items are aggregated into 2 dimensions: (1) Pain severity index, using the ~~sum~~ of the 4 items on the pain intensity, and (2) Function interference index, using the ~~sum~~ of the ~~seven~~ pain interference items. All 4 severity items must be completed for aggregating the pain severity index. 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.

New text:

The items are aggregated into 2 dimensions: (1) Pain severity index, using the mean of the 4 items on the pain intensity, and (2) Function interference index, using the mean of the 7 pain interference items. All 4 severity items must be completed for aggregating the pain severity index. 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.

Section 9.6 Safety

This section was changed as a result of Modification 11.

Old text:

- Clinical chemistry: Na, K, Cl, Ca, total cholesterol, ALT, AST, LDH, bone ALP, serum creatinine, BUN, total bilirubin, and albumin

New text:

- Clinical chemistry: Na, K, Cl, Ca, total cholesterol, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, total bilirubin, and albumin

Section 9.6.1.3 Assessments and documentation of adverse events

This section was changed as a result of Modification 14.

Added text:

Note: Specifically for this study, relevant symptoms related to SSEs should be captured as AEs or SAEs (if appropriate) regardless of the relationship to study drug from the date of first dose until the end of active follow-up.

Section 9.7.2.1 Urine, plasma, and serum based biomarker analysis

This section was changed as a result of Modification 9.

Old text:

9.7.2.1 Urine and serum based biomarker analysis

- Urine and serum from blood samples (Cycle 1, Day 1; Cycle 4, Day 1; and EOT/disease progression) may be evaluated for expression levels of bone related biomarkers. Elevated levels of bone biomarkers are indicative of more aggressive disease and are prognostic of worse long-term clinical outcome. In this study, levels of bone biomarkers (measured before, during, and after treatment) that are indicative of bone remodeling (e.g., bone ALP, procollagen type I N-terminal propeptide) and bone resorption (e.g., urine N-terminal telopeptide and I collagen telopeptide /serum C-terminal telopeptide of type I collagen) may be evaluated and correlated with clinical outcomes (including SSEs, survival, and levels of other biomarkers).

New text:

9.7.2.1 Urine, plasma, and serum based biomarker analysis

- Urine, serum, and plasma from blood samples (Cycle 1, Day 1; Cycle 4, Day 1; and EOT/disease progression) may be evaluated for expression levels of bone related biomarkers. Elevated levels of bone biomarkers are indicative of more aggressive disease and are prognostic of worse long-term clinical outcome. In this study, levels of bone biomarkers (measured before, during, and after treatment) that are indicative of bone remodeling (e.g., bone ALP, procollagen type I N-terminal propeptide) and bone resorption (e.g., urine N-terminal telopeptide and I collagen telopeptide /serum C-terminal telopeptide of type I collagen) may be evaluated and correlated with clinical outcomes (including SSEs, survival, and levels of other biomarkers).

Section 16.3 Calculation for glomerular filtration rate

This section was changed as a result of Modification 15.

Old text:

The formula ~~is as follows~~:

~~GFR (mL/min/1.73m^2) = 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.~~

New text:

The formula can be found at the following web site:

http://www.kidney.org/professionals/kdoqi/gfr_calculator

15.2 Amendment 2

Amendment 2 (dated 29 APR 2015) is an amendment to the Version 2.0 of the protocol, dated 16 DEC 2014. Changes to the protocol include:

- Clarified software used to calculate sample size and clarified calculation of dropout rate per request of the French Ethics Committee

- Updated the inclusion criteria to specify that new anticoagulants may or may not require INR/PTT monitoring are allowed
- Added exclusion for hypersensitivity for active substance or any excipients for patient safety
- Added exclusion criteria for known presence of osteonecrosis of jaw
- Revised exclusion criteria regarding platelet transfusions to be within 4 weeks prior to randomization for patient safety
- Revised exclusion criterion regarding use of biologic response modifiers to be within 4 weeks of randomization for clarification
- Clarified definition of soft tissue lesions
- Updated guidance for management of thrombocytopenia for recovery to Grade 1 or less before restarting radium-223 treatment to ensure enough bone marrow reserve for subsequent lines of chemotherapy
- Clarified that anti-cancer treatment must be continued with radium-223 and subject can continue radium-223 dichloride/placebo until completion or until any withdrawal criteria are met. Clarified that administration of radium-223 monotherapy is not allowed
- Clarified documentation of menopausal status based on feedback from the sites
- Provided updated information on dosing used in study BC1-09
- Added FDG PET scan as an adjunct to CT/MRI in line with RECIST 1.1 guidelines based on feedback from participating sites and regulatory authorities. Guidance was provided to ensure that this additional imaging modality is used for confirmation of new disease only, in compliance with the RECIST 1.1 criteria
- Updated inclusion criteria to include bone lesions asymptomatic
- Updated inclusion criteria requirements for duration of laboratory assessments prior to randomization
- Updated all relevant sections of text for consistency with timing of BPI-SF questionnaire
- Specified methods for determining HER2 status in description of screening period to be consistent with the rest of the protocol
- Clarified window between administrations of study drug must be 4 weeks
- Updated requirement for hemoglobin to be ≥8 g/dL instead of 9 g/dL as per investigator input
- Added a requirement that all relevant symptoms related to SSEs be recorded as AEs for consistency within the document

- Specified timing for coagulation panel to allow required interval prior to treatment to ensure timing is within proper safety parameters
- Changed timing of the CT/MRI confirmatory scan from 8 weeks to 6 to 8 weeks
- Clarified timing of radiological tumor assessment during active follow-up period with clinic visits
- As per PI input further treatment with exemestane and everolimus must be allowed if it is the best treatment option for the subject according to the local standard of practice
- Updated timing for obtaining samples of hematology, clinical chemistry, coagulation panel, and pregnancy test to be within 72 hours
- Clarified description of standard of care hormonal treatment background therapy per investigator feedback
- Updated all relevant protocol sections for consistency with screening procedures

15.2.1 Overview of changes to the study

Modification 1

Clarified software used to calculate sample size and clarified calculation of dropout rate per request of the French Ethics Committee.

Section affected includes:

- 10.4 Determination of sample size

Modification 2

Updated the inclusion criteria to specify that new anticoagulants may or may not require INR/PTT monitoring are allowed.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria
- Table 9-1: Schedule of assessments
- 9.2.1 Screening Period (Visits 0 to 1)

Modification 3

Added exclusion for hypersensitivity for active substance or any excipients for patient safety.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion

- 6.2 Exclusion Criteria

Modification 4

Added exclusion criteria for known presence of osteonecrosis of jaw.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.2 Exclusion Criteria
- 7.4.6 Dose adjustments, delays, and treatment discontinuations

Modification 5

Revised exclusion criteria regarding platelet transfusions to be within 4 weeks prior to randomization for patient safety.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.2 Exclusion criteria
- 8.1.2 Permitted concomitant therapy
- 9.2.3 Treatment period

Modification 6

Revised exclusion criterion regarding use of biologic response modifiers to be within 4 weeks of randomization for clarification.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.2 Exclusion criteria
- 8.1.2 Permitted concomitant therapy

Modification 7

Clarified definition of soft tissue lesions.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

- 16.2 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Modification 8

Updated guidance for management of thrombocytopenia for recovery to Grade 1 or less before restarting radium-223 treatment to ensure enough bone marrow reserve for subsequent lines of chemotherapy.

Sections affected include:

- 7.4.6 Dose adjustments, delays, and treatment discontinuations
- 7.4.7 Supportive care guidelines
- 9.2.3 Treatment period

Modification 9

Clarified that anti-cancer treatment must be continued with radium-223 and subject can continue radium-223 dichloride/placebo until completion or until any withdrawal criteria are met. Clarified that administration of radium-223 monotherapy is not allowed.

Sections affected include:

- Synopsis: Methodology
- 5.1.1 Study periods and duration
- 6.3.1.1 Withdrawal from treatment period (collection of follow-up data)

Modification 10

Clarified documentation of menopausal status based on feedback from the sites.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria
- Table 9-1: Schedule of assessments
- 9.2.1 Screening period (Visits 0 to 1)

Modification 11

Provided updated information on dosing used in study BC1-09.

Section affected includes:

- 3.4.1.3 Dosing rationale

Modification 12

Added FDG PET scan as an adjunct to CT/MRI in line with RECIST 1.1 guidelines based on feedback from participating sites and regulatory authorities. Guidance was provided to ensure that this additional imaging modality is used for confirmation of new disease only, in compliance with the RECIST 1.1 criteria.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria
- Table 9-1: Schedule of assessments
- 9.2.1 Screening period (Visit 0 to 1)
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up
- 9.2.6 Radiological assessment: tumor and response evaluation
- 16.2 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Modification 13

Updated inclusion criteria to include bone lesions asymptomatic.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 14

Updated inclusion criteria requirements for duration of laboratory assessments prior to randomization.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 15

Updated for consistency with timing of BPI-SF questionnaire.

Sections affected include:

- 8.1.2 Permitted concomitant therapy
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up
- 9.4.2.2 Secondary efficacy endpoints

Modification 16

Specified methods for determining HER2 status in description of screening period to be consistent with the rest of the protocol.

Section affected includes:

- 9.2.1 Screening period (Visits 0 to 1)

Modification 17

Clarified window between administrations of study drug must be 4 weeks.

Section affected includes:

- 9.2.3 Treatment period

Modification 18

Updated requirement for hemoglobin to be ≥8 g/dL instead of 9 g/dL as per investigator input.

Section affected includes:

- 9.2.3 Treatment period

Modification 19

Added a requirement that all relevant symptoms related to SSEs be recorded as AEs for consistency within the document.

Sections affected include:

- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

- 9.2.3.2 Visits 3, 5, and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits

Modification 20

Specified timing for coagulation panel to allow required interval prior to treatment to ensure timing is within proper safety parameters.

Section affected includes:

- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

Modification 21

Changed timing of the CT/MRI confirmatory scan from 8 weeks to 6 to 8 weeks.

Sections affected include:

- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 16.2 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Modification 22

Clarified timing of radiological tumor assessment during active follow-up period with clinic visits.

Sections affected include:

- Synopsis: Methodology
- 5.1.1 Study periods and duration

Modification 23

As per PI input further treatment with exemestane and everolimus must be allowed if it is the best treatment option for the subject according to the local standard of practice.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- Synopsis: Methodology
- 5.1.1 Study periods and duration
- 6.1 Inclusion criteria
- 7.1 Treatments to be administered

- 8.1.2 Permitted concomitant therapy
- 9.2.3 Treatment period

Modification 24

Updated timing for obtaining samples of hematology, clinical chemistry, coagulation panel, and pregnancy test to be within 72 hours.

Sections affected include:

- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up

Modification 25

Clarified description of standard of care hormonal treatment background therapy per investigator feedback

Section affected includes:

- 8.1.2 Permitted concomitant therapy

Modification 26

Updated all relevant protocol sections for consistency with screening procedures

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria
- 6.2 Exclusion criteria

15.2.2 Changes to the protocol text

Synopsis: Diagnosis and main criteria for inclusion and exclusion, and Section 6.1 Inclusion criteria

These sections were changed as a result of Modifications 2, 7, 10, 12, 13, 14, 23, and 26.

Old text:

2. Documentation of histological or cytological confirmation of estrogen receptor positive (ER+) and HER2 negative adenocarcinoma of the breast must be available. HER2 status should be determined by an accredited/Ministry of Health approved laboratory by immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), ~~or~~ chromogenic in situ hybridization (CISH).

5. Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible.

   Note: In premenopausal subjects, ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist/antagonist is permitted for induction of ovarian suppression. ~~Baseline~~ estradiol assay ~~must be~~ <20 pg/mL at screening.

   - age <55 years and one year or more of amenorrhea with an estradiol assay <20 pg/mL
   - bilateral ~~oophorectomy~~

6. Subjects with bone dominant disease ~~(with or without metastases in soft tissue including lymph nodes)~~ with at least 2 skeletal metastases identified at baseline by bone scintigraphy and confirmed by computed tomography (CT)/magnetic resonance imaging (MRI).

~~18F sodium fluoride~~ positron emission/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

Subjects enrolled in the current study will start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride/placebo. Subjects already receiving the single agent hormone treatment prior to study entry are not eligible. ~~Combination hormonal treatment is not allowed.~~

12. Asymptomatic or mildly symptomatic breast cancer. A worst pain score (WPS) of 0 to 1 on the Brief Pain Inventory-Short Form (BPI-SF) Question #3 (worst pain in the last 24 hours) will be considered asymptomatic, and a WPS of 2 to 3 will be considered mildly symptomatic. This is to be assessed once during the screening period.

15. Laboratory requirements:
    - Platelet count ≥100 x 10^9/L without platelet transfusion within ~~3~~ weeks prior to randomization
    - Hemoglobin ≥9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin within ~~6~~ weeks prior to randomization

- International normalized ratio of prothrombin time (INR) and partial thromboplastin time (PTT) or activated PTT ≤1.5 x ULN. Subjects treated with warfarin ~~or~~ heparin will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved ~~(as defined by local standard of care and based on prestudy INR/PTT values)~~

New text:

2. Documentation of histological or cytological confirmation of ER+ and HER2 negative adenocarcinoma of the breast must be available. HER2 status should be determined by an accredited/Ministry of Health approved laboratory by immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH) or other validated in situ hybridization (ISH) assay for detection of HER2 gene expression.

5. Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible.
   Note: In premenopausal subjects, ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist/antagonist is permitted for induction of ovarian suppression if the plasma/serum estradiol assay is <20 pg/mL at screening within 7 days of randomization.

   - age <55 years and one year or more of amenorrhea with a plasma/serum estradiol assay <20 pg/mL, within 7 days of randomization
   - bilateral ovariectomy

6. Subjects with bone dominant disease with at least 2 skeletal metastases identified at baseline by bone scintigraphy and confirmed by computed tomography (CT)/magnetic resonance imaging (MRI). Presence of metastases in soft tissue (skin, subcutaneous, muscle, fat, lymph nodes) is allowed.

   F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (See also Appendix 16.2).

   FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

Subjects enrolled in the current study will start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride/placebo. Subjects already receiving the single agent hormone treatment prior to study entry are not eligible.

12. Bone lesions related asymptomatic or mildly symptomatic breast cancer. A worst pain score (WPS) of 0 to 1 on the Brief Pain Inventory-Short Form (BPI-SF) Question #3 (worst pain in the last 24 hours) will be considered asymptomatic, and a WPS of 2 to 3 will be considered mildly symptomatic. This is to be assessed once during the screening period

15. Laboratory requirements:
    - Platelet count ≥100 x 10^9/L without platelet transfusion within 4 weeks prior to randomization
    - Hemoglobin ≥9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin within 4 weeks prior to randomization
    - International normalized ratio of prothrombin time (INR) and partial thromboplastin time (PTT) or activated PTT ≤1.5 x ULN at study entry. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban or aspirin (e.g. ≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label

Synopsis: Diagnosis and main criteria for inclusion and exclusion, Exclusion criteria and Section 6.2 Exclusion criteria

These sections were changed as a result of Modifications 3, 4, 5, 6, and 26.

Old text:

1. HER2-positive breast cancer (IHC=3+, positive FISH~~/or positive~~ CISH); equivocal or unknown HER2 status
   Note: Subjects with 3+ by IHC cannot be chosen regardless of their FISH/CISH status and those with positive FISH/CISH ~~(≥2 amplifications)~~ cannot be chosen either, regardless of the IHC findings. Subjects with 2+ by IHC will not be eligible if no negative FISH/CISH is available.

13. Blood transfusions or use of erythropoietin within ~~6~~ weeks prior to randomization. ~~Platelet transfusions are not allowed within 3 weeks prior to randomization.~~
14. Use of biologic response modifiers, such as granulocyte macrophage-colony-stimulating factor (GM-CSF) or granulocyte-colony-stimulating factor (G-CSF), within ~~6~~ weeks prior to randomization

New text:

1. HER2-positive breast cancer (IHC=3+, positive FISH/CISH/other ISH validated assay); equivocal or unknown HER2 status
   Note: Subjects with 3+ by IHC cannot be chosen regardless of their FISH/CISH/other ISH validated assay status and those with positive FISH/CISH/other ISH validated assay cannot be chosen either, regardless of the IHC findings. Subjects with 2+ by IHC will not be eligible if no negative FISH/CISH/other ISH validated assay for detection of HER2 gene expression is available.

13. Blood transfusions, platelet transfusions or use of erythropoietin within 4 weeks prior to randomization.
14. 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 randomization

Added text:

20. Known hypersensitivity to the active substance or to any of the excipients of radium-223 dichloride
21. Known presence of osteonecrosis of the jaw

Synopsis: Methodology, Section 5.1.1 Study periods and duration

These sections were changed as a result of Modifications 9, 22, and 23.

Old text:

All subjects will receive hormonal treatment with a single agent and supportive care as background treatment according to the local standard of practice. ~~Combination hormonal treatment is not allowed~~. Subjects enrolled in the current study will start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride or placebo. For subject's convenience injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride or placebo injection. Subjects already receiving hormone treatment prior to study entry are not eligible.

New text:

All subjects will receive hormonal treatment with a single agent and supportive care as background treatment according to the local standard of practice. Subjects enrolled in the current study will start treatment with the single hormone agent after randomization either

before or simultaneously to the first injection of radium-223 dichloride or placebo. For subject's convenience injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride or placebo injection. Subjects already receiving hormone treatment prior to study entry are not eligible.

Added text:

If radium-223 dichloride/placebo treatment is still ongoing but the background treatment is no longer considered a treatment option and the subject must start another hormonal treatment, the subject can continue radium-223 dichloride/placebo until completion or until any withdrawal criteria are met.

If however, the background hormonal treatment or further standard of care hormonal anticancer therapy are discontinued, radium-223 dichloride/placebo must also be discontinued.

Subjects who experience an SSE during radium-223 dichloride/placebo treatment may continue treatment until completion or until any withdrawal criteria are met, if in the opinion of the Investigator the subject continues to derive benefit. In case an SSE is not defined as progression, the subject will continue to be followed as per protocol until radiological progression.

Radiological tumor assessment will be performed every 12 weeks, independently of the frequency of the visits, until radiological disease progression is documented.

Section 3.4.1.3 Dosing rationale

This section was changed as result of Modification 11.

Added text:

The same dose was used in a phase II breast cancer study BC1-09 which provided preliminary evidence of the effects of radium-223 on bone markers, BPI score, and tumor metabolism assessed by serial F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging and supports further investigations to confirm effectiveness of radium-223 in treating bone metastases in patients with breast cancer and bone-dominant disease. Data were communicated at the San Antonio Breast Cancer Symposium 2011 and published in 2014. (40) The study results are presented in detail in Section 3.4.1.1.

Section 6.3.1.1 Withdrawal from treatment period (collection of follow-up data)

This section was changed as a result of Modification 9.

Added text:

- If background hormonal treatment or further standard of care protocol permitted concomitant systemic anti-cancer therapy are discontinued, radium-223 dichloride/placebo must also be discontinued.

Subjects who experience an SSE during study treatment may continue to receive radium-223 dichloride (or placebo) until completion or until any of the above withdrawal criteria are met, if the Investigator feels the subject will receive clinical benefit.

Old text:

Subjects who experience disease progression (bone or non-bone) may continue to receive radium-223 dichloride (or placebo) until completion if the Investigator feels the subject will receive clinical benefit. These subjects ~~may~~ continue to receive additional hormonal treatments according to the local standard of care. If, however, chemotherapy is required as the next line of treatment, study treatment will be permanently discontinued, as concurrent chemotherapy administration is an exclusion criterion.

New text:

Subjects who experience disease progression (bone or non-bone) may continue to receive radium-223 dichloride (or placebo) until completion or until any of the above withdrawal criteria are met, if the Investigator feels the subject will receive clinical benefit. These subjects must continue to receive additional hormonal or other protocol permitted concomitant systemic anticancer treatments according to the local standard of care. If however, chemotherapy is required as the next line of treatment, study treatment will be permanently discontinued, as concurrent chemotherapy administration is an exclusion criterion.

Section 7.1 Treatments to be administered

This section as changed as a result of Modification 23

Old text:

Subjects enrolled in the current study will start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride or placebo. For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride/placebo injection. Subjects already receiving treatment with single hormone agent prior to study entry cannot be enrolled. ~~Combination hormonal treatment is not allowed~~.

New text:

Subjects enrolled in the current study will start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride or placebo. For subject's convenience, injections of fulvestrant may be scheduled on the

same day of the radium-223 dichloride/placebo injection. Subjects already receiving treatment with single hormone agent prior to study entry cannot be enrolled.

Section 7.4.6 Dose adjustments, delays, and treatment discontinuations

This section was changed as a result of Modifications 4 and 8.

Deleted text:

~~If hormonal treatment must be delayed by more than 4 weeks for recovery of AEs, the subject should discontinue radium-223 dichloride/placebo and should enter the follow-up period.~~

Old text:

Thrombocytopenia: In case of thrombocytopenia NCI-CTCAE Grade 3 to 4, study drug administration should be delayed until recovery to CTCAE Grade ~~2~~ (minimum subjects with a platelet count ~~50~~ x 10^9/L) or better before the next study drug administration.

New text:

Thrombocytopenia: In case of thrombocytopenia NCI-CTCAE Grade 3 to 4, study drug administration should be delayed until recovery to CTCAE Grade 1 (minimum subjects with a platelet count 75 x 10^9/L) or better before the next study drug administration.

Added text:

Osteonecrosis of jaw

There is no specific radium-223 dose modification guidance for patients who develop osteonecrosis of jaw during radium-223 treatment. The management plan of individual patients who develop osteonecrosis of jaw in the course of the study should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in osteonecrosis of jaw, and in accordance with the local labeling of denosumab and bisphosphonates.

Section 7.4.7 Supportive care guidelines

This section was changed as a result of Modification 8.

Old text:

- Severe thrombocytopenia (CTCAE Grade 4 [<25.0 x 10^9/L]) or bleeding with CTCAE Grade 3 to 4 thrombocytopenia (<50.0 x 10^9/L): multiple platelet transfusions may be required to maintain platelet count >~~50~~ x 10^9/L ~~or higher~~ if clinically indicated to control bleeding. Epsilon aminocaproic acid may be given to subjects with mucosal bleeding and platelet count CTCAE Grade 3 to 4.

New text:

- Severe thrombocytopenia (CTCAE Grade 4 [<25.0 x 10^9/L]) or bleeding with CTCAE Grade 3 to 4 thrombocytopenia (<50.0 x 10^9/L): multiple platelet transfusions

may be required to maintain platelet count ≥75 x 10^9/L if clinically indicated to control bleeding. Epsilon aminocaproic acid may be given to subjects with mucosal bleeding and platelet count CTCAE Grade 3 to 4.

Section 8.1.2 Permitted concomitant therapy

This section was changed as a result of Modifications 5, 6, 15, 23, and 25.

Old text:

- Subjects enrolled in the current study will start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride/placebo. For subject's convenience injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride or placebo injection. Subjects already receiving treatment with a single hormone agent prior to study entry cannot be enrolled. ~~Combination hormonal treatment is not allowed.~~

New text:

- Subjects enrolled in the current study will start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride/placebo. For subject's convenience injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride or placebo injection. Subjects already receiving treatment with a single hormone agent prior to study entry cannot be enrolled.

Added text:

- Following discontinuation of the single agent background hormone treatment, further lines of hormone treatment as well as exemestane in combination with everolimus, may be administered concomitantly with radium-223 dichloride/placebo, in line with the local standard of practice.

Old text:

- Blood transfusions and treatment with erythropoietin stimulating agents are allowed after randomization (if required to ensure that the treatment range for Hb is met at Day 1 of each cycle) but not within ~~6~~ weeks prior to randomization. Platelet transfusions are allowed after randomization but not within ~~3~~ weeks prior to randomization.
- 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. These drugs are not allowed within ~~6~~ weeks prior to randomization.
- Analgesic use will be captured via a subject diary and the eCRF (analgesic consumption diary and recorded analgesics, respectively, see schedule of assessments, Table 9-1). Subjects will be asked to track their analgesic use on an analgesic consumption diary for 1 week prior to their clinic visit. ~~Each day the pain question is~~

~~asked of the subject, the subject should be asked to record any pain medication she took that day.~~ Any medication taken for pain, whether for palliation of bone pain or relief of other type of pain, and any changes should be recorded in the eCRF at each visit. Note that EBRT treatment should be recorded in the eCRFs until end of the active follow-up period without clinic visits.

New text:

- Blood transfusions and treatment with erythropoietin stimulating agents are allowed after randomization (if required to ensure that the treatment range for Hb is met at Day 1 of each cycle) but not within 4 weeks prior to randomization. Platelet transfusions are allowed after randomization but not within 4 weeks prior to randomization.
- 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. These drugs are not allowed within 4 weeks prior to randomization.
- Analgesic use will be captured via a subject diary and the eCRF (analgesic consumption diary and recorded analgesics, respectively, see schedule of assessments, Table 9-1). Subjects will be asked to track their analgesic use on an analgesic consumption diary for 1 week prior to their clinic visit. Any medication taken for pain, whether for palliation of bone pain or relief of other type of pain, and any changes should be recorded in the eCRF at each visit. Note that EBRT treatment should be recorded in the eCRFs until end of the active follow-up period without clinic visits.

Table-9.1 Schedule of Assessments

This section was changed as a result of Modifications 2, 10, and 12.

Old text:

k. Adverse events will be collected through ~~4 weeks~~ post the last administration of study medications. Investigator should check for occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and any new malignancy.

t. The screening clinical chemistry and hematology values are recommended to be measured within 1 week prior to randomization ~~if feasible (a 2 week maximum is permitted)~~ and the first injection should be done as soon as possible after randomization.

x. PT, INR, and PTT: Subjects treated with warfarin or heparin will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is

achieved ~~(as defined by local standard of care and based on pre-study INR/PTT values)~~.

y. Pre-menopausal women must have a negative serum pregnancy test performed within 7 days prior to randomization, prior to each study drug administration, and EOT. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. An estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea.

bb. A historic bone scan is acceptable if taken within 3 weeks of randomization. If one is not available, it will be required as part of the protocol procedures within the screening period. ~~^{18}F-sodium fluoride positron emission tomography/CT~~ scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

cc. Chest/abdominal/pelvic magnetic resonance imaging will be accepted instead of chest/abdominal/pelvic CT.

New text:

k. Adverse events will be collected through <u>30 days</u> post the last administration of study medications. Investigator should check for occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and any new malignancy.

t. The screening clinical chemistry and hematology values are recommended to be measured within 1 week prior to randomization and the first injection should be done as soon as possible after randomization.

x. PT, INR, and PTT: Subjects treated with warfarin, heparin<u>, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily)</u> will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved <u>for anticoagulants that require their monitoring as per local label.</u>

y. Pre-menopausal women must have a negative serum pregnancy test performed within 7 days prior to randomization, prior to each study drug administration, and EOT. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. A <u>plasma/serum</u> estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea.

bb. A historic bone scan is acceptable if taken within 3 weeks of randomization. If one is not available, it will be required as part of the protocol procedures within the screening period. FDG PET/CT or NaF PET /CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

cc. Chest/abdominal/pelvic magnetic resonance imaging will be accepted instead of chest/abdominal/pelvic CT. FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

Section 9.2.1 Screening period (Visits 0 to 1)

This section was changed as a result of Modifications 2, 10, 12, and 16.

Added text:

- Record disease history: HER2 status can be determined by evaluating for HER2 over-expression using IHC and/or HER2 gene amplification using in situ hybridization, e.g., FISH or CISH. For subjects with equivocal HER2 IHC (IHC 2+), it is recommended that HER2 status be confirmed using a validated assay for HER2 gene amplification.

Added text:

- FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

Old text:

- ^{18}~~F sodium fluoride~~ PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

New text:

- FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

Old text

- A coagulation panel: prothrombin time (PT), PTT, and INR. Subjects treated with warfarin ~~or~~ heparin will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of

INR/PTT will be required until stability is achieved ~~(as defined by local standard of care and based on pre-study INR/PTT values)~~.

New text:

- A coagulation panel: prothrombin time (PT), PTT, and INR. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban or aspirin (e.g. ≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label.

Old text

- Estradiol assay: a~~n~~ estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea.

New text

- Estradiol assay: a plasma/serum estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea.

Section 9.2.3 Treatment period

This section was changed as a result of Modifications 5, 8, 17, 18, and 23.

Added text:

- During the treatment period, the subject will visit the study site at regular intervals. Radium-223 dichloride or placebo will be injected at 4-week intervals for 6 cycles on an outpatient basis (Section 9.1). The minimum time window between 2 injections of radium-223 dichloride/placebo must be 4 weeks. All ongoing subjects at the time of study termination will finish study treatment with radium-223 dichloride or placebo as part of the study.

Old text:

- All subjects will receive background standard of care hormonal treatment for breast cancer. Subjects enrolled in the current study will start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride/placebo. For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride/placebo injection. Subjects already receiving treatment with a single hormone agent prior to study entry cannot be enrolled. ~~Combination hormonal treatment is not allowed.~~

Before the first administration of radium-223 dichloride/placebo (within 3 days), the ANC should be ≥1.5 x 10^9/L, the platelet count ≥100 x 10^9/L, and Hb ≥~~9~~ g/dL.

Blood transfusions and treatment with erythropoietin stimulating agents are allowed after randomization but not within ~~6~~ weeks prior randomization. Platelet transfusions are allowed after randomization but not within ~~3~~ weeks prior to randomization.

The following hematological parameters value should be met prior to each subsequent radium-223 dichloride/placebo administration: Hb level ≥8.0 g/dL, ANC ≥1.0 x 10^9/L, and the platelet count ≥~~50~~ x 10^9/L.

If ANC is lower than 1.0 x 10^9/L or platelet count is lower than ~~50~~ x 10^9/L, radium-223 dichloride/placebo injection should be delayed until recovery to ANC ≥1.0 x 10^9/L and platelet count ≥~~50~~ x 10^9/L.

New text:

- All subjects will receive background standard of care hormonal treatment for breast cancer. Subjects enrolled in the current study will start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride/placebo. For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride/placebo injection. Subjects already receiving treatment with a single hormone agent prior to study entry cannot be enrolled.

Before the first administration of radium-223 dichloride/placebo (within 3 days), the ANC should be ≥1.5 x 10^9/L, the platelet count ≥100 x 10^9/L, and Hb ≥<u>8.0</u> g/dL.

Blood transfusions and treatment with erythropoietin stimulating agents are allowed after randomization but not within <u>4</u> weeks prior randomization. Platelet transfusions are allowed after randomization but not within <u>4</u> weeks prior to randomization.

The following hematological parameters value should be met prior to each subsequent radium-223 dichloride/placebo administration: Hb level ≥8.0 g/dL, ANC ≥1.0 x 10^9/L, and the platelet count ≥<u>75</u> x 10^9/L.

If ANC is lower than 1.0 x 10^9/L or platelet count is lower than <u>75</u> x 10^9/L, radium-223 dichloride/placebo injection should be delayed until recovery to ANC ≥1.0 x 10^9/L and platelet count ≥<u>75</u> x 10^9/L.

Section 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

This section was changed as a result of Modifications 12, 15, 19, 20, and 21.

Old text:

- BPI-SF questionnaire will be completed ~~for1 week (6 days plus the day of the visit)~~ prior to ~~the visit~~ and should be checked for completion at the visit.

New text:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit.

Added text:

Note: Specifically for this study, relevant symptoms related to SSEs should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug

Old text:

A coagulation panel (within 72 hours prior ~~before radium-223 dichloride or placebo~~ administration) PT, PTT, and INR.

New text:

A coagulation panel (blood sample to be taken within 72 hours prior to each study drug administration: PT, PTT, and INR.

Old text:

- Bone technetium-99m scan with careful identification of all disease-related hotspots. All visible bone lesions must also be imaged with conventional anatomical imaging procedures, such as SPECT-CT/MRI or CT or MRI scan (with or without contrast media). All new bone lesions or progression of existing bone lesion(s) identified on a technetium-99m bone scan will need confirmatory CT or MRI imaging. In case of a new lesion or of progression of existing bone lesion(s) observed on a bone scan that is not confirmed by CT/MRI, progression will not be declared until the CT/MRI confirmation of progression occurs. A CT/MRI confirmatory scan must take place 8 weeks after the new lesion or progression of existing lesion(s) was observed on bone scan. Modified RECIST version 1.1 (mRECIST 1.1) criteria will be applied to declare a PFS event.

New text:

- Bone technetium-99m scan with careful identification of all disease-related hotspots. All visible bone lesions must also be imaged with conventional anatomical imaging procedures, such as SPECT-CT/MRI or CT or MRI scan (with or without contrast media). All new bone lesions or progression of existing bone lesion(s) identified on a technetium-99m bone scan will need confirmatory CT or MRI imaging. In case of a new lesion or of progression of existing bone lesion(s) observed on a bone scan that is not confirmed by CT/MRI, progression will not be declared until the CT/MRI confirmation of progression occurs. A CT/MRI confirmatory scan must take place 6 to 8 weeks after the new lesion or progression of existing lesion(s) was observed on

bone scan. Modified RECIST version 1.1 (mRECIST 1.1) criteria will be applied to declare a PFS event.

Added text:

FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

Old text:

- ~~^{18}F sodium fluoride~~ PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

New text:

- FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

Section 9.2.3.2 Visits 3, 5, and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits

This section was changed as a result of Modification 19.

Added text:

Note: Specifically for this study, relevant symptoms related to SSEs should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.

Section 9.2.3.3 End of treatment visit

This section was changed was changed as a result of Modifications 12, 15, 21, and 24.

Old text:

- BPI-SF questionnaire will be completed for ~~1 week (6 days plus the day of the visit)~~ prior to ~~the visit~~ and should be checked for completion at the visit

New text:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit

Added text:

- Blood draws for hematology (within 72 hours of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential
- Blood draws for clinical chemistry (within 72 hours of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin
- A coagulation panel (within 72 hours of the visit): PT, PTT, and INR.
- Pregnancy test (within 72 hours of the visit): pre-menopausal women must have a negative serum pregnancy test. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.

    - Bone technetium-99m scan with careful identification of all disease-related hotspots. All visible bone lesions must also be imaged with conventional anatomical imaging procedures such as SPECT-CT/MRI or CT or MRI scan (with or without contrast media). All new bone lesions or progression of existing bone lesion(s) identified on a technetium-99m bone scan will need confirmatory CT or MRI imaging. In case of a new lesion or of progression of existing bone lesion(s) observed on a bone scan that is not confirmed by CT/MRI, progression will not be declared until the CT/MRI confirmation of progression occurs. A CT/MRI confirmatory scan must take place 6 to 8 weeks after the new lesion or progression of existing lesion(s) was observed on bone scan.

Added text:

FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

Old text:

- ^{18}~~F sodium fluoride PET~~/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

New text:

- FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

Section 9.2.4.1 Active follow-up with clinic visits

This section was changed as a result of Modifications 12, 15, and 24.

Old text:

- BPI-SF questionnaire will be completed ~~for 1 week (6 days plus the day of the visit)~~ prior to the visit and should be checked for completion at the visit

New text:

- BPI-SF questionnaire will be completed prior to <u>any other study assessments/procedures</u> and should be checked for completion at the visit

Old text:

- Record concomitant medications/therapy ~~(concomitant medications used to treat any grade adverse drug reaction only)~~

New text:

- Record concomitant medications/therapy

Added text:

- Blood draws for hematology <u>(within 72 hours of the visit)</u>: hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential
- Blood draws for clinical chemistry <u>(within 72 hours of the visit)</u>: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin[1]

Added text:

<u>FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).</u>

Old text:

- ^{18}~~F-sodim fluoride~~ PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

New text:

- <u>FDG PET/CT or NaF</u> PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

Section 9.2.4.3 End of active follow-up

This section was changed as a result of Modifications 12, 15, and 24.

Old text:

- BPI-SF questionnaire will be completed ~~for 1 week (6 days plus the day of the visit)~~ prior to the visit and should be checked for completion at the visit

New text:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit

Added text:

- Blood draws for hematology (within 72 hours of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential
- Blood draws for clinical chemistry (within 72 hours of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin

Added text:

FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

Old text:

- ^{18}~~F-sodium fluoride~~ PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

New text:

- FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

Section 9.2.6 Radiological assessment: tumor and response evaluation

This section was changed as a result of Modification 12.

Old text:

Radiological tumor evaluation, using the mRECIST 1.1 guidelines (See Section 16.2), must be performed ~~at baseline (~~within 3 weeks prior to randomization~~)~~, 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration and every 12 weeks thereafter until PD

(radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS.

New text:

Radiological tumor evaluation, using the mRECIST 1.1 guidelines (See Section 16.2), must be performed within 3 weeks prior to randomization, at 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration and every 12 weeks thereafter until PD (radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS.

Old text:

Standard of care CT/MRI and standard of care bone scans done within 3 weeks ~~prior to~~ randomization are acceptable provided they are in line with protocol requirements criteria (anatomic coverage chest/abdomen/pelvis and in line with RECIST 1.1/mRECIST 1.1 guidelines for image acquisition). All suspected sites of disease should be imaged.

New text:

Standard of care CT/MRI done within 3 weeks of randomization and standard of care bone scans done within 3 weeks of randomization are acceptable provided they are in line with protocol requirements criteria (anatomic coverage chest/abdomen/pelvis and in line with RECIST 1.1/mRECIST 1.1 guidelines for image acquisition). All suspected sites of disease should be imaged.

Added text:

FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study. The same lesions identified at baseline must be evaluated at follow-up assessments using the same technique and preferably by the same Investigator/radiologist.

Section 9.4.2.2 Secondary efficacy endpoints

This section was changed as a result of Modification 15.

Old text:

Time to pain progression is defined as the interval from randomization to the first date a subject experiences pain progression based on WPS. Pain progression 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

New text:

Time to pain progression is defined as the interval from randomization to the first date a subject experiences pain progression based on WPS. Pain progression is defined as an increase of 2 or more points in the "Worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥4 weeks apart

Old text:

Assessments will occur ~~daily for one week (including~~ the visit ~~date)~~. An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 ~~daily~~ questions.

New text:

Assessments will occur on the day of the visit. An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 questions.

Section 9.6.1.4 Reporting of serious adverse events

This section was changed as a result of consistency.

Old text:

For subjects who die ~~>4 weeks~~ after the administration of the last study treatment, submission of the AE page of the eCRF is not required.

New text:

For subjects who die >30 days after the administration of the last study treatment, submission of the AE page of the eCRF is not required.

Section 10.4 Determination of sample size

This section was changed as a result of Modification 1.

Old text:

Sample size is calculated based on the primary endpoint, SSE-FS. Assuming a one-sided alpha of 0.1, power of 90%, with a median SSE-FS for the control group of ~~7 months~~ and a randomization ratio of 1:1 between treatments, approximately 119 events will be required to detect a 60% increase in SSE-FS for a total of 227 subjects in the 2 treatment groups combined. The targeted improvement of 60% is not based on a bibliographical reference.

New text:

Sample size is calculated based on the primary endpoint, SSE-FS. EAST 6.3 was used to calculate event number. Assuming a one-sided alpha of 0.1, power of 90%, with a median SSE-FS for the control group of 8.3 months and a randomization ratio of 1:1 between treatments, approximately 119 events will be required to detect a 60% increase in SSE-FS for

a total of 227 subjects in the 2 treatment groups combined. The dropout rate is assumed to be 15%. Dropout was taken into account when calculating the sample size and study duration. The targeted improvement of 60% is not based on a bibliographical reference.

Section 16.2 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

This section was changed as a result of Modifications 7, 12, and 21.

Old text:

Soft tissue lesions: Malignant finding in soft tissue (skin, subcutaneous, ~~and~~ muscle), including lymph nodes.

New text:

Soft tissue lesions: Malignant finding in soft tissue (skin, subcutaneous, muscle, fat, lymph nodes).

Added text:

If FDG PET/CT or FDG PET scan is performed as part of the standard of practice imaging, the results of the FDG PET scan can be used as a complement to CT scanning in the assessment of disease progression – based on occurrence of new lesions – as per the RECIST 1.1 algorithm (See section on New lesions and FDG PET imaging in this appendix).

FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

Added text:

- A new bone lesion or progression of existing bone lesion/s initially identified on a technetium-99m bone scan must be confirmed by CT or MRI. If confirmed by CT/MRI, the date of occurrence of the new lesion or of progression of existing bone lesion/s will be the date it was initially detected (by technetium-99m bone scan) even if the confirmation by CT/MRI was done at a subsequent scan. A CT/MRI confirmatory scan must take place 6 to 8 weeks after the new lesion or progression of existing lesion/s was observed on bone scan

Added text:

New lesions and FDG PET imaging

New lesions on the basis of FDG PET imaging can be identified according to the following algorithm:

- (-) FDG PET at baseline and (+) FDG PET at follow-up = PD based on a new lesion
- No FDG PET at baseline and (+) FDG PET at follow-up = PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of PD is the date of the initial FDG PET scan.

- No FDG PET at baseline and (+) FDG PET at follow-up corresponding to a pre-existing lesion on CT that is not progressing is **not** PD

Note: A 'positive' FDG PET scan lesion means one with uptake greater than twice that of the surrounding tissue on the attenuation corrected image

15.3 Amendment 4

Amendment 4 (dated 29 JUL 2015) is an amendment to the Version 3.0 of the protocol, dated 29 APR 2015. Changes to the protocol include:

- Added pain improvement as a secondary endpoint as patients can now be evaluated for pain improvement based on revision of exclusion criteria.
- Updated text to allow background hormonal treatment to be started as soon as possible after progression.
- Updated the quantification of radium-223 radioactivity in Xofigo® based on the revised primary standardization performed by the US NIST.
- Added text related to counting of SREs for clarification.
- Removed inclusion criteria 12 per objection from participating sites that majority of subjects with advanced breast cancer and bone disease would not be asymptomatic or mildly symptomatic.
- Changed estimated glomerular filtration rate from 60 to 30 to align with denosumab and bisphosphonates labeling and exclude only patients with severe renal impairment.
- Changed thrombocytopenia from grade 3 to grade 2 to for consistency.
- Removed completion of BPI-SF at screening based on revision of inclusion criteria.
- Changed body weight to be taken within 5 days to allow more time to receive results.
- Changed blood samples to be taken within 5 days to allow more time to receive results.
- Added collection time period for biomarkers to be within 5 days to allow more flexibility.
- Added text for the collection of scans that will be reviewed for retrospective analysis.
- Added new appendix to provide detailed guidance for the administration of the BPI-SF questionnaire.
- Added 12-week time interval for performance of assessments during active follow-up.
- Changed pregnancy test to be taken within 5 days to allow more time to receive results.
- Removed requirement for first dose of study treatment to occur 1 to 3 weeks after randomization.

- Removed requirement that bisphosphonates or denosumab to be administered at least 2 hours before study treatment.
- Modified text for clarification.
- The list of abbreviations was updated to reflect the usage of abbreviations in the amended protocol.

15.3.1 Overview of changes to the study

Modification 1

Added pain improvement as a secondary endpoint as patients can now be evaluated for pain improvement based on revision of inclusion criteria.

Sections affected include:

- Synopsis: Study objectives
- 4. Study objectives
- 5.1.2 Study endpoints
- 9.4.1 Efficacy variables
- 9.4.2.2 Secondary efficacy endpoints
- 10.3 Efficacy variables and planned statistical analyses

Modification 2

Updated text to allow background hormonal treatment to be started as soon as possible after progression. Subjects who initiated a new line of background hormone treatment within 15 days of randomization can be considered for the study, provided the other eligibility criteria are met. The change was discussed and agreed with the study statistician.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- Synopsis: Methodology
- 5.1.1 Study periods and duration
- 6.1 Inclusion criteria
- 7.1 Treatments to be administered
- 8.1.2 Permitted concomitant therapy
- 9.2.3 Treatment period

Modification 3

The quantification of radium-223 radioactivity in Xofigo® is based on the primary standardization performed by the US National Institute of Standards and Technology (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 Institute for Energy Technology (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 (52) and current measurements was confirmed and a revised NIST primary reference standard has been issued (53). 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 [53]) 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 CTAs have been initiated. The current standard (NIST 2010 [52]), dial setting and dose **will remain in effect** until a unique implementation date in Q2 2016 as agreed with FDA and EMA. 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 [52]) 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 [53]). 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 [52]) 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 [52]) 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 [53]), 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 [52]); 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 [53]) only), though the volume of radium-223 dichloride given to each subject will remain the same.

Sections affected include:

- Synopsis: Dose
- Synopsis: Methodology
- List of Abbreviations
- 3.4.1.3 Dosing rationale
- 5.1.1 Study periods and duration
- 7.1 Treatments to be administered
- 7.2.1.1 Radium-223 dichloride
- 7.4.1 Dose calibration
- 7.4.3 Radium-223 dose calculation
- 14. Reference list

Modification 4

Added text related to counting of SREs for clarification.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 5.1 Design overview
- 6.1 Inclusion criteria
- 10.1 General considerations

Modification 5

Removed inclusion criteria 12 per objection from participating sites that majority of subjects with advanced breast cancer and bone disease would not be asymptomatic or mildly symptomatic.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 6

Changed estimated glomerular filtration rate from 60 to 30 to align with denosumab and bisphosphonates labeling and exclude only patients with severe renal impairment.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 7

Changed thrombocytopenia from grade 3 to grade 2 to for consistency.

Sections affected include:

- 7.4.6 Dose adjustments, delays, and treatment discontinuations

Modification 8

Removed completion of BPI-SF at screening based on revision of inclusion criteria.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.1 Screening period (Visit 0 to 1)

Modification 9

Changed body weight to be taken within 5 days to allow more time to receive results.

Sections affected include:

- 7.4.3 Radium-223 dose calculation
- 9.1 Tabular schedule of evaluations
- 9.2.3 Treatment period
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

Modification 10

Changed blood samples to be taken within 5 days to allow more time to receive results.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.3 Treatment period
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up

Modification 11

Added collection time period for biomarkers to be within 5 days to allow more flexibility.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 9.7.2.1 Urine, plasma, and serum based biomarker analysis

Modification 12

Added text for the collection of scans that will be reviewed for retrospective analysis.

Sections affected include:

- 9.2.6 Radiological assessment: tumor and response evaluation

Modification 13

Added new appendix to provide detailed guidance for the administration of the BPI-SF questionnaire.

Sections affected include:

- Appendix 16.6 BPI-SF
- 14. Reference list

Modification 14

Added 12-week time interval for performance of assessments during active follow-up.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.4.1 Active follow-up with clinic visits

Modification 15

Changed pregnancy test to be taken within 5 days to allow more time to receive results.

Sections affected include:

- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit

Modification 16

Removed requirement for first dose of study treatment to occur 1 to 3 weeks after randomization as some countries will not be able to meet this requirement. It is not expected that the change will affect the safety of the subjects on study because they will undergo safety laboratory tests and will be assessed for AEs before first administration of Ra-223 dichloride to ensure they continue to meet the protocol requirements.

Sections affected include:

- 6. Study population
- 9.1 Tabular schedule of evaluations

Modification 17

Removed requirement that bisphosphonates or denosumab to be administered at least 2 hours before study treatment based on feedback from Clinical Pharmacology that any potential risk for interaction could be excluded. The change is being implemented across the Ra-223 clinical program.

Sections affected include:

- 7.1 Treatments to be administered
- 8.1.2 Permitted concomitant therapy

Modification 18

Modified text for clarification.

Sections affected include:

- 8.1.1 Prohibited concomitant therapy
- 9.1 Tabular schedule of evaluations
- 9.2.4.3 End of active follow-up

Modification 19

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

Sections affected include:

- List of abbreviations

15.3.2 Changes to the protocol text

Changes to the protocol text are highlighted as specified at the beginning of Section 15.

Global Change

This was changed as a result of modification 3.

Old text:

50 kBq/kg

New text:

50 kBq/kg (55 kBq/kg after implementation of NIST update)

Section List of abbreviations

This section was changed as a result of modification 3 and 19.

Added text:

FDG	Fluorodeoxyglucose
NIST	National Institute of Standards and Technology
NTX	N-terminal telopeptide
SC	Subcutaneously

Deleted text:

~~SERM~~	~~Selective estrogen receptors modulator~~

Added text:

W/O	Without

Synopsis: Study objectives

This section was changed as a result of modification 1.

Old text:

4. Time to pain progression

New text:

4. Time to pain progression (only in subjects with baseline worst pain score ≤8)

Added text:

7. Pain improvement rate

Synopsis: Diagnosis and main criteria for inclusion and exclusion, Section 6 Inclusion criteria

These sections were changed as a result of modifications 2, 4, 5, and 6.

Old text:

9. Subjects who are eligible for further standard of care endocrine treatment with any of the following administered as in second line or greater of hormone therapy in metastatic setting:

- Selective estrogen receptors modulators such as tamoxifen and toremifene
- Non-steroidal aromatase inhibitors such as anastrozole and letrozole
- Steroidal aromatase inhibitors such as exemestane
- Estrogen receptor down-regulators such as fulvestrant

Subjects enrolled in the current study will start treatment with the single hormone agent after randomization ~~either~~ before or simultaneously to the first injection of radium-223 dichloride/placebo. ~~Subjects already receiving the single agent hormone treatment prior to study entry are not eligible.~~

10. Subjects must have experienced no more than 2 skeletal-related events (SREs) prior to study entry defined as: external beam radiotherapy (EBRT) for bone pain, pathological bone fracture (excluding major trauma), spinal cord compression and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.
    Note: ~~For the purpose of counting prior SREs any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture should not be counted as a separate event.~~ All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization.

New text:

9. Subjects who are eligible for further standard of care endocrine treatment with any of the following administered as in second line or greater of hormone therapy in metastatic setting:
    - Selective estrogen receptors modulators such as tamoxifen and toremifene
    - Non-steroidal aromatase inhibitors such as anastrozole and letrozole
    - Steroidal aromatase inhibitors such as exemestane
    - Estrogen receptor down-regulators such as fulvestrant

Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (before or simultaneously to the first injection of radium-223 dichloride/placebo).

10. Subjects must have experienced no more than 2 skeletal-related events (SREs) prior to study entry defined as: external beam radiotherapy (EBRT) for bone pain, pathological bone fracture (excluding major trauma), spinal cord compression and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.
    Note: All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization. Separate SRE events are the ones that occur at least 21 days apart from each other to ensure that linked events (e.g., surgery to repair a fracture or multiple doses of radiation during a course of treatment) are not counted as separate events. In case of bone pain that occurs in several anatomical locations and requires separate EBRT sessions, it should be counted as one event if the EBRT sessions are administered within a period of 21 days.

Deleted Text:

12. ~~Bone lesions related asymptomatic or mildly symptomatic breast cancer. A worst pain score (WPS) of 0 to 1 on the Brief Pain Inventory-Short Form (BPI-SF) Question #3 (worst pain in the last 24 hours) will be considered asymptomatic, and a WPS of 2 to 3 will be considered mildly symptomatic. This is to be assessed once during the screening period.~~

Old text:

14. ~~60~~ mL/min/1.73m^2 according to the Modification of Diet in Renal Disease abbreviated formula.

New text:

14. 30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease abbreviated formula. (Note: please refer to local labelling for administration of full dose of bisphosphonates)

Synopsis: Study Design, Section 5.1 Design overview

This section was changed as a result of modification 4

Old text:

- Prior SREs (1 versus 2): for the purpose of prior SREs stratification, any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture, should not be counted as a separate event.

New text:

- Prior SREs (1 versus 2): for the purpose of prior SREs stratification, separate SREs are those that occur at least 21 days apart from each other. Any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture or multiple doses of radiation during a course of treatment, should not be counted as a separate event. In case of bone pain that occurs in several anatomical locations and requires separate EBRT sessions, it should be counted as one event if the EBRT sessions are administered within a period of 21 days.

Synopsis: Methodology, Section 5.1.1 Study periods and duration

This section was changed as a result of modification 2.

Old text:

All subjects will receive hormonal treatment with a single agent and supportive care as background treatment according to the local standard of practice. Subjects enrolled in the current study ~~will~~ start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride or placebo. For subject's convenience, injections of fulvestrant may be scheduled on the same day of the

radium-223 dichloride or placebo injection. ~~Subjects already receiving treatment with hormone treatment prior to study entry are not eligible.~~

New text:

All subjects will receive hormonal treatment with a single agent and supportive care as background treatment according to the local standard of practice. Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (either before or simultaneously to the first injection of radium-223 dichloride or placebo). For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride or placebo injection.

Section 4. Study objectives, Section 5.1.2 Study endpoints, Section 9.4.1 Efficacy variables, and Section 10.3 Efficacy variables and planned statistical analyses

This section was changed as a result of modification 1.

Old text:

- Time to pain progression

New text:

- Time to pain progression (only in subjects with baseline WPS ≤8)

Added text:

- Pain improvement rate

Section 6. Study Population

This section was changed as a result of modification 16.

Old text:

Eligibility is confirmed at the end of the screening period. At that time the subject is randomized and enters the treatment period. ~~Administration of the first radium-223 dichloride/placebo dose may occur 1 to 3 weeks after randomization. This time is required for dose ordering and shipment.~~ Laboratory values will be verified prior to first study drug administration as per protocol. Hematological support will be provided as needed according to the protocol guidance during the treatment period.

New text:

Eligibility is confirmed at the end of the screening period. At that time the subject is randomized and enters the treatment period. Laboratory values will be verified prior to first study drug administration as per protocol. Hematological support will be provided as needed according to the protocol guidance during the treatment period.

Section 7.1 Treatments to be administered

This section was changed as a result of modification 2 and 17.

Old text:

Subjects enrolled in the current study ~~will~~ start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride or placebo. For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride/placebo injection. ~~Subjects already receiving treatment with single hormone agent prior to study entry cannot be enrolled.~~

New text:

Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (either before or simultaneously to the first injection of radium-223 dichloride or placebo). For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride/placebo injection.

Deleted text:

~~Administration of bisphosphonates or denosumab should be done at least 2 hours before or after radium-223 dichloride/placebo administration.~~

Section 7.2.1.1 Radium-223 dichloride

This section was changed as a result of modification 3.

Old text:

The alpha particle emitting radiopharmaceutical BAY-88-8223 is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of radium-223 dichloride for IV administration. Radium-223 dichloride 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 1000 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 supplied with each shipment.

The volume per vial is 6 mL, corresponding to 6 MBq at the calibration 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 (2°C to 8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing.

New text:

The alpha particle emitting radiopharmaceutical BAY-88-8223 is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of radium-223 dichloride for IV administration. Radium-223 dichloride 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 1000 kBq/mL (1100 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 supplied with each shipment.

The volume per vial is 6 mL, corresponding to 6 MBq (6.6 MBq after implementation of NIST update) at the calibration 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 (2°C to 8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing.

Section 7.4.1 Dose calibration

This section was changed as a result of modification 3.

Added text:

As of Amendment 4, 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 [52]) 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 [53]), 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 [53]) in place at the time of implementation. The current dial setting (NIST 2010 [52]) 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 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.

Section 7.4.3 Radium-223 dose calculation

This section was changed as a result of modifications 3 and 9.

Old text:

The dosage of radium-223 dichloride is 50 kBq/kg body weight. The total activity to be injected will be calculated volumetrically using the subject's body weight within ~~3~~ days of injection (kg), the 50 kBq/kg 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 according to the recommended formula below:

$$\frac{\text{Body weight (kg)} \times 50 \text{ kBq/kg}}{\text{DK} \times 1000 \text{ kBq/mL}} = \text{volume to be injected (mL)}$$

New text:

The dosage of radium-223 dichloride is 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update). The total activity to be injected will be calculated volumetrically using the subject's body weight within 5 days of injection (kg), the 50 kBq/kg (55 kBq/kg after implementation of NIST update) 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 according to the recommended formula below:

$$\frac{\text{Body weight (kg)} \times 50 \text{ kBq/kg}^{a}}{\text{DK} \times 1000 \text{ kBq/mL}^{b}} = \text{volume to be injected (mL)}$$

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

[b] 1100 kBq/mL after implementation of NIST update

Section 7.4.6 Dose adjustments, delays, and treatment discontinuations

This section was changed as a result of modification 7.

Old text:

Thrombocytopenia: In case of thrombocytopenia NCI-CTCAE Grade 3 to 4, study drug administration should be delayed until recovery to CTCAE Grade 1 (minimum subjects with a platelet count 75 x 10^9 /L) or better before next study drug administration.

New text:

Thrombocytopenia: In case of thrombocytopenia NCI-CTCAE Grade 2 to 4, study drug administration should be delayed until recovery to CTCAE Grade 1 (minimum subjects with a platelet count 75 x 10^9 /L) or better before next study drug administration.

Section 8.1.2 Permitted concomitant therapy

This section was changed as a result of modification 2 and 17.

Old text:

- All subjects are expected to have been on therapy with either denosumab or bisphosphonates for at least 1 month before the start of study treatment and to continue on this therapy during the course of the study, with no change to therapy expected during the treatment phase of the study, except for toxicity reasons. ~~Injection of bisphosphonates should be done at least 2 hours before or after study drug administration.~~
- Subjects enrolled in the current study ~~will~~ start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride/placebo. For subject's convenience injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride or placebo injection. ~~Subjects already receiving treatment with a single hormone agent prior to study entry cannot be enrolled.~~

New text:

- All subjects are expected to have been on therapy with either denosumab or bisphosphonates for at least 1 month before the start of study treatment and to continue on this therapy during the course of the study, with no change to therapy expected during the treatment phase of the study, except for toxicity reasons.
- Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (either before or simultaneously to the first injection of radium-223 dichloride/placebo). For subject's convenience injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride or placebo injection.

Section 8.1.1 Prohibited concomitant therapy

This section was changed as a result of modification 19.

Old text:

Other cancer treatment with established efficacy in breast cancer except hormonal treatments should not be used during the treatment period.

New text:

Other cancer treatment with established efficacy in breast cancer except hormonal treatments or the permissible therapies mentioned in Section 8.1.2 should not be used during the treatment period.

Section 9.1 Tabular schedule of evaluations

This section was changed as a result of modifications 8, 9, 10, 11, 14, 16, and 18.

Old text:

Table 9-1: Schedule of assessments

Study Period	Screening[a]	Randomization	Treatment[b,c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	0-1	-	2	3	4	5	6	7	8	9	10		-	-	-	-
Cycle:	-	-	1		2		3		4	5	6	-	-	-	-	-
Timing:	3 wk pre-random.	~~1 to 3 wk pre-Dose 1~~	C1, Day 1	C1, Day 15[d]	C2, Day 1	C2, Day 15	C3, Day 1	C3, Day 15	C4, Day 1	C5, Day 1	C6, Day 1	4 wk post-last dose[e]	q4 wk until SSE; q12 wk after SSE[f]	q4 wk until SSE; q12 wk after SSE[g]		
Window (days):			~~±7~~	±3	± 7	±3	± 7	±3	± 7	± 7	± 7	± 7	±7	±7	±7	±7
BPI-SF[i]	X		X		X		X		X	X	X	X	X		X	
Vital signs[p]	X		X	X	X	X	X	X	X	X	X	X	X		X	
Physical examination[r]	X		X		X		X		X	X	X	X	X		X	
Hematology[s]	X[t]		X[u]	X	X[u]	X	X[u]		X[u]	X[u]	X[u]	X	X		X	
Clinical chemistry[v]	X[t]		X[w]	X	X[w]	X	X[w]		X[w]	X[w]	X[w]	X	X		X	

New text:

Table 9-1: Schedule of assessments

Study Period	Screening[a]	Randomization	Treatment[b,c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	**0-1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		**-**	**-**	**-**	**-**
Cycle:	**-**	**-**	**1**		**2**		**3**		**4**	**5**	**6**	**-**	**-**	**-**	**-**	**-**
Timing:	**3 wk pre-random.**		**C1, Day 1**	**C1, Day 15[d]**	**C2, Day 1**	**C2, Day 15**	**C3, Day 1**	**C3, Day 15**	**C4, Day 1**	**C5, Day 1**	**C6, Day 1**	**4 wk post-last dose[e]**	**q4 wk until SSE; q12 wk after SSE[f]**	**q4 wk until SSE; q12 wk after SSE[g]**		
Window (days):				**±3**	**± 7**	**±3**	**± 7**	**±3**	**± 7**	**± 7**	**± 7**	**± 7**	**±7**	**±7**	**±7**	**±7**
BPI-SF[i]			X		X		X		X	X	X	X	X		X	
Vital signs[p]	X		X	X	X	X	X	X	X	X	X	X	X[hh]		X	
Physical examination[r]	X		X		X		X		X	X	X	X	X[hh]		X	
Hematology[s]	X[t]		X[u]	X	X[u]	X	X[u]		X[u]	X[u]	X[u]	X	X[hh]		X	
Clinical chemistry[v]	X[t]		X[w]	X	X[w]	X	X[w]		X[w]	X[w]	X[w]	X	X[hh]		X	

Old text:

i. BPI-SF will be dispensed to the subject at ~~Screening and~~ the visit just before Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1; Cycle 5, Day 1; Cycle 6, Day 1; EOT; and follow-up clinic visits.

o. ~~At screening~~ an individual analgesic consumption diary will be dispensed to the subject just the visit before Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1; Cycle 5, Day 1; Cycle 6, Day 1; EOT; and follow-up clinic visits. Subjects will be asked to record analgesic use daily for one week (6 days prior to visit plus day of visit). Pain medication will also be assessed at each treatment and follow-up visit by study site; subjects should be requested to bring all pain medication to each visit. Analgesic use will be recorded in the appropriate eCRF page.

q. Subject's weight should be re-checked prior to each injection to calculate appropriate drug dosing. At all sites, weight is to be taken only once for each dose and it should be measured within ~~72 hours~~ prior to dosing. For US sites using the central PRD depot only, the subject weight for the dose day must be reported in a timely manner to the country PRD depot to allow adequate time for the 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 to avoid 2 pre-dose clinic visits.

u. Blood sample for hematology must be taken, analyzed, and evaluated within the ~~72 hours~~ prior to each study drug administration.

w. Blood sample for clinical chemistry must be taken within ~~72 hours~~ prior to each study drug administration, ~~but may~~ be evaluated ~~after~~ the administration.

x. PT, INR, and PTT: Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label.

y. Pre-menopausal women must have a negative serum pregnancy test performed within 7 days prior to randomization, prior to each study drug administration 3 and EOT. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. A plasma/serum estradiol assay is required within 7 days prior to randomization in pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea.

z. Blood and/or urine sample for exploratory evaluation of biomarkers, prior to radium-223 dichloride/placebo administration. Serum and plasma samples will be collected

at Cycle 1, Day 1; Cycle 4, Day 1; and EOT or disease progression, whichever occurs first. Urine samples will be collected at Cycle 1, Day 1; Cycle 4, Day 1; and EOT visits (or at the time of disease progression, whichever occurs earlier).

New text:

i. BPI-SF will be dispensed to the subject at the visit just before Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1; Cycle 5, Day 1; Cycle 6, Day 1; EOT; and follow-up clinic visits.

o. An individual analgesic consumption diary will be dispensed to the subject just the visit before Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1; Cycle 5, Day 1; Cycle 6, Day 1; EOT; and follow-up clinic visits. Subjects will be asked to record analgesic use daily for one week (6 days prior to visit plus day of visit). Pain medication will also be assessed at each treatment and follow-up visit by study site; subjects should be requested to bring all pain medication to each visit. Analgesic use will be recorded in the appropriate eCRF page.

q. Subject's weight should be re-checked prior to each injection to calculate appropriate drug dosing. At all sites, weight is to be taken only once for each dose and it should be measured within 5 days prior to dosing. For US sites using the central PRD depot only, the subject weight for the dose day must be reported in a timely manner to the country PRD depot to allow adequate time for the 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 to avoid 2 pre-dose clinic visits.

u. Blood sample for hematology must be taken, analyzed, and evaluated within the 5 days prior to each study drug administration.

w. Blood sample for clinical chemistry must be taken within 5 days prior to each study drug administration, and must be evaluated prior to the administration.

x. PT, INR, and PTT: Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label. Blood sample for coagulation tests must be taken and evaluated within 5 days prior to each study drug administration.

y. Pre-menopausal women must have a negative serum pregnancy test performed within 7 days prior to randomization, prior to each study drug administration (taken and evaluated within 5 days prior to administration), and EOT. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. A plasma/serum estradiol assay is required within 7 days prior to randomization in

pre-menopausal women with radiotherapy ovarian ablation or medical ovarian suppression and post-menopausal women age <55 years and one year or more of amenorrhea.

z. Blood and/or urine sample for exploratory evaluation of biomarkers, prior to radium-223 dichloride or placebo administration. Serum and plasma samples will be collected within 5 days of dosing at Cycle 1, Day 1; Cycle 4, Day 1; and EOT visits or disease progression, whichever occurs first. Urine samples will be collected at Cycle 1, Day 1; Cycle 4, Day 1; and EOT visits or disease progression, whichever occurs first.

Added text:

hh. Performed every 12 weeks

Section 9.2.1 Screening period (Visit 0 to 1)

This section was changed as a result of modification 8.

Old text:

One week prior to randomization, the subject should be given a subject diary to be used for subject questionnaires and the analgesic consumption and should receive training in its use. ~~Subjects will then complete the following assessments:~~

~~BPI-SF questionnaire will be completed only once prior to randomization to assess WPS in the last 24 hours: a worst pain score of 0 to 1 on the BPI-SF Question #3 (worst pain in the last 24 hours) will be considered asymptomatic, and a WPS of 2 to 3 will be considered mildly symptomatic.~~

New text:

One week prior to randomization, the subject should be given a subject diary to be used for subject questionnaires and the analgesic consumption and should receive training in its use.

Section 9.2.3 Treatment period

This section was changed as a result of modification 2, 9 and 10.

Old text:

- All subjects will receive background standard of care hormonal treatment for breast cancer. Subjects enrolled in the current study ~~will~~ start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride/placebo. For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride/placebo injection. ~~Subjects already receiving treatment with a single hormone agent prior to study entry cannot be enrolled.~~

It is the responsibility of the unblinded person to calculate the required volume of study drug (i.e., dose of radium-223 dichloride/placebo) for the subject based on the subject's body weight within ~~3~~ days of administration and the reference date of the received study medication (Section 7.4.3).

For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported to the country PRD depot in a timely manner to allow adequate time for the PRD preparation and delivery. The subject's weight measurement, order confirmation call to the IXRS, and prescription for the central PRD depot are to be performed ~~3~~ days prior to injection. 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 blood samples for clinical chemistry and hematology should be taken within ~~3~~ days before each study drug administration, and the hematology parameters must be evaluated before each study drug administration (within ~~3~~ days).

Before the first administration of radium-223 dichloride/placebo (within 3 days), the ANC should be ≥1.5 x 10^9/L, the platelet count ≥100 x 10^9/L, and Hb ≥8.0 g/dL.

New text:

- All subjects will receive background standard of care hormonal treatment for breast cancer. Subjects enrolled in the current study must start treatment with the single hormone agent either within 15 days prior to randomization or after randomization (either before or simultaneously to the first injection of radium-223 dichloride/placebo). For subject's convenience, injections of fulvestrant may be scheduled on the same day of the radium-223 dichloride/placebo injection.

- It is the responsibility of the unblinded person to calculate the required volume of study drug (i.e., dose of radium-223 dichloride/placebo) for the subject based on the subject's body weight within 5 days of administration and the reference date of the received study medication (Section 7.4.3).

For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported to the country PRD depot in a timely manner to allow adequate time for the PRD preparation and delivery. The subject's weight measurement, order confirmation call to the IXRS, and prescription for the central PRD depot are to be performed 5 days prior to injection. 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 blood samples for clinical chemistry and hematology should be taken within 5 days before each study drug administration, and the hematology parameters must be evaluated before each study drug administration (within 5 days).

Before the first administration of radium-223 dichloride/placebo (within 5 days), the ANC should be ≥1.5 x 10^9/L, the platelet count ≥100 x 10^9/L, and Hb ≥8.0 g/dL.

Section 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

This section was changed as a result of modification 9, 10, 11, and 15.

Old text:

- Record weight (kg), within ~~3~~ days prior to dosing

- Blood draw for hematology evaluation (within ~~72 hours~~ before radium-223 dichloride or placebo administration): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC. Results to be assessed and documented prior to study drug treatment. The Hb values need to be confirmed to be at least 8 g/dL prior to each dose. If blood is drawn the day of the administration of radium-223 dichloride/placebo, results must be available prior to study drug administration.

- Blood draw for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin (blood sample for clinical chemistry must be taken within ~~72 hours~~ prior to each study drug administration).
- A coagulation panel (blood sample to be taken within ~~72 hours~~ prior to each study drug administration): PT, PTT, and INR.
- Pregnancy test: pre-menopausal women must have a negative serum pregnancy test performed within ~~72 hours~~ before radium-223 dichloride or placebo administration. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Blood draw and urine sample for exploratory biomarker analysis: serum, plasma, and urine samples will be collected at Visit 2 (Cycle 1, Day 1) and Visit 8 (Cycle 4, Day 1).

- For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported to the country PRD depot in a timely manner to allow adequate time for the PRD preparation and delivery. The subject's weight measurement, order confirmation call to the IXRS, and prescription for the central PRD depot are to be performed ~~3~~ days prior to injection. 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:

- Record weight (kg), within 5 days prior to dosing

- Blood draw for hematology evaluation (must be taken and evaluated within 5 days before radium-223 dichloride or placebo administration): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC. Results to be assessed and documented prior to study drug treatment. The Hb values need to be confirmed to be at least 8 g/dL prior to each dose. If blood is drawn the day of the administration of radium-223 dichloride/placebo, results must be available prior to study drug administration.

- Blood draw for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin (blood sample for clinical chemistry must be taken and evaluated within 5 days prior to each study drug administration).
- A coagulation panel (blood sample to be taken and evaluated within 5 days prior to each study drug administration): PT, PTT, and INR.
- Pregnancy test: pre-menopausal women must have a negative serum pregnancy test performed and evaluated within 5 days before radium-223 dichloride or placebo administration. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Blood draw and urine sample for exploratory biomarker analysis: serum, plasma, and urine samples will be collected within 5 days of Visit 2 (Cycle 1, Day 1) and within 5 days of Visit 8 (Cycle 4, Day 1).

- For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported to the country PRD depot in a timely manner to allow adequate time for the PRD preparation and delivery. The subject's weight measurement, order confirmation call to the IXRS, and prescription for the central PRD depot are to be performed 5 days prior to injection. 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.

Section 9.2.3.3 End of treatment visit

This section was changed as a result of modification 10, 11, and 15.

Old text:

- Blood draws for hematology (within ~~72 hours~~ of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC.
- Blood draws for clinical chemistry (within ~~72 hours~~ of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin.
- A coagulation panel (within ~~72 hours~~ of the visit): PT, PTT, and INR.
- Pregnancy test (within ~~72 hours~~ of the visit): pre-menopausal women must have a negative serum pregnancy test. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Blood draw and urine sample for exploratory biomarker analysis (serum, plasma, and urine samples will be collected ~~at the EOT~~ or at the time of disease progression, whichever occurs earlier)

New text:

- Blood draws for hematology (within 5 days prior to the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC.
- Blood draws for clinical chemistry (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin.
- A coagulation panel (within 5 days of the visit): PT, PTT, and INR.
- Pregnancy test (within 5 days of the visit): pre-menopausal women must have a negative serum pregnancy test. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Blood draw and urine sample for exploratory biomarker analysis (serum, plasma, and urine samples will be collected within 5 days or at the time of disease progression, whichever occurs earlier)

Section 9.2.4.1 Active follow-up with clinic visits

This section was changed as a result of modifications 10 and 14

Old text:

The following procedures/evaluations should be performed at these visits.

- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Perform full physical examination: A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems.

- Blood draws for hematology (within ~~72 hours~~ of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, WBC differential
- Blood draws for clinical chemistry (within ~~72 hours~~ of visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin
- Radiological tumor assessment: to be performed until radiological disease progression is documented.

New text:

The following procedures/evaluations should be performed at these visits. (Note that vital signs measurement, full physical examination, blood draws, and radiological tumor assessment are only to be performed every 12 weeks ±7 days)

- Record vital signs (every 12 weeks): blood pressure, heart rate, respiratory rate, and temperature
- Perform full physical examination (every 12 weeks): A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems.

- Blood draws for hematology every 12 weeks (within 5 days of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, WBC differential
- Blood draws for clinical chemistry every 12 weeks (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin
- Radiological tumor assessment: to be performed every 12 weeks until radiological disease progression is documented

Section 9.2.4.3 End of active follow-up

This section was changed as a result of modification 10 and 18.

Old text:

- Blood draws for hematology (within ~~72 hours~~ of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential
- Blood draws for clinical chemistry (within ~~72 hours~~ of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin

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/placebo. For all deaths, the date of death information will be collected in the end-of-follow-up page of the eCRF.

New text:

- Blood draws for hematology (within 5 days of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential
- Blood draws for clinical chemistry (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin

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

Section 9.2.6 Radiological assessment: tumor and response evaluation

This section was changed as a result of modification 12.

Added text:

All digitized images/scans (both baseline and post-baseline) will be collected for retrospective analysis.

Section 9.4.2.2 Secondary efficacy endpoints

This section was changed as a result of modification 1.

Old text:

Time to pain progression is defined as the interval from randomization to the first date a subject experiences pain progression based on WPS. Pain progression is defined as an increase of 2 or more points in the "Worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥4 weeks apart

New text:

Time to pain progression will be evaluated in subjects with baseline WPS ≤ 8. **Time to pain progression** is defined as the interval from randomization to the first date a subject experiences pain progression based on WPS. Pain progression is defined as an increase of 2 or more points in the "Worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥4 weeks apart

Added text:

Pain improvement is defined for subjects evaluable for pain improvement, i.e. subjects with baseline WPS > 3, as a 2-point decrease or more in WPS from baseline over 2 consecutive measurements conducted at least 4 weeks apart.

Pain improvement rate is defined as the number of subjects with pain improvement as defined above, divided by the total number of subjects evaluable for pain improvement (i.e., subjects with baseline WPS>3). Both pain improvement rate at all visits and by visit will be considered.

Section 9.7.2.1 Urine, plasma, and serum based biomarker analysis

This section was changed as a result of modification 11.

Old text:

Blood samples will be obtained from all subjects at the following time points: (1) Cycle 1, Day 1 (Visit 2) and Cycle 4, Day 1 (Visit 8) prior to radium-223 dichloride or placebo administration, and at EOT visit or disease progression, whichever occurs first. At these time points, urine samples will also be collected.

New text:

Blood samples will be obtained from all subjects at the following time points: (1) Cycle 1, Day 1 (Visit 2) and Cycle 4, Day 1 (Visit 8) within 5 days of the visit prior to radium-223 dichloride or placebo administration, and within 5 days of the EOT visit or disease progression, whichever occurs first. At these time points, urine samples will also be collected.

Section 10.1 General considerations

This section was changed as a result of modification 4.

Old text:

Prior SREs (1 versus 2): for the purpose of prior SREs stratification, any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture, should not be counted as a separate event.

New text:

Prior SREs (1 versus 2): for the purpose of prior SREs stratification, separate SREs are those that occur at least 21 days apart from each other. Any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture or multiple doses of radiation during a course of treatment, should not be counted as a separate event. In case of bone pain that occurs in several anatomical locations and requires separate EBRT sessions, it should be counted as one event if the EBRT sessions are administered within a period of 21 days.

Section 14. Reference list

This section was changed as a result of modification 3 and 13.

Added text:

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

53 Zimmerman BE, Bergeron DE, Cessna JT, Fitzgerald R, Pibida L. Revision of the NIST standard for 223Ra: new measurements and review of 2008 data. Journal of Research of the National Institute of Standards and Technology. 2015;120:37-57.

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

Appendix 16.6 BPI-SF

This section was changed as a result of modification 13.

Added text:

The severity of pain and its impact on daily functions will be self-assessed by the study subjects using the BPI-SF (54) 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.

The BPI-SF will be self-administered by the subject at Dose 1, Day 1 (before the start of study treatment), at each treatment visit, at the end of treatment visit and follow-up clinic visits. 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 her 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 her.

How should the Questionnaire be introduced?

A sample script for introducing the questionnaire 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 complete this questionnaire about your health on the day of each clinic visit. 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 her 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

At the beginning of each visit, please check that 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 her whether she had any difficulty completing the questionnaire. If the subject says that she had trouble understanding a question, ask her why she had difficulty with that item. Re-read the question for her 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.

15.4 Amendment 5

Amendment 5 (dated 11 Mar 2016) is an amendment to the Version 4.0 of the protocol, dated 29 JUL 2015. Changes to the protocol include:

- Updated text for estradiol assay as postmenopausal ranges and detection limit for serum/plasma estradiol assay vary per laboratory.
- Deleted text for exclusion of bilateral and 2 distinct breast cancers.
- Clarified data collection for pain medication in alignment with completion of the BPI-SF questionnaire.
- Added text for completion of PRO Questionnaire Information Sheet by study staff for when BPI questionnaire is required to be completed.
- Clarified the process for unblinded personnel to obtain subject's treatment assignment.
- Clarified the drug order process at sites in the US.
- Clarified radium-223 administration timelines.
- Changed the SRE definition used for eligibility to make in line with the SRE definition used in prior studies with other bone targeted agents (denosumab, bisphosphonates).
- Updated text to be consistent with rest of protocol.
- Updated time period for recording of analgesic use in diary.
- Added text as biomarkers are to be collected before study drug dosing.
- Added PRO Questionnaire Information Sheet for completeness.
- Updated text for clarification.
- Revised definition of pain progression.
- Added separate collection of opiate use to allow calculation of time to opiate use.
- Removed progression as a separate assessment because progression is assessed radiologically as per tumor assessment schedule.
- Clarified that clinical chemistry assessment will include bone marrow ALP only if that testing can be performed locally.
- Clarified timing of technetium-99m bone scans and CT scans.
- Updated study medical expert and contact information.
- Added sampling for CTCs, which are believed to represent a surrogate for tumor cells and can be used as a surrogate to demonstrate efficacy of the drug by enumeration of CTCs but also as a source of tumor molecular characterizations.

15.4.1 Overview of changes to the study

Modification 1

Updated text for estradiol assay as postmenopausal ranges and detection limit for serum/plasma estradiol assay vary per laboratory.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion Criteria

Modification 2

Deleted text for exclusion of bilateral and 2 distinct breast cancers. Eligible patients for this study must have stage IV (Any T, Any N, M1) metastatic disease and be considered candidates for second or further line of therapy. None of the recent studies (i.e. BOLERO, PALOMA) in metastatic setting excluded patients with such conditions.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.2 Exclusion Criteria

Modification 3

Clarified data collection for pain medication in alignment with completion of the BPI-SF questionnaire.

Sections affected include:

- 8.1.2 Permitted concomitant therapy
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up
- 9.4.2.2 Secondary efficacy endpoints

Modification 4

Added text for completion of PRO Questionnaire Information Sheet by study staff for when BPI questionnaire is required to be completed.

Sections affected include:

- 9.1 Tabular schedule of evaluations

- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up

Modification 5

Clarified the process for unblinded personnel to obtain subject's treatment assignment.

Section affected includes:

- 7.3 Treatment assignment

Modification 6

Clarified the drug order process at sites in the US.

Section affected includes:

- 7.3 Treatment assignment

Modification 7

Clarified radium-223 administration timelines.

Section affected includes:

- 7.2.1.1 Radium-223 dichloride

Modification 8

Changed the SRE definition used for eligibility to make in line with the SRE definition used in prior studies with other bone targeted agents (denosumab, bisphosphonates).

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion Criteria

Modification 9

Updated text to be consistent with rest of protocol.

Section affected includes:

- Figure 5-1: Study design schematic

Modification 10

Updated time period for recording of analgesic use in diary.

Section affected includes:

- 9.1 Tabular schedule of evaluations

Modification 11

Added text as biomarkers are to be collected before study drug dosing.

Sections affected include:

- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

Modification 12

Added PRO Questionnaire Information Sheet for completeness.

Sections affected include:

- 16.8 Patient Reported Questionnaire Information Sheet

Modification 13

Updated text for clarification.

Sections affected include:

- 6. Study population
- 9.1 Tabular schedule of evaluations
- 9.2.6 Radiological assessment
- 9.4.2.2 Secondary efficacy endpoints
- 9.4.2.3 Exploratory efficacy endpoints
- 9.6.1.3 Assessments and documentation of adverse events
- 9.7.2 Biomarker assessments

Modification 14

Revised definition of pain progression.

Sections affected include:

- List of abbreviations
- 9.4.2.2 Secondary efficacy endpoints

Modification 15

Added separate collection of opiate use to allow calculation of time to opiate use.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up

Modification 16

Removed progression as a separate assessment because progression is assessed radiologically as per tumor assessment schedule.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.2 Visits 3, 5, and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up

Modification 17

Clarified that clinical chemistry assessment will include bone marrow ALP only if that testing can be performed locally.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.1 Screening period (Visits 0 to 1)
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.2 Visits 3, 5, and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits

- 9.2.4.3 End of active follow-up
- 9.3.3 Other baseline characteristics

Modification 18

Clarified timing of technetium-99m bone scans and CT scans.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.6 Radiological assessment: tumor and response evaluation
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up

Modification 19

Updated study medical expert and contact information.

Section affected includes:

- Title page

Modification 20

Added sampling for CTCs, which are believed to represent a surrogate for tumor cells and can be used as a surrogate to demonstrate efficacy of the drug by enumeration of CTCs but also as a source of tumor molecular characterizations.

Sections affected include:

- List of Abbreviations
- 9.1 Tabular schedule of evaluations
- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 End of treatment visit
- 9.7.2.2 Collection of Circulating Tumor Cells for Biomarker Analyses

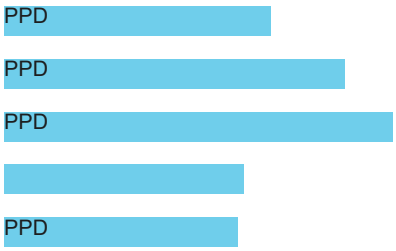
15.4.2 Changes to the protocol text

Changes to the protocol text are highlighted as specified at the beginning of Section 15.4.1.

Title page

This was changed as a result of modification 19.

Old text:



New text:

Synopsis: Diagnosis and main criteria for inclusion and exclusion, Section 6.1 Inclusion criteria

This was changed as a result of modifications 1 and 8.

Old text:

5. Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible.

Note: In premenopausal subjects, ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist/antagonist is permitted for induction of ovarian suppression if the plasma/serum estradiol assay is ~~<20 pg/mL~~ at screening within 7 days of randomization.

- **Pre-menopausal subjects** with or without ovarian radiation or concomitant treatment with an LH-RH agonist/antagonist must have a negative pregnancy test at screening and agree to use an adequate method of contraception as recommended by their treating physicians
- **Post-menopausal** status is defined either by:

- age ≥55 years and one year or more of amenorrhea,
- age <55 years and one year or more of amenorrhea with a plasma/serum estradiol assay ~~<20 pg/mL~~, within 7 days of randomization
- bilateral ovariectomy

10. Subjects must have experienced no more than 2 skeletal-related events (SREs) prior to study entry defined as: External beam radiotherapy (EBRT) ~~for~~ bone ~~pain~~, pathological bone fracture (excluding major trauma), spinal cord compression, and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.

New text:

5. Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible.

Note: In premenopausal subjects, ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist/antagonist is permitted for induction of ovarian suppression if the plasma/serum estradiol assay is within local laboratory postmenopausal range at screening, performed within 7 days of randomization.

- **Pre-menopausal subjects** with or without ovarian radiation or concomitant treatment with an LH-RH agonist/antagonist must have a negative pregnancy test at screening and agree to use an adequate method of contraception as recommended by their treating physicians
- **Post-menopausal** status is defined either by:
  - age ≥55 years and one year or more of amenorrhea,
  - age <55 years and one year or more of amenorrhea with a plasma/serum estradiol assay within local laboratory postmenopausal range, performed within 7 days of randomization
  - bilateral ovariectomy

10. Subjects must have experienced no more than 2 skeletal-related events (SREs) prior to study entry defined as: Need for external beam radiotherapy (EBRT) to bone, pathological bone fracture (excluding major trauma), spinal cord compression, and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.

Synopsis: Diagnosis and main criteria for inclusion and exclusion, Section 6.2 Exclusion criteria

This was changed as a result of modification 2.

Old text:

3. Subjects with ~~any of the following cancers:~~
   - ~~o~~ i~~I~~nflammatory breast cancer
   - ~~o Bilateral breast cancer or a history of 2 distinct breast cancers~~

New text:

3. Subjects with inflammatory breast cancer

Section: List of abbreviations

This was changed as a result of modification 14 and 20.

Added text:

IPM	Increase in pain management
CTC	Circulating tumor cell

Section: Figure 5-1 Study design schematic

This was changed as a result of modification 9.

Old text:

Subjects who discontinue treatment, had an EOT visit, and can travel to the investigational site will be followed until the subject can no longer travel to the clinic, dies, is lost to follow up, or withdrawals informed consent and actively objects to collection of further data. The maximum duration of the active follow up is until study termination.

New text:

Subjects who discontinue treatment, had an EOT visit, and can travel to the investigational site will be followed until the subject can no longer travel to the clinic, experiences an SSE and radiological progression, dies, is lost to follow up, or withdrawals informed consent and actively objects to collection of further data. The maximum duration of the active follow up is until study termination.

Section 6. Study population

This was changed as a result of modification 13.

Old text:

Approximately 227 subjects with HER2 negative, hormone receptor positive breast cancer with bone metastases will be ~~enrolled and treated~~.

New text:

Approximately 227 subjects with HER2 negative, hormone receptor positive breast cancer with bone metastases will be randomized.

Section 7.2.1.1 Radium-223 dichloride

This was changed as a result of modification 7.

Old text:

It is important to note that, in general (unless otherwise agreed), in cases where study drug has been ordered, the time window for administration should be within 3 days of the day ~~of receipt~~. If administration must be postponed more than 3 days ~~after receipt~~, replacement of the drug order is required.

New text:

It is important to note that, in general (unless otherwise agreed), in cases where study drug has been ordered, the time window for administration should be within 3 days of the planned treatment day. If administration must be postponed more than 3 days, replacement of the drug order is required.

Section 7.3 Treatment assignment

This was changed as a result of modifications 5 and 6.

Old text:

The IXRS will provide only the randomization number to the caller, i.e., blinded personnel, but not the assigned treatment. A confirmation e-mail containing randomization number ~~and treatment~~ will be sent to the unblinded ~~staff member~~ who will be responsible for preparing the study drug for the subject for the first administration. ~~When the subject is~~ allocated to radium-223 dichloride, the unblinded ~~person will use IXRS to send an order to the manufacturer for drug shipment~~. The timing for the drug order should be based on the planned subject visit date. If the subject is allocated to placebo, the unblinded person at the study site will be responsible for providing saline corresponding to the IXRS treatment day. This should not be made available before to avoid unblinding the subject and blinded study personnel.

New text:

The IXRS will provide only the randomization number to the caller, i.e., blinded personnel, but not the assigned treatment. A confirmation e-mail containing randomization number will be sent to the unblinded personnel who will have to log into IXRS in order to know the treatment arm assigned to the patient. The unblinded personnel will be responsible for preparing the study drug for the subject for the first administration. For US only, if a subject is allocated to radium-223 dichloride, the unblinded personnel will fax shipment request to Cardinal Health for pre-filled syringe. The timing for the drug order should be based on the planned subject visit date. If the subject is allocated to placebo, the unblinded person at the study site will be responsible for providing saline corresponding to the IXRS treatment day. This should not be made available before to avoid unblinding the subject and blinded study personnel.

Section 8.1.2 Permitted concomitant therapy

This was changed as a result of modification 3.

Old text:

- Analgesic use will be captured via a subject diary ~~and the eCRF (analgesic consumption diary and recorded analgesics, respectively,~~ see schedule of assessments, Table 9-1). Subjects will be asked to track their analgesic use on an analgesic consumption diary for ~~1 week~~ prior to their clinic visit. Any medication taken for pain, whether for palliation of bone pain or relief of other type of pain, and any changes should be recorded in the eCRF at each visit. Note that EBRT treatment should be recorded in the eCRFs until end of the active follow-up period without clinic visits.

New text:

- Analgesic use will be captured via a subject diary (analgesic consumption diary) and the eCRF (24-hour analgesics use page and regular analgesics concomitant medication page, see schedule of assessments, Table 9-1). Subjects will be asked to track their analgesic use on an analgesic consumption diary for 24 hours prior to their clinic visit. Any medication taken for pain, whether for palliation of bone pain or relief of other type of pain, and any changes should be recorded in the eCRF at each visit. Note that EBRT treatment should be recorded in the eCRFs until end of the active follow-up period without clinic visits.

Section 9.1 Tabular schedule of evaluations

This was changed as a result of modifications 4, 10, 13, 15, 16, 17, 18, and 20.

Old text:

Study Period	Screening[a]	Randomization	Treatment[b,c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	0-1	-	2	3	4	5	6	7	8	9	10		-	-	-	-
Cycle:	-	-	1		2		3		4	5	6	-	-	-	-	-
Timing:	3 wk pre-random.		C1, Day 1[1]	C1, Day 15[d]	C2, Day 1	C2, Day 15	C3, Day 1	C3, Day 15	C4, Day 1	C5, Day 1	C6, Day 1	4 wk post-last dose[e]	q4 wk until SSE; q12 wk after SSE[f]	q4 wk until SSE; q12 wk after SSE[g]		
Window (days):				±3	± 7	±3	± 7	±3	± 7	± 7	± 7	± 7	±7	±7	±7	±7
Technetium-99m bone scan[aa]	X[bb]						~~X~~[aa]				X[aa]	~~X~~[aa]	~~X~~[aa]		~~X~~[aa]	
Chest, abdominal and pelvic CT scan[aa,cc,dd,ee]	X						~~X~~[aa]				X[aa]	~~X~~[aa]	~~X~~[aa]		~~X~~[aa]	
~~Progression~~			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	

New text:

Study Period	Screening[a]	Randomization	Treatment[b,c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	0-1	-	2	3	4	5	6	7	8	9	10		-	-	-	-
Cycle:	-	-	1		2		3		4	5	6	-	-	-	-	-
Timing:	3 wk pre-random.		C1, Day 1[1]	C1, Day 15[d]	C2, Day 1	C2, Day 15	C3, Day 1	C3, Day 15	C4, Day 1	C5, Day 1	C6, Day 1	4 wk post-last dose[e]	q4 wk until SSE; q12 wk after SSE[f]	q4 wk until SSE; q12 wk after SSE[g]		
Window (days):				±3	± 7	±3	± 7	±3	± 7	± 7	± 7	± 7	±7	±7	±7	±7
Record opiate use			X		X		X		X	X	X	X	X		X	

Whole Blood for CTCs[ii]			X		X		X		X	X	X	X				
Technetium-99m bone scan[aa,bb]	X	X														
Chest, abdominal and pelvic CT scan[aa,cc,dd,ee]	X	X														

Old text:

i. BPI-SF will be dispensed to the subject at the visit just before Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1; Cycle 5, Day 1; Cycle 6, Day 1; EOT; and follow-up clinic visits.

o. An individual analgesic consumption diary will be dispensed to the subject just the visit before Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1; Cycle 5, Day 1; Cycle 6, Day 1; EOT; and follow-up clinic visits. Subjects will be asked to record analgesic use ~~daily for one week (6 days prior to visit plus day of visit). Pain medication will also be assessed at each treatment and follow-up visit by study site; subjects should be requested to bring all pain medication to each visit. Analgesic use will be recorded in the appropriate eCRF page~~.

v. Sodium, potassium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, bone alkaline phosphatase, serum creatinine, phosphate, blood urea nitrogen, bilirubin (total), total cholesterol, and albumin.

aa. Radiological tumor evaluation must be performed 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration and every 12 weeks thereafter until PD (radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS. This schedule is to be maintained and will not be shifted because of treatment interruptions/delays. Scans will be read locally. The time window for the scans is ±7 days.

New text:

i. BPI-SF will be dispensed to the subject at the visit just before Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1; Cycle 5, Day 1; Cycle 6, Day 1; EOT; and follow-up clinic visits. Additionally PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire.

o. An individual analgesic consumption diary will be dispensed to the subject just the visit before Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1; Cycle 5, Day 1;

Cycle 6, Day 1; EOT; and follow-up clinic visits. Subjects will be asked to record analgesic use 24 hours prior to their clinic visit.

v. Sodium, potassium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, bone alkaline phosphatase (if testing is available and can be performed locally), serum creatinine, phosphate, blood urea nitrogen, bilirubin (total), total cholesterol, and albumin.

aa. Radiological tumor evaluation must be performed 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration and every 12 weeks thereafter until PD (radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS till bone progression. This schedule is to be maintained and will not be shifted because of treatment interruptions/delays. Scans will be read locally. The time window for the scans is ±7 days.

ii. Details of sampling are described in the Laboratory Manual. Blood samples for analysis of circulating tumor cells will be collected within 5 days of Visits 2, 4, 6, 8, 9, 10 (ie, Day 1 of Cycles 1 through 6) prior to study drug dosing, and within 5 days of the EOT visit or disease progression, whichever occurs first.

Section 9.2.1 Screening period (Visits 0 to 1)

This was changed as a result of modification 17.

Old text:

- Blood draw for clinical chemistry: sodium (Na), potassium (K), chloride (Cl), calcium (Ca), ALT, AST, lactate dehydrogenase (LDH), bone ALP, serum creatinine, phosphate, blood urea nitrogen (BUN), total bilirubin, total cholesterol, and albumin.

New text:

- Blood draw for clinical chemistry: sodium (Na), potassium (K), chloride (Cl), calcium (Ca), ALT, AST, lactate dehydrogenase (LDH), bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, blood urea nitrogen (BUN), total bilirubin, total cholesterol, and albumin.

Section 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

This was changed as a result of modifications 3, 4, 11, 15, 16, 17, 18, and 20.

Old text:

BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit

- Recording of analgesic use will be performed by:
  - Analgesic use recorded via the analgesic concomitant medication eCRF
  - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for ~~one week (6 days prior to visit plus day of visit)~~
  - ~~Analgesic use during the last 24 hours recorded in eCRF, by site, assessing subject pain medication. Subject should bring all pain medication to each visit~~

New text:

BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit. Additionally PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire.

- Recording of analgesic use will be performed by:
  - Analgesic use recorded via the analgesic concomitant medication eCRF
  - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for 24 hours prior to visit. The analgesic use for 24 hours prior to the visit will be recorded by the investigator on the eCRF.

Added text:

- Record opiate use

Old text:

- Blood draw for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin (blood sample for clinical chemistry must be taken and evaluated within 5 days prior to each study drug administration).

- Blood draw and urine sample for exploratory biomarker analysis: serum, plasma, and urine samples will be collected within 5 days of Visit 2 (Cycle 1, Day 1) and within 5 days of Visit 8 (Cycle 4, Day 1).

New text:

- Blood draw for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, total bilirubin, total cholesterol, and albumin (blood sample for clinical chemistry must be taken and evaluated within 5 days prior to each study drug administration).

- Blood draw and urine sample for exploratory biomarker analysis: serum, plasma, and urine samples will be collected within 5 days of Visit 2 (Cycle 1, Day 1) and within 5 days of[4] Visit 8 (Cycle 4, Day 1) prior to study drug dosing.

Deleted text:

- ~~At Visit 6 and Visit 10 (Cycle 3, Day 1 and Cycle 6, Day 1) only (see also Section 9.2.6):~~
  - ~~A chest/abdominal/pelvic CT or MRI. The same imaging modalities are to be used as were used at baseline.~~
  - ~~Bone technetium-99m scan with careful identification of all disease-related hotspots. All visible bone lesions must also be imaged with conventional anatomical imaging procedures, such as SPECT-CT/MRI or CT or MRI scan (with or without contrast media). All new bone lesions or progression of existing bone lesion(s) identified on a technetium-99m bone scan will need confirmatory CT or MRI imaging. In case of a new lesion or of progression of existing bone lesion(s) observed on a bone scan that is not confirmed by CT/MRI, progression will not be declared until the CT/MRI confirmation of progression occurs. A CT/MRI confirmatory scan must take place 6 to 8 weeks after the new lesion or progression of existing lesion(s) was observed on bone scan. Modified RECIST version 1.1 (mRECIST 1.1) criteria will be applied to declare a PFS event.~~

    ~~In case of new bone lesions or progression of existing bone lesions is identified on CT/MRI but not on a technetium-99m bone scan, progression will be declared at the time of the lesion identification or progression was observed on the CT/MRI scan.~~

    ~~FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).~~
  - ~~FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.~~
  - ~~The time window for the scans is ±7 days.~~
  - ~~For radiologic progression confirmed during the treatment period:~~

- ~~If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS~~

~~Record progression~~

Added text:

- Blood draw for analysis of circulating tumor cells (CTCs) collected within 5 days of Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6), prior to study drug dosing.
- Radiological tumor assessments: please refer to Section 9.2.6 and Appendix 16.2.

Section 9.2.3.2 Visits 3, 5, and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits

This was changed as a result of modification 16 and 17.

Old text:

- Blood draw for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, total bilirubin, total cholesterol, and albumin.

New text:

- Blood draw for clinical chemistry is only required at Visit 3 (Cycle 1, Day 15) and Visit 5 (Cycle 2, Day 15): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin.

Deleted text:

~~Record progression~~

Section 9.2.3.3 End of treatment visit 9.2.4.1 Active follow-up with clinic visits

This was changed as a result of modifications 3, 4, 15, 16, 17, 18, and 20.

Old text:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit

- Recording of analgesic use will be performed by:
  - Analgesic use recorded via the analgesic concomitant medication eCRF
  - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for ~~one week (6 days prior to visit plus day of visit)~~

- ~~Analgesic use during the last 24 hours recorded in eCRF, by site, assessing subject pain medication. Subject should bring all pain medication to each visit~~

New text:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit. Additionally PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire.

- Recording of analgesic use will be performed by:
  - Analgesic use recorded via the analgesic concomitant medication eCRF
  - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for 24 hours prior to visit. The analgesic use for 24 hours prior to the visit will be recorded by the investigator on the eCRF.

Added text:

- Record opiate use

Old text:

- Blood draws for clinical chemistry (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin

~~Record progression~~

- Radiological tumor assessment~~ to be performed only if prior assessment has been done more than 8 weeks prior to EOT visit. mRECIST 1.1 criteria will be applied to declare a PFS event.~~
  - ~~A chest/abdominal/pelvic CT or MRI.~~
  - ~~Bone technetium-99m scan with careful identification of all disease-related hotspots. All visible bone lesions must also be imaged with conventional anatomical imaging procedures such as SPECT-CT/MRI or CT or MRI scan (with or without contrast media). All new bone lesions or progression of existing bone lesion(s) identified on a technetium-99m bone scan will need confirmatory CT or MRI imaging. In case of a new lesion or of progression of existing bone lesion(s) observed on a bone scan that is not confirmed by CT/MRI, progression will not be declared until the CT/MRI confirmation of progression occurs. A CT/MRI confirmatory scan must take place 6 to 8 weeks after the new lesion or progression of existing lesion(s) was observed on bone scan.~~

    ~~In case of new bone lesions or progression of existing bone lesions is identified on CT/MRI but not on a technetium-99m bone scan, progression will be declared at the time of the lesion identification or progression was observed on the CT/MRI scan.~~

~~FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).~~

- ~~FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.~~
- ~~The time window for the scans is ±7 days.~~
- ~~For confirmed radiologic progression:~~
- ~~If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS~~

New text:

- Blood draws for clinical chemistry (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin
- Blood draw for analysis of CTCs (within 5 days of the visit).
- Radiological tumor assessments: please refer to Section 9.2.6 and Appendix 16.2

Section 9.2.4.1 Active follow-up with clinic visits

This was changed as a result of modifications 3, 4, 15, 16, 17, 18, and 20.

Old text:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit

- Recording of analgesic use will be performed by:
  - Analgesic use recorded via the analgesic concomitant medication eCRF
  - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects ~~for one week (6 days prior to visit plus day of visit)~~
  - ~~Analgesic use during the last 24 hours recorded in eCRF, by site, assessing subject pain medication. Subject should bring all pain medication to each visit~~

New text:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit. Additionally PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire.

- Recording of analgesic use will be performed by:
  - Analgesic use recorded via the analgesic concomitant medication eCRF
  - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for 24 hours prior to visit. The analgesic use for 24 hours prior to the visit will be recorded by the investigator on the eCRF.

Added text:

- Record opiate use

Old text:

Blood draws for clinical chemistry every 12 weeks (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin

Radiological tumor assessment: ~~to be performed every 12 weeks until radiological disease progression is documented~~

- ~~A chest/abdominal/pelvic CT or MRI. The same imaging modalities are to be used as were used at baseline.~~
- ~~Bone technetium-99m scan with careful identification of all disease-related hotspots and associated SPECT-CT/MRI or CT/ MRI scan (with or without contrast media).~~

  ~~FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).~~
- ~~FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.~~
- ~~The time window for the scans is ±7 days.~~
- ~~If a subject experiences radiological progression during the active follow-up period with visits:~~
  - ~~If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria), is observed, bone imaging and MRI/CT scan~~

~~of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS.~~

New text:

- Blood draws for clinical chemistry every 12 weeks (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin
- Radiological tumor assessments: please refer to Section 9.2.6 and Appendix 16.2.

Deleted text:

- ~~Record progression~~

Section 9.2.4.3 End of active follow-up

This was changed as a result of modifications 3, 4, 15, 16, 17, and 18.

Old text:

BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit

- Recording of analgesic use will be performed by:
  - Analgesic use recorded via the analgesic concomitant medication eCRF
  - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for ~~one week (6 days prior to visit plus day of visit)~~
  - ~~Analgesic use during the last 24 hours recorded in eCRF, by site, assessing subject pain medication. Subject should bring all pain medication to each visit~~

New text:

- BPI-SF questionnaire will be completed prior to any other study assessments/procedures and should be checked for completion at the visit. Additionally PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire

- Recording of analgesic use will be performed by:
  - Analgesic use recorded via the analgesic concomitant medication eCRF
  - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for 24 hours prior to visit. The analgesic use for 24 hours prior to the visit will be recorded by the investigator on the eCRF.

Added text:

- Record opiate use

Old text:

- Blood draws for clinical chemistry (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin

Radiological tumor assessment ~~to be performed only for subjects who had no previously documented progression~~

- ~~A chest/abdominal/pelvic CT or MRI. The same imaging modalities are to be used as were used at baseline. An abdominal/pelvic MRI will be accepted instead of abdominal/pelvic CT only if MRI abdomen/pelvis was performed at baseline.~~
- ~~Bone technetium-99m scan with careful identification of all disease-related hotspots and any confirmatory SPECT-CT/MRI or CT or MRI scan (with and without contrast media).~~

  ~~FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).~~
- ~~FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.~~
- ~~The time window for the scans is ±7 days.~~

~~Record progression~~

New text:

- Blood draws for clinical chemistry (within 5 days of the visit): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, bilirubin (total), total cholesterol, and albumin
- Radiological tumor assessments: please refer to Section 9.2.6 and Appendix 16.2

Section 9.2.6 Radiological assessment: tumor and response evaluation

This was changed as a result of modifications 13 and 18.

Old text:

Radiological tumor evaluation, using the mRECIST 1.1 guidelines (See Section 16.2), must be performed within 3 weeks prior to randomization, at 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration and every 12 weeks thereafter until PD

(radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS.

This schedule is to be maintained and will not be shifted because of treatment interruptions/delays. Subjects who discontinue study treatment for reasons other than disease progression will continue to undergo tumor response evaluations until PD is documented (radiological progression).

FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study. The same lesions identified at baseline must be evaluated at follow-up assessments using the same technique and preferably by the same Investigator/radiologist.

New text:

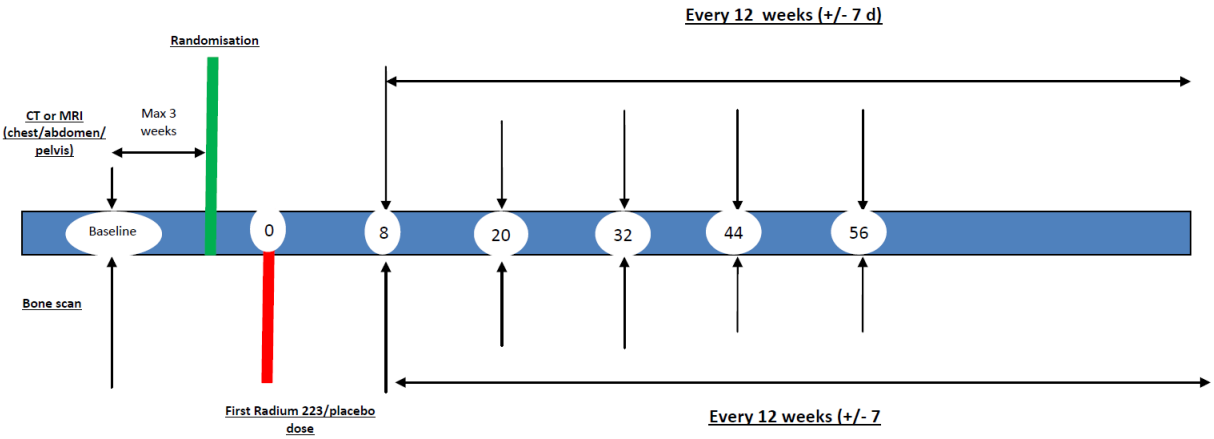
Radiological tumor evaluation, using the mRECIST 1.1 guidelines (See Section 16.2), must be performed as follows (see also Figure 9–1):

- Within 3 weeks prior to randomization,
- 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration
- Every 12 weeks (±7 days) thereafter until PD (radiological progression) is documented.

A technetium-99m bone scan and CT or MRI (chest/abdomen/pelvis and any additional sites of disease, as applicable) should be performed at all the above mentioned timepoints.

This schedule is to be maintained and will not be shifted because of treatment interruptions/delays.

Figure 9-1: Radiological tumor evaluation schedule



If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS until bone progression occurs or start of a new anticancer treatment.

If radiologic bone progression occurs prior to occurrence of visceral metastases, MRI/CT scan of the chest, abdomen, and pelvis should continue until occurrence of visceral metastasis or start of a new anticancer treatment after the end of the current study treatment. This will allow assessment of time to visceral metastases onset.

Subjects who discontinue study treatment for reasons other than disease progression will continue to undergo tumor response evaluations until PD is documented (radiological progression).

Note: FDG PET scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT. (See also Appendix 16.2).

A technetium-99m bone scan with careful identification of all disease-related hotspots should be performed for all patients at the above mentioned timepoints. All visible bone lesions must also be imaged with conventional anatomical imaging procedures such as CT or MRI scan. During the study a new bone lesion or progression of existing bone lesion/s initially identified on a technetium-99m bone scan must be confirmed by CT or MRI. If confirmed by CT/MRI, the date of occurrence of the new lesion or of progression of existing bone lesion/s will be the date it was initially detected (by technetium-99m bone scan) even if the confirmation by CT/MRI was done at a subsequent scan. (See also Section 16.2).

Note: FDG PET/CT or NaF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study. The same lesions identified at baseline must

be evaluated at follow-up assessments using the same technique and preferably by the same Investigator/radiologist.

Added text:

For details on radiological tumor assessment please also refer to Section 16.2.

Section 9.3.3 Other baseline characteristics

This was changed as a result of modification 17.

Old text:

- Clinical chemistry: Na, K, Cl, Ca, total cholesterol, ALT, AST, LDH, bone ALP, serum creatinine, phosphate, BUN, total bilirubin, and albumin

New text:

- Clinical chemistry: Na, K, Cl, Ca, total cholesterol, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), serum creatinine, phosphate, BUN, total bilirubin, and albumin

Section 9.4.2.2 Secondary efficacy endpoints

This was changed as a result of modifications 3, 13, and 14.

Old text:

Time to opiate use for cancer pain is defined as the interval from the date of randomization to the date of opiate use. Subjects who have no opiate use at the time of analysis will be censored at the last ~~known~~ date of no opiate use. Subjects with no on-study assessment or no baseline assessment will be censored at the date of randomization.

Time to opiate use will be determined by analgesic use captured via ~~subject analgesic consumption diary and/or the~~ eCRF (analgesic ~~consumption diary~~ and ~~recorded analgesics~~, respectively, see Table 9-1 Schedule of assessments).

Time to pain progression will be evaluated in subjects with baseline WPS ≤ 8. ~~**Time to pain progression** is defined as the interval from randomization to the first date a subject experiences pain progression based on WPS.~~ Pain progression is defined as an increase of 2 or more points in the "Worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥4 weeks apart

OR

~~initiation of short- or long-acting opioid use for pain.~~

Assessments will occur on the day of the visit. An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 questions. Subjects who have not experienced pain progression at the time of analysis will be censored on the last date the subject was known to have not progressed. Subjects with no on-study assessment or no baseline assessment will be censored at the date of randomization.

Pain improvement is defined for subjects evaluable for pain improvement, i.e. subjects with baseline WPS ~~>~~ ~~3~~, as a 2-point decrease or more in WPS from baseline over 2 consecutive measurements conducted at least 4 weeks apart.

Pain improvement rate is defined as the number of subjects with pain improvement as defined above, divided by the total number of subjects evaluable for pain improvement (i.e., subjects with baseline WPS~~>3~~). Both pain improvement rate at ~~all visits and by~~ visit will be considered.

New text:

Time to opiate use for cancer pain is defined as the interval from the date of randomization to the date of opiate use. Subjects who have no opiate use at the time of analysis will be censored at the last assessment date of no opiate use. Subjects with no on-study assessment or no baseline assessment will be censored at the date of randomization.

Time to opiate use will be determined by analgesic use captured via different eCRF pages (24 hour analgesic use page, analgesic concomitant medication page and opiate use page, respectively, see Table 9-1 Schedule of assessments)**.**

Time to pain progression is defined as the interval from randomization to the first date a subject experiences pain progression based on WPS and analgesics use. Time to pain progression will be evaluated in subjects with baseline WPS ≤ 8. Pain progression is defined as an increase of 2 or more points in the "Worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥4 weeks apart

OR

an increase in pain management (IPM) with respect to baseline, whichever occurs first.

Assessments will occur on the day of the visit. An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 questions. Subjects who have not experienced pain progression at the time of analysis will be censored on the last post-baseline pain assessment date the subject was known to have not progressed. Subjects with no on-study assessment or no baseline assessment will be censored at the date of randomization.

Pain improvement is defined for subjects evaluable for pain improvement, i.e. subjects with baseline WPS ≥ 2, as a 2-point decrease or more in WPS from baseline over 2 consecutive measurements conducted at least 4 weeks apart, without an IPM.

Pain improvement rate is defined as the number of subjects with pain improvement as defined above, divided by the total number of subjects evaluable for pain improvement (i.e., subjects with baseline WPS≥ 2). Pain improvement rate at week 12, EOT and any visit will be considered.

Section 9.4.2.3 Exploratory efficacy endpoints

This was changed as a result of modification 13.

Old text:

Time to bone ALP progression is defined as the time (days) from the date of randomization to the date of first bone ALP progression. Bone ALP progression is defined as a ≥25% increase from the baseline value, at least 12 weeks from baseline in subjects with no bone ALP decline from baseline; or a ≥25% increase above the nadir value, which is confirmed by a second value obtained ~~3~~ or more weeks later in subjects with an initial bone ALP decline from baseline.

New text:

Time to bone ALP progression is defined as the time (days) from the date of randomization to the date of first bone ALP progression. Bone ALP progression is defined as a ≥25% increase from the baseline value, at least 12 weeks from baseline in subjects with no bone ALP decline from baseline; or a ≥25% increase above the nadir value, which is confirmed by a second value obtained 4 or more weeks later in subjects with an initial bone ALP decline from baseline.

Section 9.6.1.3 Assessments and documentation of adverse events

This was changed as a result of modification 13.

Old text:

All AEs and SAEs occurring ~~after the EOT visit until the EOS~~ must be documented and reported if considered to be related to study medication or to study-related procedures.

New text:

All AEs and SAEs occurring beyond 30 days after the last dose of study treatment must be documented and reported if considered to be related to study medication or to study-related procedures.

Section 9.7.2 Biomarker assessments

This was changed as a result of modification 13.

Old text:

Biomarker analyses planned within this study may include predictive, prognostic, and pharmacodynamic biomarkers analyzed from serum and urine. Serum, urine, and biomarker analyses will be dependent upon the availability of appropriate biomarker assays and may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will have no scientific value, or there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated

early or does not reach a positive primary endpoint, completion of the biomarker assessments will be based on justification and intended utility of the data.

New text:

Biomarker analyses planned within this study may include predictive, prognostic, and pharmacodynamic biomarkers analyzed from serum and urine. Serum, urine, and biomarker analyses will be dependent upon the availability of appropriate biomarker assays and may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will have no scientific value, or there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or does not reach a positive primary endpoint, completion of the biomarker assessments will be based on justification and intended utility of the data. Exploratory biomarker data including CTC analysis will be reported in a separated biomarker report.

Section 9.7.2.2 Collection of Circulating Tumor Cells for Biomarker Analyses

This was changed as a result of modification 20.

Added text:

9.7.2.2 Collection of Circulating Tumor Cells for Biomarker Analyses

Circulating Tumor Cells (CTCs) are believed to represent a surrogate for tumor cells and can be used as surrogate to demonstrate efficacy of the drug by enumeration of CTCs, but also as source of tumor molecular characterization.

Blood samples will be obtained from all subjects at the following time points: (1) Cycle 1, Day 1 (Visit 2) and every subsequent cycle, Day 1 within 5 days of the visit prior to radium-223 dichloride or placebo administration, and within 5 days of the EOT visit or disease progression, whichever occurs first.

Section 16.8 Patient Reported Questionnaire Information Sheet

This was changed as a result of modification 12.

Added text:

**Subject Number / **

**Visit: **

Instructions:

- This information sheet is to be completed by the study nurse/investigator.
- This information sheet must be competed for all patients at each visit in which the protocol requires the questionnaire to be administered, whether or not the questionnaire was completed by the patient.
- When the patient returns the questionnaire
    - Please complete this information sheet.

- Please check that the patient has answered all the questions and no question has more than one answer.

1. Was the questionnaire provided to the patient at this visit? ☐ 1 No ☐ 2 Yes

If YES, please continue
If NO, please go to question 5

2. Date questionnaire completed

d d m m y y y y

3. Was the questionnaire provided prior to clinical examination? ☐ 1 No ☐ 2 Yes

4. Were all questions answered? ☐ 1 No ☐ 2 Yes

If YES, please STOP
If NO, please continue

5. If No, specify reason questionnaire/questions was not answered:

☐ Patient felt too ill

☐ Patient refused to complete questionnaire for reason other than illness

☐ Patient did not keep appointment

☐ Questionnaire not administered due to institution error

☐ Questionnaire not available in the appropriate language

☐ Other, please specify: _____

15.5 Amendment 6

Amendment 6 (dated 11 JUL 2016) is an amendment to the Version 5.0 of the protocol, dated 11 MAR 2015. Changes to the protocol include:

- Modified inclusion/exclusion criteria to allow entry of patients with visceral metastases.
- Deleted BPI-SF text to avoid redundancy with Appendix 16.6.
- Added text for visceral metastases at baseline, for consistency with modification 1.
- Removed timeframe for prior chemotherapy administered for adjuvant/neo-adjuvant disease.
- Removed timeframe for CT/MRI confirmatory scan for consistency with 17096 and to avoid an additional scan and associated radiation without affecting outcome.
- Updated company name.
- Added text for consistency within protocol.

15.5.1 Overview of changes to the study

Modification 1

Modified inclusion/exclusion criteria to allow entry of patients with visceral metastases. Inclusion of patients with visceral metastases improves enrollment without significantly impacting the patient population. This modification allows entry of patients with asymptomatic visceral metastases with good organ function. The inclusion of asymptomatic visceral disease should have negligible impact on the primary endpoint of SSE-FS.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria
- 6.2 Exclusion criteria
- 16.2 Response evaluation criteria in solid tumors (RECIST 1.1)

Modification 2

Deleted BPI-SF text to avoid redundancy with Appendix 16.6.

Sections affected include:

- 9.4.2.2 Secondary efficacy endpoints

Modification 3

Added text for visceral metastases at baseline, for consistency with modification 1.

Sections affected include:

- 9.4.2.3 Exploratory efficacy endpoints

Modification 4

Removed timeframe for prior chemotherapy administered for adjuvant/neo-adjuvant disease. More recent data from chemotherapy combination studies with Xofigo shows good safety profile of the combination. In addition, long term safety follow up data from ALSYMPCA showed good safety profile for patients that received subsequent chemotherapy. At the time of the current study set up this data was not available.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.2 Exclusion criteria

Modification 5

Removed timeframe for CT/MRI confirmatory scan for consistency with 17096 and to avoid an additional scan and associated radiation without affecting outcome.

Sections affected include:

- 16.2 Response evaluation criteria in solid tumors (RECIST 1.1)

Modification 6

Updated company name. 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.

Sections affected include:

- Header
- Title page

Modification 7

Added text for consistency within protocol.

Sections affected include:

- 9.1 Tabular schedule of evaluations

15.5.2 Changes to the protocol text

Changes to the protocol text are highlighted as specified at the beginning of Section 15.5.1.

Header

This was changed as a result of modification 6.

Deleted text:

~~Bayer HealthCare~~

Title page

This was changed as a result of modification 6.

Old text:

Bayer HealthCare AG, D-51368 Leverkusen, Germany

New text:

Bayer AG, D-51368 Leverkusen, Germany

US territory: Bayer Healthcare Pharmaceuticals Inc.,

100 Bayer Boulevard, P.O. Box 915

Whippany NJ 07981-0915 USA

Synopsis: Diagnosis and main criteria for inclusion and exclusion, Section 6.1 Inclusion criteria

This was changed as a result of modification 1.

Old text:

6. Subjects with bone dominant disease with at least 2 skeletal metastases identified at baseline by bone scintigraphy and confirmed by CT/magnetic resonance imaging (MRI). Presence of metastases in soft tissue (skin, subcutaneous, muscle, fat, lymph nodes) is allowed.

14. Laboratory requirements:

- Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L without platelet transfusion within 4 weeks prior to randomization
- Hemoglobin ≥9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin within 4 weeks prior to randomization

- Total bilirubin level ≤1.5 x institutional upper limit of normal (ULN) (except for subjects with documented Gilbert's disease)
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x institutional ULN. ~~AST and ALT values above the ULN must not be related to liver metastases~~
- Creatinine ≤1.5 x ULN
- Estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula (Note: please refer to local labelling for administration of full dose of bisphosphonates)
- International normalized ratio of prothrombin time (INR) and partial thromboplastin time (PTT) or activated PTT ≤1.5 x ULN at study entry. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label.
- Serum albumin >30 g/L

New text:

6. Subjects with bone dominant disease with at least 2 skeletal metastases identified at baseline by bone scintigraphy and confirmed by CT/magnetic resonance imaging (MRI). Presence of metastases in soft tissue (skin, subcutaneous, muscle, fat, lymph nodes) <u>and/or visceral metastases</u> is allowed.

14. Laboratory requirements:

- Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L without platelet transfusion within 4 weeks prior to randomization
- Hemoglobin ≥9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin within 4 weeks prior to randomization
- Total bilirubin level ≤1.5 x institutional upper limit of normal (ULN) (except for subjects with documented Gilbert's disease)
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x institutional ULN.
- Creatinine ≤1.5 x ULN
- Estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula

(Note: please refer to local labelling for administration of full dose of bisphosphonates)

- International normalized ratio of prothrombin time (INR) and partial thromboplastin time (PTT) or activated PTT ≤1.5 x ULN at study entry. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label.
- Serum albumin >30 g/L
- Pulse oximetry O2 saturation >92% if lung metastases are present

Synopsis: Diagnosis and main criteria for inclusion and exclusion, Section 6.2 Exclusion criteria

This was changed as a result of modification 1 and 4.

Old text:

~~4. History and/or presence of confirmed visceral metastases~~

5. Subjects who have either received chemotherapy for metastatic disease or are considered by the treating Investigator to be appropriate candidates for chemotherapy as current treatment for metastatic breast cancer are excluded. Chemotherapy administered for adjuvant/neo-adjuvant disease is acceptable ~~provided it was administered at least 1 year prior to study entry~~.
6. Subjects with any previous untreated or concurrent cancer that is distinct in primary site or histology from the cancer under study, except treated basal cell carcinoma or superficial bladder tumor (Ta and Tis, American Joint Committee on Cancer, 7th edition). Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before enrollment are allowed. All cancer treatments must be completed at least 3 years prior to study entry (i.e., signature date of ICF).
7. Subjects with known or history of brain metastases or leptomeningeal disease: subjects with neurological symptoms must undergo a contrast CT scan or MRI of the brain within 28 days prior to randomization to exclude active brain metastasis. Imaging of the central nervous system is otherwise not required
8. 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.
9. Prior treatment with radium-223 dichloride

10. Prior hemibody external radiotherapy. Subjects who received other types of prior external radiotherapy are allowed provided that bone marrow function is assessed and meets the protocol requirements for hemoglobin, ANC, and platelets.
11. Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186, or rhenium-188
12. ECOG Performance Status ≥2
13. Blood transfusions, platelet transfusions or use of erythropoietin within 4 weeks prior to randomization.
14. 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 randomization
15. Treatment with an investigational drug or with any anti-cancer treatments not permitted by the protocol, within 4 weeks prior to randomization
16. Chronic conditions associated with non-malignant abnormal bone growth (e.g., confirmed Paget's disease of bone)
17. 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
18. Previous assignment to treatment in this study
19. Breastfeeding women
20. Known hypersensitivity to the active substance or to any of the excipients of radium-223 dichloride
21. Known presence of osteonecrosis of jaw

New text:

5. Subjects who have either received chemotherapy for metastatic disease or are considered by the treating Investigator to be appropriate candidates for chemotherapy as current treatment for metastatic breast cancer are excluded. Chemotherapy administered for adjuvant/neo-adjuvant disease is acceptable.
6. Subjects with any previous untreated or concurrent cancer that is distinct in primary site or histology from the cancer under study, except treated basal cell carcinoma or superficial bladder tumor (Ta and Tis, American Joint Committee on Cancer, 7th edition). Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before enrollment are allowed. All cancer treatments must be completed at least 3 years prior to study entry (i.e., signature date of ICF).

7. Subjects with known or history of brain metastases or leptomeningeal disease: subjects with neurological symptoms must undergo a contrast CT scan or MRI of the brain within 28 days prior to randomization to exclude active brain metastasis. Imaging of the central nervous system is otherwise not required
8. 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.
9. Prior treatment with radium-223 dichloride
10. Prior hemibody external radiotherapy. Subjects who received other types of prior external radiotherapy are allowed provided that bone marrow function is assessed and meets the protocol requirements for hemoglobin, ANC, and platelets.
11. Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186, or rhenium-188
12. ECOG Performance Status ≥2
13. Blood transfusions, platelet transfusions or use of erythropoietin within 4 weeks prior to randomization.
14. 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 randomization
15. Treatment with an investigational drug or with any anti-cancer treatments not permitted by the protocol, within 4 weeks prior to randomization
16. Chronic conditions associated with non-malignant abnormal bone growth (e.g., confirmed Paget's disease of bone)
17. 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
18. Previous assignment to treatment in this study
19. Breastfeeding women
20. Known hypersensitivity to the active substance or to any of the excipients of radium-223 dichloride
21. Known presence of osteonecrosis of jaw
22. Patients with immediately life-threatening visceral disease, for whom chemotherapy is the preferred treatment option.
23. Lymphangitic carcinomatosis.

24. Patients with ascites requiring paracentesis within 2 weeks prior to study entry (signature of informed consent) and during the screening period.

Section 9.1 Tabular schedule of evaluations

This was changed as a result of modification 7.

Old text:

Study Period	Screening[a]	Randomization	Treatment[b,c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	0-1	-	2	3	4	5	6	7	8	9	10		-	-	-	-
Cycle:	-	-	1		2		3		4	5	6	-	-	-	-	-
Timing:	3 wk pre-random		C1, Day 1[1]	C1, Day 15[d]	C2, Day 1	C2, Day 15	C3, Day 1	C3, Day 15	C4, Day 1	C5, Day 1	C6, Day 1	4 wk post-last dose[e]	q4 wk until SSE; q12 wk after SSE[f]	q4 wk until SSE; q12 wk after SSE[g]		
Window (days):				±3	±7	±3	±7	±3	±7	±7	±7	±7	±7	±7	±7	±7

Technetium-99m bone scan [aa,bb]	X	X

New text:

Study Period	Screening[a]	Randomization	Treatment[b,c]										Active Follow-up		End of Active Follow-up	
			Radium-223 dichloride or Placebo									EOT visit	With Clinic Visits	W/O Clinic Visits	With Clinic Visits	W/O Clinic Visits
Visit:	0-1	-	2	3	4	5	6	7	8	9	10		-	-	-	-
Cycle:	-	-	1		2		3		4	5	6	-	-	-	-	-
Timing:	3 wk pre-random		C1, Day 1	C1, Day 15[d]	C2, Day 1	C2, Day 15	C3, Day 1	C3, Day 15	C4, Day 1	C5, Day 1	C6, Day 1	4 wk post-last dose[e]	q4 wk until SSE; q12 wk after SSE[f]	q4 wk until SSE; q12 wk after SSE[g]		
Window (days):				±3	±7	±3	±7	±3	±7	±7	±7	±7	±7	±7	±7	±7

Technetium-99m bone scan or FDG PET/CT or NaF PET/CT, same technique for all assessments[aa,bb]	X	X

Section 9.1 Tabular schedule of evaluations

This was changed as a result of modification 7.

Old text:

aa. Radiological tumor evaluation must be performed 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration and every 12 weeks thereafter until PD (radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS ~~till~~ bone progression. This schedule is to be maintained and will not be shifted because of treatment interruptions/delays. Scans will be read locally. The time window for the scans is ±7 days.

New text:

aa. Radiological tumor evaluation must be performed 8 weeks (±7 days) after the first radium-223 dichloride/placebo administration and every 12 weeks thereafter until PD (radiological progression) is documented. If radiologic soft tissue or visceral progression in absence of bone progression (according to mRECIST 1.1 criteria) is observed, bone imaging and MRI/CT scan of the chest, abdomen, and pelvis should continue to allow assessment of bone-specific rPFS until bone progression occurs or start of a new anticancer treatment. This schedule is to be maintained and will not be shifted because of treatment interruptions/delays. Scans will be read locally. The time window for the scans is ±7 days.

Section 9.4.2.2 Secondary efficacy endpoints

This was changed as a result of modification 2.

Old text:

Pain improvement rate is defined as the number of subjects with pain improvement as defined above, divided by the total number of subjects evaluable for pain improvement (i.e., subjects with baseline WPS ≥2). Pain improvement rate at week 12, EOT and any visit will be considered.

~~The BPI-SF (Section 16.6) is a short, self-administered questionnaire with 9 items, which was designed to evaluate the intensity of, and the impairment caused by pain. Questions #2 (locating areas of pain on a diagram) and question #7 (regarding use of pain medication) of the BPI-SF questionnaire will not be answered, as they do not affect the global pain score. All BPI-SF 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 (does not interfere) to 10 (completely interferes) rating scales.~~

~~The items are aggregated into 2 dimensions: (1) Pain severity index, using the mean of the 4 items on the pain intensity, and (2) Function interference index, using the mean of the 7 pain interference items. All 4 severity items must be completed for aggregating the pain severity index. 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.~~

New text:

Pain improvement rate is defined as the number of subjects with pain improvement as defined above, divided by the total number of subjects evaluable for pain improvement (i.e., subjects with baseline WPS ≥2). Pain improvement rate at week 12, EOT and any visit will be considered.

Section 9.4.2.3 Exploratory efficacy endpoints

This was changed as a result of modification 3.

Old text:

Time to visceral metastases onset is defined as the time (days) from the date of randomization to the date of the first scan showing visceral metastatic disease.

New text:

Time to visceral metastases onset is defined as the time (days) from the date of randomization to the date of the first scan showing visceral metastatic disease. Subjects with visceral metastases at baseline will be censored at randomization date.

Section 16.2 Response evaluation criteria in solid tumors (RECIST 1.1)

This was changed as a result of modifications 1 and 5.

Old text:

Visceral lesions: Malignant finding in visceral organs: lung, liver, brain, etc.

~~*Note: patients with visceral lesions will not be considered eligible for this study.*~~

Measurable lesions: Lesions that, at baseline, meet the requirements for being reproducibly quantifiable (see section below for detailed definition of measurable lesions).

- A new bone lesion or progression of existing bone lesion/s initially identified on a technetium-99m bone scan must be confirmed by CT or MRI. If confirmed by CT/MRI, the date of occurrence of the new lesion or of progression of existing bone lesion/s will be

the date it was initially detected (by technetium-99m bone scan) even if the confirmation by CT/MRI was done at a subsequent scan. ~~A CT/MRI confirmatory scan must take place 6 to 8 weeks after the new lesion or progression of existing lesion/s was observed on bone scan~~

New text:

Visceral lesions: Malignant finding in visceral organs: lung, liver, brain, etc.

Measurable lesions: Lesions that, at baseline, meet the requirements for being reproducibly quantifiable (see section below for detailed definition of measurable lesions).

- A new bone lesion or progression of existing bone lesion/s initially identified on a technetium-99m bone scan must be confirmed by CT or MRI. If confirmed by CT/MRI, the date of occurrence of the new lesion or of progression of existing bone lesion/s will be the date it was initially detected (by technetium-99m bone scan) even if the confirmation by CT/MRI was done at a subsequent scan.

15.6 Amendment 7

Amendment 7 (dated 18 MAY 2017) is an amendment to the Version 6.0 of the protocol, dated 11 JUL 2016. Changes to the protocol include:

- Updated study medical expert and contact information
- Added text to provide tolerance limits for permitted radiation.
- Text was updated to provide clarity to study sites.
- Text was added for consistency with Table 9-1: Schedule of assessments.
- Clarified sites at which CTCs are collected.
- Added interim data review.
- Updated text for independent radiological review.
- Added text for the establishment of an independent unblinded data review committee.
- Reformatted page for signature of the sponsor's medically responsible person.

15.6.1 Overview of changes to the study

Modification 1

Updated study medical expert and contact information.

Sections affected include:

- Title page

Modification 2

Added text to provide tolerance limits for permitted radiation.

Sections affected include:

- 7.4.4 Study drug dose preparation

Modification 3

Text was updated to provide clarity to study sites.

Sections affected include:

- 9.1 Tabular schedule of evaluations

Modification 4

Text was added for consistency with Table 9-1: Schedule of assessments. Although monthly visits might not be possible for some patients, tumor assessments as per time schedule

described in Section 9.2.6 might be feasible and will allow collection of data for disease response assessment related to some efficacy endpoints (radiological PFS, radiological bone specific PFS, etc.).

Sections affected include:

- 9.2.4.2 Active follow-up without clinic visits

Modification 5

Clarified sites at which CTCs are collected.

Sections affected include:

- 9.7.2.2 Collection of circulating tumor cells for biomarker analyses

Modification 6

Added interim data review.

Sections affected include:

- 10.5 Planned interim data review

Modification 7

Updated text for independent radiological review.

Sections affected include:

- 9.2.6 Radiological assessment: tumor and response evaluation
- 13.1.2 Independent radiological review

Modification 8

Added text for the establishment of an independent unblinded data review committee.

Sections affected include:

- List of abbreviations
- 13.1.3 Independent Data Review Committee

Modification 9

Added text for the establishment of an independent unblinded data review committee.

Section affected includes:

- Signature of the sponsor’s medically responsible person

15.6.2 Changes to the protocol text

Changes to the protocol text are highlighted as specified at the beginning of Section 15.6.1.

Title Page

This was changed as a result of modification 1.

Old text:

PPD
PPD
PPD
PPD

New text:

PPD
PPD
PPD
PPD

Signature of the sponsor's medically responsible person

This was changed as a result of modification 9.

Old text:

Name: PPD

Affiliation: Bayer Pharmaceuticals

Date: ..... Signature: .....

New text:

Name: PPD Role: PPD

Date: ..... Signature: .....

List of abbreviations

This was changed as a result of modification 8.

Added text:

IDRC Independent Data Review Committee

Section 7.4.4 Study drug dose preparation

This was changed as a result of modification 2.

Old text:

The study medication will be administered as a slow bolus IV injection. After administration, the equipment used in connection with the preparation and administration of drug, are to be treated as radioactive waste and should be disposed in accordance with hospital procedure for the handling of radioactive material and according to local laws. Written information about radium-223 dichloride and instructions for the handling and injection of radioactive material will be provided to study personnel.

New text:

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, are to be treated as radioactive waste and should be disposed in accordance with hospital procedure for the handling of radioactive material and according to local laws. Written information about radium-223 dichloride and instructions for the handling and injection of radioactive material will be provided to study personnel.

Section 9.1 Tabular schedule of evaluations

This was changed as a result of modification 3.

Old text:

ii. Details of sampling are described in the Laboratory Manual. Blood samples for analysis of circulating tumor cells will be collected within 5 days of ~~Visits 2, 4, 6, 8, 9, 10 (ie,~~ Day 1 of Cycles 1 through 6~~)~~ prior to study drug dosing, and within 5 days of the EOT visit or disease progression, whichever occurs first.

New text:

ii. Details of sampling are described in the Laboratory Manual. Blood samples for analysis of circulating tumor cells will be collected within 5 days of Day 1 of Cycles 1 through 6 prior to study drug dosing, and within 5 days of the EOT visit or disease progression, whichever occurs first.

Section 9.2.4.2 Active follow-up without clinic visits

This was changed as a result of modification 4.

Added text:

If possible, Radiological tumor assessments as per timepoints and guidelines specified in Section 9.2.6 and Appendix 16.2 to be performed as applicable.

Section 9.2.6 Radiological assessment: tumor and response evaluation

This was changed as a result of modification 7.

Deleted text:

~~All digitized images/scans (both baseline and post-baseline) will be collected for retrospective analysis.~~

Section 9.7.2.2 Collection of circulating tumor cells for biomarker analyses

This was changed as a result of modification 5.

Old text:

Blood samples will be obtained from all subjects at the following time points: (1) Cycle 1, Day 1 (Visit 2) and every subsequent cycles, Day 1 within 5 days of the visit prior to radium-223 dichloride or placebo administration, and within 5 days of the EOT visit or disease progression, whichever occurs first.

New text:

Blood samples will be obtained from all subjects at sites in France, Germany, Israel, Spain, and the United Kingdom at the following time points: (1) Cycle 1, Day 1 (Visit 2) and every subsequent cycles, Day 1 within 5 days of the visit prior to radium-223 dichloride or placebo administration, and within 5 days of the EOT visit or disease progression, whichever occurs first.

Section 10.5 Planned interim data review

This was changed as a result of modification 6.

Old text:

~~There is no formal interim analysis for efficacy planned for the primary endpoint SSE-FS. At the final analysis for SSE-FS, the secondary endpoints will be analyzed as well, but no alpha adjustment will be applied for secondary endpoints.~~

New text:

An administrative interim data review will be performed when approximately 40 rPFS events are reached. The interim data review will be primarily focused on the rPFS, and the results will inform on future radium-223 clinical development plans in this indication. An independent unblinded data review committee will be formed.

No formal statistical testing will be performed for either SSE-FS or rPFS at the time of this interim review. Only summary statistics will be produced. There is no plan to stop the trial due to superior efficacy; therefore, no alpha adjustment is applied for this interim look at the primary endpoint of SSE-FS. The study will remain blinded after the interim data review.

Details of the interim data review will be provided in the statistical analysis plan.

Section 13.1.2 Independent radiological review

This was changed as a result of modification 7.

Old text:

This study will have no central review. ~~However, all digitized images/scans (both baseline and post-baseline) will be collected for retrospective analysis.~~

New text:

This study will have no central review.

Section 13.1.3 Independent Data Review Committee (IDRC)

This was changed as a result of modification 8.

Added text:

An independent unblinded data review committee will be established.

The IDRC will conduct a one-time unblinded review of the data. IDRC review will be supported by an independent unblinded statistical analysis center, as further described in the IDRC operational plan.

15.7 Amendment 8

Amendment 8 (dated 03 APR 2018) is an amendment to the Version 7.0 of the protocol, dated 23 MAY 2017. Changes to the integrated protocol include:

- 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 the investigator's causality assessment.
- Addition of possibility to transition to long-term follow-up study for subjects who have completed at a minimum the end of treatment visit or 30 days from last study treatment dose, whichever is latest
- Updated sponsor's medically responsible person
- Clarification to AE and SAE reporting requirements during active follow-up in the Schedule of Assessments
- Minor clarifications

15.7.1 Overview of changes

15.7.1.1 Modification 1

Bone fractures and bone associated events (e.g., osteoporosis) need to be reported as (S)AEs, including during long-term follow-up, regardless of the investigator's causality assessment.

Sections affected include:

- Synopsis
- 5.1.1 Study periods and duration
- 9.1 Tabular schedule of evaluations
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.2 Active follow-up without clinic visits
- 9.2.4.3 End of active follow-up
- 9.6.1.3 Assessments and documentation of adverse events
- 9.6.1.4 Reporting of serious adverse events

Rationale:

The ERA 223 study, a phase III randomized trial in prostate cancer patients examining radium-223 dichloride vs 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 the investigator's causality assessment.

15.7.1.2 Modification 2

Clarification of transition to long-term extension study, to allow collection of long term safety data

Sections affected include:

- Synopsis
- 5.1.1 Study periods and duration
- 5.3 End of study
- 9.2.5 End of Study

Rationale:

To allow collection of long-term safety data, subjects who have completed at a minimum the end of treatment visit or 30 days from last study treatment dose, whichever is latest, may be transitioned into a separate long-term follow-up study. Until the transition to the long-term follow up study, subjects will continue to follow all the required procedures and visits described in the current protocol.

15.7.1.3 Modification 3

The sponsor's medically responsible person has changed and signature page was updated to reflect this.

Sections affected include:

- Signature of the sponsor's medically responsible person

15.7.1.4 Modification 4

Clarification of footnotes in the schedule of assessment to reflect consistency with the body text. The AEs and SAEs reporting requirements during active follow-up apply regardless of whether the patient has clinic visits or not. The footnotes previously indicated these reporting requirements applied only in the case without clinic visits, which is inconsistent with the active follow up description in Section 9.2.4.1.

Sections affected include:

- 9.1 Tabular schedule of evaluations

15.7.1.5 Minor clarifications

For Word-related technical reasons, numbered footnotes have been replaced with a summary of changes at the start of each amended section.

15.7.2 Changes to the protocol text

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

16. Appendices

16.1 National Cancer Institute-Common Terminology Criteria, version 4.03

This study will utilize the NCI-CTCAE v4.03 for toxicity and SAE reporting. A copy of the CTCAE v4.03 can be downloaded from the website: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. All appropriate treatment areas should have access to a copy of the CTCAE v4.03.

16.2 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Section modified by Amendment 2 (Section 15.2) and Amendment 6 (Section 15.5).

Disease response and progression will be evaluated in this study using a modified version of RECIST version 1.1 (51). The modification refers to bone lesions assessment: **all bone lesions are considered non measurable** and new bone lesions identified by bone scan will need to be confirmed by further imaging (CT/MRI).

Definitions:

Bone lesions: Malignant findings in skeleton.

Soft tissue lesions: Malignant finding in soft tissue (skin, subcutaneous, muscle, fat, lymph nodes).

Visceral lesions: Malignant finding in visceral organs: lung, liver, brain, etc.

Measurable lesions: Lesions that, at baseline, meet the requirements for being reproducibly quantifiable (see section below for detailed definition of measurable lesions).

Non-measurable lesions: Lesions that, at baseline, do not meet the below-described requirements. These lesions cannot be chosen for quantitative assessment, and must be assessed qualitatively only.

Target lesions: Lesions that are chosen at baseline (from the set of measurable lesions) for quantitative assessment throughout the trial, using rules outlined below. A lesion that has been selected as a target lesion remains a target lesion for the rest of the study.

Non-target lesions: Lesions that are not chosen at baseline for quantitative assessment, and must be assessed qualitatively throughout the trial. A lesion that has been selected as a non-target lesion remains a non-target lesion for the rest of the study.

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.

All measurements must be recorded in millimeters (or decimal fractions of centimeters).

For measurements of tumors other than lymph nodes, the longest unbroken diameter seen on an axial slice is recorded.

Lymph nodes must always be measured in the short axis (the longest measurement on an axial slice perpendicular to the longest diameter of the lymph node). Lymph nodes less than 10 mm in short axis diameter are defined as normal.

CT/MRI of chest/abdomen/pelvis and any additional sites of disease (if clinically indicated) will be performed for all subjects.

In addition, all subjects will have their bone disease assessed by technetium-99m bone scan with careful identification of all disease-related hotspots.

If FDG PET/CT or FDG PET scan is performed as part of the standard of practice imaging, the results of the FDG PET scan can be used as a complement to CT scanning in the assessment of disease progression – based on occurrence of new lesions – as per the RECIST 1.1 algorithm (See section on New lesions in this appendix).

FDG PET/CT or NAF PET/CT scan is acceptable as an alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

Clinical lesions might be assessed clinically only as per the following rules: clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes) and ≥10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Baseline Assessment:

Identifying measurable disease:

Non-nodal malignant lesions: Measurable lesions are those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI. If scans with slice thickness greater than 5mm are used, the minimum size should be twice the slice thickness.
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant lymph nodes: To be considered pathologically enlarged, a lymph node must be ≥10 mm in short axis when assessed by CT scan. To be considered measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan.

Tumor lesions situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Identifying non-measurable disease:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with short axis 10 to 14 mm) are considered non-measurable disease.

Bone lesions:

Bone lesions (blastic, lytic, mixed type) will be considered non-measurable lesions.

Selection of target and non-target lesions:

At baseline, lesions are divided into those that will be followed quantitatively (target lesions) and those that will be followed qualitatively (non-target lesions).

Target lesions:

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and be recorded and measured at baseline. These lesions should be selected on the basis of their size (lesion with the longest diameter/short axis for lymph nodes), be representative of all involved organs, and should be suitable for reproducible repeated measurements.

For the purposes of this selection, all lymph nodes should be regarded as a single organ. If there are multiple chains/regions, one from each should be selected.

The sum of the diameters (longest diameter for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated by adding all target lesion diameters/short axis (for lymph nodes) and reported as the baseline sum of diameters. The baseline sum of diameters will be used as the reference measurement when looking for evidence of objective response at later visits.

If there are more than 5 measurable lesions, those not selected as target lesions will be considered together with non-measurable disease as non-target lesions.

Non-target lesions:

Non-target lesions include all non-measurable lesions, plus any measurable lesions over and above the maximum 5 listed as target lesions.

Bone lesions are considered non-measurable and therefore should all be classified as non-target lesions.

Post-baseline assessment:

At every response assessment visit after baseline, the Investigator will assess the following:

- target lesions selected at baseline, and
- non-target lesions selected at baseline, and
- search for new lesions.

The lesion assessments are then combined into an assessment of the entire subject at that visit (called the visit response or the overall response).

Target lesion assessment:

The Investigator will measure each target lesion in the same manner as at baseline.

Malignant lymph nodes will be measured in short axis diameter.

If a lesion decreases in size to the point where it is still present, but cannot be measured accurately, a default value of 5 mm should be recorded for its diameter.

If a lesion has disappeared, a value of 0 mm should be recorded for its diameter.

If a lesion has split into distinct fragments, the longest diameter of each fragment should be measured, and the diameters added together.

If 2 lesions have merged, the longest diameter of the entire resulting lesion should be measured.

The sum of diameters will be calculated by adding all target lesion diameters/short axis (for lymph nodes).

The sum of diameters is always compared to 2 reference points: the baseline sum of diameters, and the smallest sum of diameters seen during the study (also called the nadir). The baseline may actually be the nadir, if there has been no reduction in the sum of diameters during the study. The target lesion response is then classified as follows in Table 16–1.

Table 16–1: Target lesion response

Response	Response characteristics
Complete response (CR)	Complete disappearance of target lesions All target lymph nodes <10 mm
Partial response (PR)	At least a **30% decrease** in the sum of diameters from baseline
Progressive disease (PD)	At least a **20% increase** in the sum of diameters from the smallest value seen during the trial (including baseline), with at least a **5 mm** absolute increase in the sum
Stable disease (SD)	Neither enough shrinkage to qualify as PR, nor enough growth to qualify as PD
Non-evaluable (NE)	One or more target lesions not evaluated because of imaging issues, coverage, or change in imaging technique

Please note that when lymph nodes are included as target lesions, a CR may occur even when the sum of diameters is not zero, since a normal lymph node will have a diameter greater than zero but less than 10 mm.

Non-target lesion assessment:

Non-target lesions are assessed as a whole. After examining each non-target lesion, the Investigator will classify the non-target lesion response as follows in Table 16–2.

Table 16–2: Non-target lesion response

Response	Response characteristics
Complete response (CR)	Complete disappearance of all non-target lesions All non-target lymph nodes <10 mm
Progressive disease (PD)	Unequivocal progression of non-target lesions as a whole. • Subjective call by expert reviewer • Evaluated as a group, not lesion by lesion
Non-CR/Non-PD	Non-target lesions still present, without unequivocal progression
Non-evaluable (NE)	One or more non-target lesions not evaluated because of imaging issues, coverage, or change in imaging technique

To achieve unequivocal progression in subjects with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease (SD) or partial response (PR) in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression.

New lesions:

Any new lesion that is considered unequivocally malignant is evidence of progression, with no minimum size requirement.

An individual radiological event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiological testing. This means that if a new lesion is not unequivocal at the time of initial detection, but later becomes unequivocal, the date of progression will be the date it was first detected.

Specific considerations for new bone lesions and for unequivocal progression of existing bone lesions:

The finding of a new bone lesion or progression of existing bone lesions should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor: some new bone lesions or unequivocal increase in size of existing lesions may be simply healing or flare of pre-existing lesions.

The following rules will apply:

- A new bone lesion or progression of existing bone lesion/s initially identified on a technetium-99m bone scan must be confirmed by CT or MRI. If confirmed by CT/MRI, the date of occurrence of the new lesion or of progression of existing bone

lesion/s will be the date it was initially detected (by technetium-99m bone scan) even if the confirmation by CT/MRI was done at a subsequent scan.

- A new bone lesion or progression of existing bone lesions initially identified by CT/MRI (and not visible on a technetium-99m bone scan) will not need further confirmation by CT/MRI unless not considered unequivocal at time of initial documentation. The date of occurrence of new lesion or progression of existing lesions will be the date it was initially detected by CT/MRI.

New lesions and FDG PET imaging

New lesions on the basis of FDG PET imaging can be identified according to the following algorithm:

- (-) FDG PET at baseline and (+) FDG PET at follow-up = Progressive Disease (PD) based on a new lesion
- No FDG PET at baseline and (+) FDG PET at follow-up = PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of PD is the date of the initial FDG PET scan.
- No FDG PET at baseline and (+) FDG PET at follow-up corresponding to a pre-existing lesion on CT that is not progressing is **not** PD

Note: A 'positive' FDG PET scan lesion means one with uptake greater than twice that of the surrounding tissue on the attenuation corrected image

Visit response:

The response of the target lesions, the response of the non-target lesions, and the presence or absence of new lesions are combined into the visit response for the entire subject at this visit, using the tables below.

Table 16–3: Visit Response: Subjects with target lesions (with or without non-target lesions)

Target lesions	Non-target lesions	New lesions	Overall response
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
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 = non-evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

The following text descriptions of the visit response are logically equivalent to the tables above.

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 (SD): 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 (PD): At least a 20% increase in the sum of diameters of target lesions from 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 also constitute PD. Ascites or pleural effusion will be recorded as disease progression only if proven malignant.

In the absence of target disease, the following will apply (Table 16–4).

Table 16–4: Time Point Response: Subjects with non-target lesions only

Non-Target Lesions	New Lesions[a]	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[b]
Not all evaluated	No	NE
Unequivocal PD[c]	Yes or no	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = non-evaluable; PD = progressive disease.
[a] New lesions must be unequivocal (see bone lesions specifications)
[b] "Non-CR/non-PD" is preferred over "stable disease"
[c] "Unequivocal PD": Subjective call by expert reviewer. Evaluated as a group, not lesion by lesion

16.3 Calculation for glomerular filtration rate

Section modified by Amendment 1 (Section 15.1).

In accordance with established nephrology practice and guidelines, renal function at baseline 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 can be found at the following web site:
http://www.kidney.org/professionals/kdoqi/gfr_calculator.

16.4 New York Heart Association Functional Classification

Class	New York Health Association Functional Classification
I	Subjects have cardiac disease but *without* the resulting *limitations* of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects have cardiac disease resulting in *slight limitation* of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects have cardiac disease resulting in *marked limitation* of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects have cardiac disease resulting in *inability* to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

16.5 ECOG 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)

16.6 BPI-SF

Section modified by Amendment 4 (Section 15.3).

The severity of pain and its impact on daily functions will be self-assessed by the study subjects using the BPI-SF (54) 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.

The BPI-SF will be self-administered by the subject at Dose 1, Day 1 (before the start of study treatment), at each treatment visit, at the end of treatment visit and follow-up clinic visits. 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 her 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 her.

How should the Questionnaire be introduced?

A sample script for introducing the questionnaire 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 complete this questionnaire about your health on the day of each clinic visit. 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 her 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.

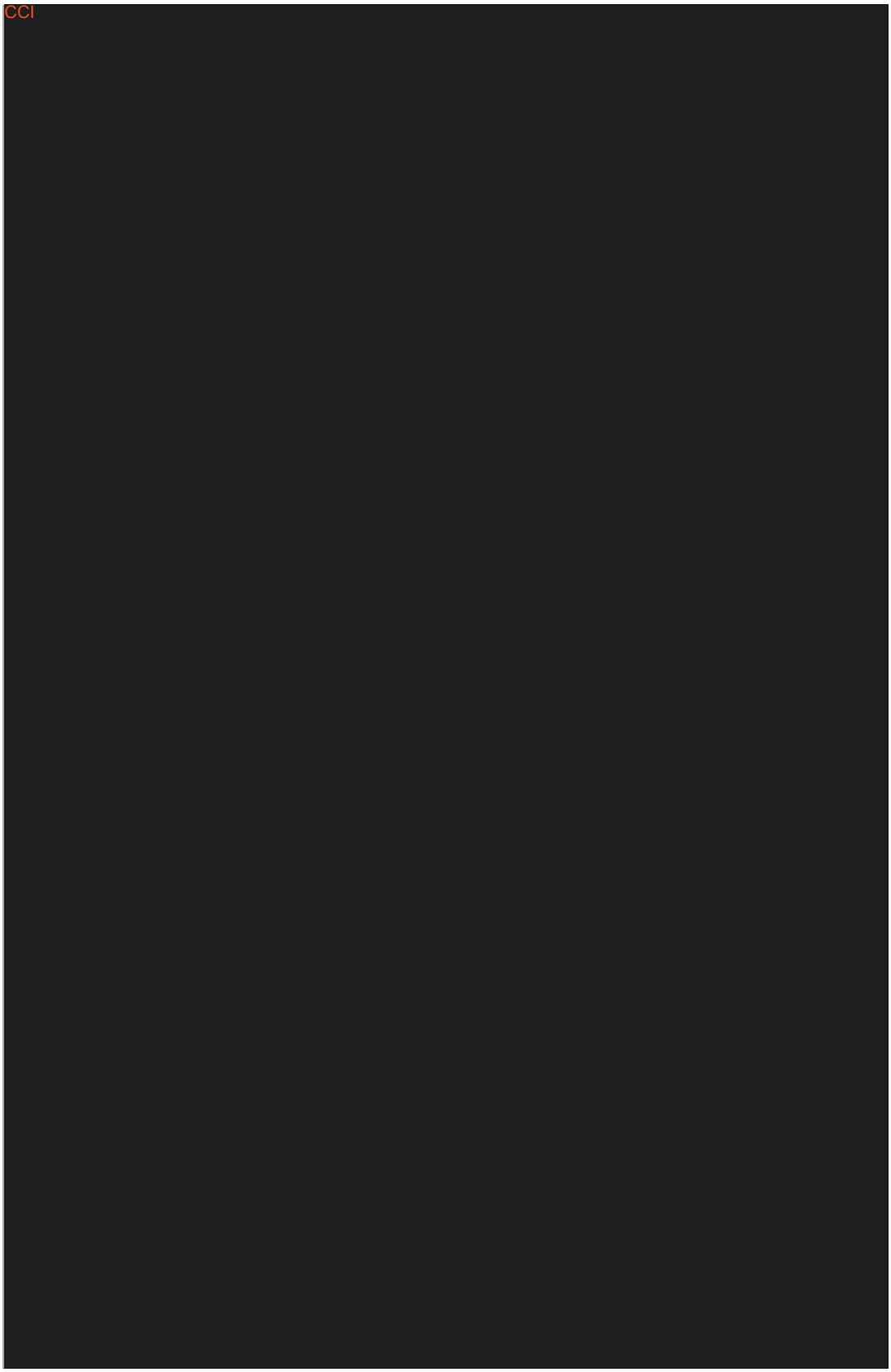
Questionnaire completion

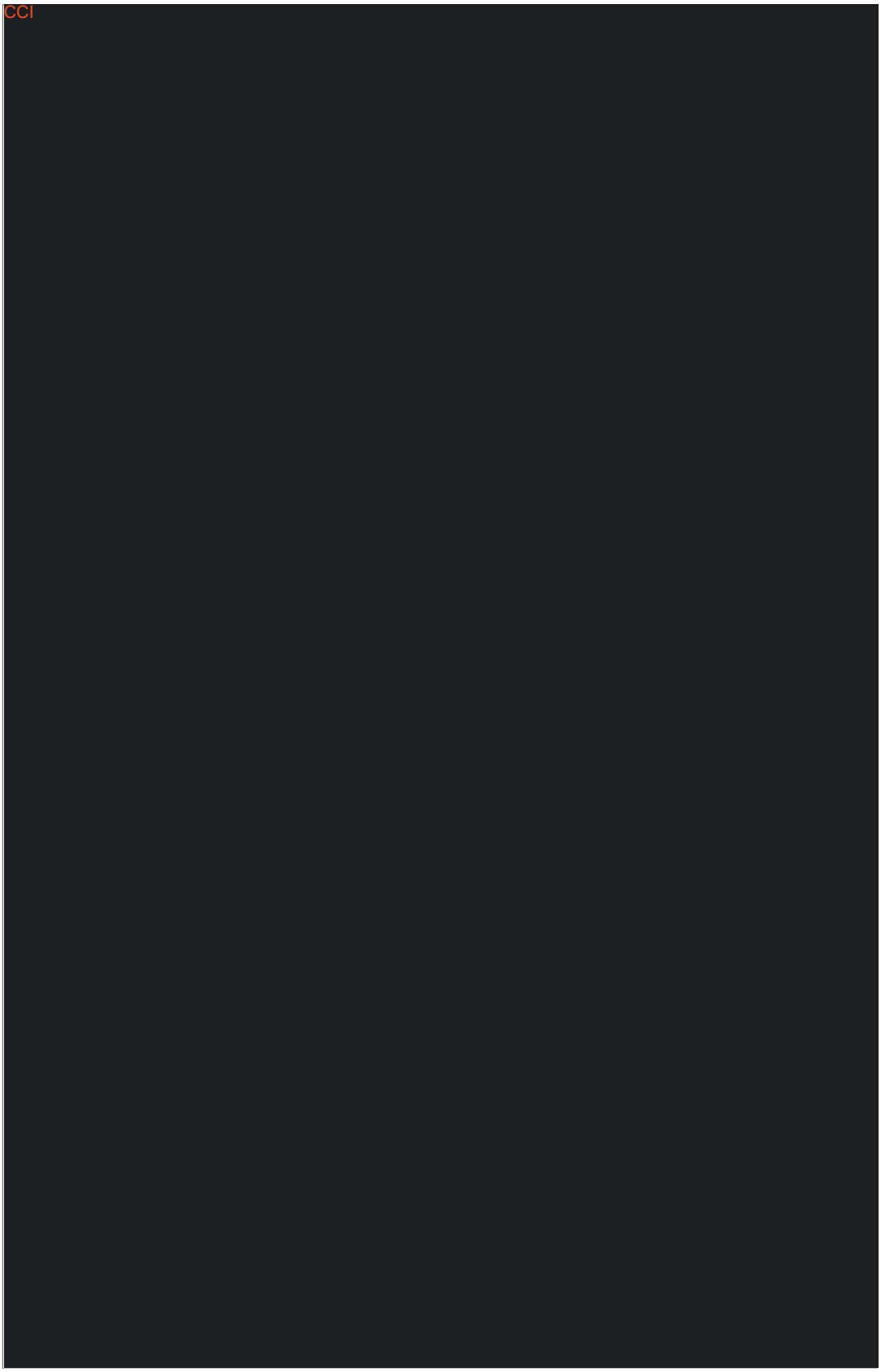
At the beginning of each visit, please check that the subject has completed the questionnaire, check that all of the questions have been answered. If the questionnaire is not complete, point out to the subject that some of the questions were not answered. If the subject does not quickly volunteer to answer these items, ask her whether she had any difficulty completing the questionnaire. If the subject says that she had trouble understanding a question, ask her why she had difficulty with that item. Re-read the question for her 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.

BPI-SF: questionnaire without questions 2 and 7, which does not affect the global pain score.




CCI

16.7 Resource utilization questionnaire

CCI


CCI

16.8 Patient Reported Questionnaire Information Sheet