A phase 1b/2 trial to evaluate the safety of radium-223 dichloride (BAY 88-8223) in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma.

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

- **Original protocol,** Version 1.0, dated 11 JUL 2016
- **Amendment no. 1** (described in Section 15.1)
  forming integrated protocol Version 2.0, dated 08 AUG 2017
- **Amendment no. 2** (described in Section 15.2)
  forming integrated protocol Version 3.0, dated 18 MAY 2018

This document integrates the original protocol and all global amendments.

1. Title page

A phase 1b/2 trial to evaluate the safety of radium-223 dichloride (BAY 88-8223) in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma.

Short title:	Phase 1b/2 study testing radium-223 dichloride in relapsed multiple myeloma		
Test drug:	BAY 88-8223 / radium-223 dichloride / Xofigo		
Study purpose:	Safety and early signals of anti-multiple myeloma activity		
Clinical study phase:	1b/2	Date:	18 MAY 2018
Registration:	EudraCT: 2016-002438-58	Version no.:	3.0
Sponsor's study no.:	18987		
Sponsor:	Non-US: Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer Healthcare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, USA		

Sponsor's medical expert: PPD
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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the Sponsor's medically responsible person

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

Name: PPD Role: Global Clinical Leader

Date: 18 May 2018 Signature: PPD

Signature of Principal Investigator

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

Name:

Affiliation:

Date: Signature:

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

2. Synopsis

Title	A phase 1b/2 trial to evaluate the safety of radium-223 dichloride (BAY 88-8223) in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma.
Short title	Phase 1b/2 study evaluating radium-223 dichloride in relapsed multiple myeloma
Clinical study phase	Phase 1b/2
Study objective(s)	**Phase 1b part (open-label)** Primary objectives: • To evaluate the safety of the combination of radium-223 dichloride plus bortezomib (BOR) and dexamethasone (DEX) • To determine the dose of radium-223 dichloride that will be used in the phase 2 part of the study (maximum tolerated dose [MTD] or recommended phase 2 dose [RP2D]) Secondary objectives: • To evaluate the combined complete response (CR) + very good partial response (VGPR), as determined by International Myeloma Working Group (IMWG) uniform response criteria **Phase 2 part (double-blind, randomized)** Primary objectives: • To compare radium-223 dichloride versus placebo in addition to background treatment with BOR plus DEX in terms of combined CR+VGPR rate in relapsed multiple myeloma subjects, as determined by International Myeloma Working Group (IMWG) uniform response criteria. Secondary objectives: • To evaluate safety • To evaluate the objective response rate (ORR), as determined by IMWG uniform response criteria • To evaluate overall survival (OS) • To evaluate progression-free survival (PFS) • To evaluate duration of response (DOR) Exploratory objectives: • To evaluate time to first on-study symptomatic skeletal event (SSE) • To evaluate bone biomarkers • To evaluate change in bone lesions • To evaluate change in MM disease markers • To evaluate circulating tumor DNA (ctDNA) and circulating

	tumor cells (CTCs) • To evaluate time to opioid use for cancer pain in subjects without opioid use at baseline • To evaluate time to pain progression
Test drug(s)	BAY 88-8223
Name of active ingredient	Radium-223 dichloride
Dose(s)	For the **Phase 1b** open-label part of the study, 2 dose levels of radium-223 dichloride may be administered, following sequential dose escalation using a '3 + 3' design: • **Cohort 1**: 33 kiloBecquerel (kBq)/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses in combination with BOR and DEX • **Cohort 2**: 55 kBq/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses in combination with BOR and DEX For the **Phase 2** double-blind randomized part of the study, the MTD/RP2D, as determined by the phase 1b part of the study, will be administered once every 6 weeks for a total of 6 radium-223 dichloride doses.
Route of administration	Intravenous (IV) injection (slow bolus)
Duration of treatment	Approximately 36 weeks: 6 doses; 1 dose every 6 weeks
Reference drug(s)	Matching placebo (isotonic saline) for the phase 2 part of the study
Name of active ingredient	Not applicable
Dose(s)	One dose every 6 weeks for a total of 6 doses
Route of administration	Intravenous (IV) injection (slow bolus)
Duration of treatment	Approximately 36 weeks: 6 doses; 1 dose every 6 weeks
Background treatment	(Applicable to both phase 1b and 2 parts of the study) **Bortezomib** will be administered subcutaneous (SC) at 1.3 mg/m^2/dose, on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles. For extended therapy beyond 8 cycles, BOR will be administered on Days 1 and 15 of a 28-day cycle for up to 2 years after the first dose of study treatment, or until progression-free survival (PFS) event occurs, the subject withdraws consent or unacceptable toxicity develops, whichever occurs first. **Dexamethasone** will be administered orally at 40 mg, on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles. DEX administration may be split over 2 days (on the day of BOR administration and the day after BOR administration) at the discretion of the Investigator. For extended therapy beyond 8 cycles, DEX will be administered orally at 20 mg/dose, on Days 1 and 15 of a 28-day cycle along with BOR for up to

	2 years after the first dose of study treatment or until a progression-free survival (PFS) event occurs, the subject withdraws consent or unacceptable toxicity develops, whichever occurs first.
Indication	Relapsed multiple myeloma
Diagnosis and main criteria for inclusion /exclusion	**Inclusion criteria** Subjects must meet **all** the following criteria for inclusion in the study: 1. Males or females ≥18 years of age 2. Have provided written informed consent. Subjects must be able to understand and be willing to sign the written informed consent, expressing their willingness and ability to comply with protocol-required treatment and assessment schedule, including follow-up visits. A signed informed consent form (ICF) must be appropriately obtained prior to the conduct of any trial-specific procedure. 3. Subject must have documented monoclonal plasma cells in the bone marrow of ≥10%, as defined by their institutional standard at some point in their disease history or the presence of a biopsy proven plasmacytoma 4. Subjects must have received at least 1 and not more than 3 previous lines of treatment and have had a response to at least 1 prior treatment in the past (i.e., achieved a minimal response [MR] or better) according to the IMWG uniform response criteria 5. Subject must be non-refractory to bortezomib (Refractory is defined: progression of disease while receiving bortezomib therapy or within 60 days of ending bortezomib therapy) 6. Subjects must have documented evidence of progressive disease according to the IMWG uniform response criteria following the last multiple myeloma treatment 7. Subjects must have measurable disease defined as at least 1 of the following: o Serum M-protein defined by the following: ▪ IgG multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL (measured by protein electrophoresis [PEP]) ▪ IgA, IgD, IgE, IgM multiple myeloma: serum M-protein level ≥0.5 g/dL (measured by PEP) o Urine M-protein ≥200 mg/24 hours (any immunoglobulin heavy chain type measured by PEP) o Serum free light chain (FLC) ≥10 mg/dL with abnormal ratio in subjects with unmeasurable disease by serum or urine PEP 8. ≥1 bone lesion identifiable by radiograph, computed tomography (CT), positron emission tomography – computed tomography (PET-CT), or magnetic resonance imaging (MRI) 9. Life expectancy of at least 3 months 10. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2 11. For subjects experiencing toxicities resulting from a previous therapy (including peripheral neuropathy), the toxicities must be resolved or stabilized to ≤Grade 1 12. Adequate hepatic function, with total bilirubin ≤1.5 x upper limit of normal (ULN) (except for Gilbert Syndrome: total bilirubin < 3.0 x ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x ULN

13. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L, hemoglobin (Hb) ≥9.0 g/dL, and platelet count ≥75.0 × 10^9/L independent of transfusion of red blood cells (RBC) or platelet concentrates and independent of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF)
    Note: Transfusion of RBC or platelet concentrates, use of G-CSF or GM-CSF within 21 days from ICF signature is not allowed.
14. International normalized ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) ≤ 1.5 x ULN. Prothrombin time (PT) may be used instead of INR if ≤ 1.5 x ULN
15. Estimated creatinine clearance of ≥30 mL/minute, according to the Cockcroft and Gault formula
16. Serum potassium levels >3.0 mEq/L
17. Corrected serum calcium <14.0 mg/dL (3.5 mmol/L)
18. Female subjects of child-bearing potential must have a negative urine pregnancy test within 72 hours before the first dose. Postmenopausal females (age ≥55 years and 1 year or more of amenorrhea; **or** age <55 years and 1 year or more of amenorrhea with an estradiol assay <20 pg/mL; **or** bilateral oophorectomy) and surgically sterilized females are exempt from a pregnancy test.
    a) Female subjects of child-bearing potential who are sexually active must agree to utilize 2 reliable and acceptable methods of contraception used simultaneously: a barrier method such as
    (i) condoms (male or female) with spermicidal agent, or
    (ii) diaphragm or cervical cap with spermicide, combined with a highly effective non-hormonal birth control method such as intra-uterine device, during treatment with and for 6 months following the last dose of radium-223 dichloride/placebo or 3 months after the last administration of bortezomib/dexamethasone, whichever occurs later.
    b) Male subjects with partners of child-bearing potential must be willing to use 2 reliable and acceptable methods of birth control (including adequate barrier protection) used simultaneously as determined to be acceptable by the principal investigator and the sponsor during the study and for 6 months following completion of treatment with radium-223 dichloride/placebo or 3 months after the last administration of bortezomib /dexamethasone, whichever occurs later. The contraception measures must be discussed with the subject. Suitable contraception could be, for example, the use of condoms combined with an oral contraceptive taken by the female partner of a study subject.

Exclusion criteria

Subjects must not meet any of the exclusion criteria listed below:

1. Systemic glucocorticoid therapy (prednisone >10 mg/day orally or equivalent) within the last 4 weeks prior to first dose, unless tapered and on a stable dose (prednisone ≤10 mg/day orally or equivalent) for at least 1 week
2. Subjects with known POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or light-chain (AL) amyloidosis
3. Plasma cell leukemia (defined by plasma cell >20%, and/or an absolute plasma cell count of >2 x 10^9/L in peripheral blood)
4. Subject has received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic (PK) half-lives ($t_{1/2}$) of the treatment, whichever is longer, before the date of start of treatment.

	5. Radiation therapy in the previous 4 weeks prior to first dose. Note: Subjects treated with local radiotherapy which is recommended to be limited fields for pain control are eligible. 6. Administration of an investigational therapeutic study drug (including investigational vaccines) within 4 weeks or within 5 PK ($t_{1/2}$) of the treatment, whichever time is greater, before the date of start of treatment 7. Prior treatment with radium-223 dichloride or any experimental radiopharmaceutical 8. Major surgery within 4 weeks prior to first dose (central line placement and kyphoplasty are not considered major surgery) 9. Congestive heart failure (New York Heart Association [NYHA] class III to IV), symptomatic cardiac ischemia, unstable angina or myocardial infarction in the previous 6 months prior to first dose, or with a known left ventricular ejection fraction (LVEF) <40%, cardiomyopathy, pericardial disease, clinically relevant cardiac arrhythmia (CTCAE version 4.03 Grade 2 or higher), clinically significant ECG abnormalities, or screening 12-lead ECG showing a baseline prolonged QT interval (baseline QT interval as corrected by Fridericia's formula > 470 msec). Note: LVEF values will not be collected, however the investigator must verify and subjects must be excluded if LVEF <40% at study entry. 10. Acute diffuse infiltrative pulmonary disease 11. Acute active infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks prior to first dose 12. Known HIV infection or subjects who are known to be HIV seropositive 13. Subjects with active hepatitis B or C infection at screening. Subjects with a known history of occult hepatitis B virus (HBV) infection (defined as positive hepatitis B core antibody [HBcAb] and negative hepatitis B surface antigen [HBsAg]), but who have undetectable HBV DNA at screening may be included. Subjects with a history of positive hepatitis C virus (HCV) antibody must be negative for HCV RNA by polymerase chain reaction (PCR) assessment or similar technology to be included. 14. Any history of malignancy within the past 3 years except adequately treated a) basal cell or squamous cell skin cancer, b) carcinoma in situ of the cervix, c) prostate carcinoma in situ < Gleason Score 6 with stable prostate-specific antigen (PSA), or d) breast carcinoma in situ 15. Neuropathy ≥ Grade 2 16. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis 17. Subjects with known meningeal and/or extramedullary involvement of MM 18. Known allergies, hypersensitivity or intolerance to radium-223 dichloride, bortezomib, or dexamethasone or their excipients. 19. Any clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent 20. Female subjects who are pregnant or lactating 21. Serious psychiatric condition that could interfere with compliance of treatment 22. Close affiliation with the investigational site (e.g., a close relative of the Investigator, dependent person [e.g., employee or student of the investigational site])

	23. Previous assignment to treatment during this study
Study design	Phase 1b part: International, open-label, dose-escalation study consisting of up to 2 cohorts at different dose levels to determine maximum tolerated dose/recommended phase 2 dose for phase 2. Phase 2 part: International, double-blind, randomized, placebo-controlled efficacy and safety study.
Methodology	This phase 1b study will evaluate 2 dose levels of radium-223 dichloride in combination with BOR and DEX (Cohort 1 and Cohort 2) in subjects with relapsed MM. Subjects will be treated at 2 different dose levels with radium-223 dichloride following sequential dose escalation using a "3+3" design. The starting dose of 33 kBq/kg body weight will be combined in Cohort 1 with BOR and DEX every 6 weeks for a total of up to 6 doses of radium-223 dichloride, which is a lower dose than the dose of radium-223 dichloride monotherapy approved for CRPC (55 kBq/kg body weight). The next dose level of 55 kBq/kg body weight will be evaluated with BOR and DEX in Cohort 2. The dose escalation will follow a '3 + 3' design for all evaluated combinations in Cohort 1 and Cohort 2. No intra-subject dose escalation or overlapping recruitment of cohorts will be permitted. All subjects enrolled in the study, must be evaluated for the occurrence of dose-limiting toxicities (DLTs) during the DLT observation window, which is defined as the time from the first dose of study treatment through 3 weeks after administration of the second dose of radium-223 dichloride. Subjects not evaluable for assessment of DLT due to early discontinuation for reasons other than DLT or subjects who have not completed 2 doses of radium-223 dichloride and 2 cycles of BOR/DEX will be replaced until the MTD/RP2D has been determined. Dose-limiting toxicities, using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for the severity grade, are defined as follows: 1. Grade 4 neutropenia for > 7 days, or febrile neutropenia with or without supportive care* 2. Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with ≥ Grade 2 bleeding, or Grade 3 thrombocytopenia lasting > 2 weeks with or without supportive care* 3. Grade 3 to 4 anemia lasting > 2 weeks with or without supportive care* 4. Grade 3 non-hematological toxicity, except: ▪ diarrhea, vomiting, and fatigue that resolve within 72 hours with or without supportive care ▪ neuropathy 5. Any Grade 4 non-hematological toxicity (lab abnormalities of any grade will not be considered toxicity unless deemed clinically significant by the investigator) * Any toxicity can be treated according to the institutional guidelines which may include G-CSF, RBC and platelet transfusions. In order to determine the DLT, such supportive care measures should not be given prophylactically during the DLT assessment period but are allowed to start

after cycle 3 of BOR/DEX.

Decisions on whether to step up to the next dose level will follow the rules described below:

- If 0 out of 3 experience DLT: proceed to next dose level
- If 1 out of 3 experience DLT: enter 3 more subjects at this dose level
- If 1 out of the 6 subjects experience a DLT: proceed to next dose level
- If 2 or more subjects experience a DLT: do not proceed to next dose level and the current dose level will be declared as the non-tolerable dose. The dose level immediately below will be the MTD/RP2D.
- If 2 subjects experience a DLT at 33 kBq/kg body weight with any combination, the study will be terminated.
- Alternatively, once the safety and tolerability of the non-tolerable dose level are reviewed, the investigators and the sponsor may decide to investigate an appropriate dose level.

Safety monitoring will occur by telephone conferences (safety calls) between the Investigators and Sponsor. Dose escalation meetings (DEM) involving the Steering Committee, Investigators, and the Sponsor will be organized after all subjects of each dose cohort have been sufficiently observed for the DLT assessment. If no DLTs are experienced in any dose cohort, MTD/RP2D will be based on a safety data summary review (including, but not limited to, AEs, dose modifications, and laboratory changes) conducted by the Steering Committee, participating Investigators, and the Sponsor. All subjects will stay in the study and continue receiving study drug at the assigned dose level until the withdrawal criteria are met or the subjects complete the study.

The Phase part 2 of the study will evaluate the activity and safety of radium-223 dichloride in combination with BOR and DEX versus placebo in combination with BOR and DEX. For the phase 2 part of the study, an Independent Data Monitoring Committee (IDMC) will review the safety data once 20 and 50 subjects have completed 2 doses of radium-223 dichloride or placebo in combination with BOR/DEX (plus a follow-up of at least 3 weeks after the second radium-223 dichloride/placebo dose) treatment, and every 6 months thereafter.

After the first IDMC meeting, the following events will initiate ad-hoc IDMC meetings:

- ≥ 33% of subjects discontinue study treatment due to TEAEs or
- ≥ 33% of subjects experience Grade 4 treatment-related hematologic toxicities.

The IDMC members will provide recommendations about the continuation of study with or without any modifications based on safety data and if any of the stopping criteria have been observed with an absolute increase of ≥ 33 percentage points in the active arm over the placebo controlled arm of the study (using CTCAE version 4.03 for the severity grade). Stopping criteria are defined as follows in alignment with the Phase 1b portion of the trial if they occurred within the time from the first dose of study treatment through 2 doses of radium-223 administration + 3 weeks after 2nd radium-223 administration:

- Grade 4 neutropenia for > 7 days, or febrile neutropenia with or

	without supportive care • Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with ≥ Grade 2 bleeding, or Grade 3 thrombocytopenia lasting > 2 weeks with or without supportive care • Grade 3 to 4 anemia lasting > 2 weeks with or without supportive care • Grade 3 non-hematological toxicity, except: o diarrhea, vomiting, and fatigue that resolve within 72 hours with or without supportive care o neuropathy Any Grade 4 non-hematological toxicity (lab abnormalities of any grade will not be considered a toxicity unless deemed clinically significant by the investigator). The study participation for each subject in both study phases will comprise 3 periods: screening, treatment, and the follow up period (active follow-up with clinic visits, as per local standard of care and long-term follow-up with telephone calls). A randomization step is planned for phase 2 only. Subjects will stay in the study until they have completed the 2 year active follow up period after the last administration of radium-223 dichloride. Subjects who have completed the 2 year active follow-up will be followed with a telephone call every 6 months (±28 days) for up to 5 years. A 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. All subjects will be asked to transition into this separate study to complete their long-term follow-up. The long-term follow-up may start in the current trial and subjects will then be asked to transition into the separate roll-over study. **Screening period**: Applicable to Phase 1b and Phase 2. 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 21 days starting from the time of ICF signature, to ensure that all eligibility criteria are met. Bone marrow biopsy or aspirate, skeletal survey and local blood and urine protein-M tests (as well as any other specific multiple myeloma tumor assessment blood and urine tests) previously done as part of routine care will be accepted for eligibility confirmation purposes even if done prior to ICF signature, as long as these tests have been performed up to 14 days prior to ICF signature. If logistical reasons require, local lab results for blood and urine protein-M and other specific multiple myeloma tumor assessment tests ordered after ICF signature can also be used for eligibility assessment only, to ensure that eligibility confirmation timelines are met. If any local lab samples are used to run tumor assessment tests for eligibility confirmation, blood and urine samples for central lab analysis will still be collected and used as the final baseline value for data analysis. Given the complexity of screening assessments, investigators are encouraged to have subjects sign ICF on the same day in which protocol procedures will be undertaken, to avoid starting the screening period too early and reducing the number of screening days actually available in

practice.

After eligibility has been confirmed and documented, an additional period of up to a total of 21 days may take place before the administration of the first study drug, to account for all logistical needs related to radium-223 dichloride dose preparation and transportation. All efforts will be made to shorten this period as much as possible.

Randomization step (only for phase 2):

Once eligibility is confirmed and documented, eligible subjects will be randomized in a ratio of 1:1 to treatment with radium-223 dichloride plus BOR and DEX (Arm A) or placebo (isotonic saline) plus BOR and DEX (Arm B).

Treatment period:

Phase 1b part: Treatment consists of up to 6 doses of radium-223 dichloride (1 dose every 6 weeks) at 2 different planned dose levels administered to ascending dose cohorts, in combination with 10 cycles (3 weeks per cycle for the first 8 cycles, then 4 weeks per cycle) of BOR and DEX, followed by ongoing maintenance treatment with BOR and DEX (4 weeks per cycle) up to 2 years after the first dose of study treatment or until a PFS event occurs (death or MM progression as per IMWG uniform criteria), unacceptable toxicity develops, or the subject withdraws consent, whichever occurs first.

Phase 2 part: Treatment consists of up to 6 doses (1 dose every 6 weeks) of radium-223 dichloride (Arm A) or placebo (Arm B) in combination with 10 cycles (3 weeks per cycle for the first 8 cycles, then 4 weeks per cycle) of BOR and DEX, followed by ongoing maintenance treatment with BOR and DEX (4 weeks per cycle) up to 2 years after the first dose of study treatment or until a PFS event occurs (death or MM progression as per IMWG uniform criteria), unacceptable toxicity develops, or the subject withdraws consent, whichever occurs first.

All subjects must have safety evaluations for 30 days after the last dose of study treatment. If the subject does not return for a 30-day safety follow-up visit regardless of the reason, the site should at a minimum contact the subject for the 30-day safety follow-up by telephone, email, or letter.

Active follow-up period:

Subjects who have discontinued study treatment for any reason including progressive disease (PD) will be followed with a clinical visit every 8 weeks (±7 days) up to 2 years after the last dose of radium-223 dichloride/placebo treatment or until death occurs, or the subject withdraws consent, whichever occurs first.

During active follow-up subjects will be followed for response/disease progression (in case not progressed), treatment-related AEs/SAEs, any anti-cancer treatment and bone health agent (BHA), and SSEs.

Particularly: new primary malignancy (including AML) or hematological conditions (e.g., MDS, aplastic anemia, myelofibrosis) must be reported as SAEs at any time and regardless of the investigator's causality assessment; all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment, through the active follow-up. Radium-223 dichloride-related occurrences of febrile neutropenia or hemorrhage will also be collected.

	In addition to protocol requirements, subjects will be treated and followed as per the institutional standard of care and/or according to the physician's clinical judgment. **Long-term follow-up period**: Subjects who have completed the 2 year active follow-up will be followed with a telephone call every 6 months (±28 days) for up to 5 years. A 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. All subjects will be asked to transition into this separate study to complete their long-term follow-up. The long-term follow-up may start in the current trial and subjects will then be asked to transition into the separate roll-over study. During long-term follow-up subjects will be followed for survival status, treatment-related AEs/SAEs, any anti-cancer treatment and bone health agent (BHA). Particularly: new primary malignancy (including AML) or hematological conditions (e.g., MDS, aplastic anemia, myelofibrosis) must be reported as SAEs at any time and regardless of the investigator's causality assessment; all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment, through the long-term follow-up. Radium-223 dichloride-related occurrences of febrile neutropenia or hemorrhage will also be collected. Subject management, unless defined otherwise in this protocol, will be in accordance with routine clinical practice, at the discretion of the Investigator.
Type of control	Placebo in combination with bortezomib/dexamethasone (for the phase 2 part of the study only)
Steering Committee/Data Monitoring Committee	For the phase 1b part of the study, decisions involving dose escalation, dose de-escalation, cohort expansion, or the MTD/RP2D will be determined by the Steering Committee, participating Investigators, and the Sponsor. The Steering Committee (SC) will be established comprising investigators participating in the trial and external experts in the treatment of multiple myeloma. For the phase 2 part of the study, decisions involving how to proceed with blinded randomized study will be determined by an Independent Data Monitoring Committee (IDMC) responsible for safety data review. The SC role includes providing input on study design and conduct, decisions during dose escalation meetings and recommendations to continue, modify or to stop the study. The IDMC role is to periodically monitor the study for safety, study progress, and protocol compliance, as well as to assess the risk/benefit of the trial.
Number of subjects	Phase 1b part: Up to approximately 12 total subjects in all dose cohorts combined Phase 2 part: Approximately 100 subjects in total (with 1:1 randomization)

Primary variable(s)	For phase 1b part: Number of subjects with DLTs For phase 2 part: Combined CR/VGPR rate after 6 cycles of radium-223 dichloride, as per the IMWG uniform response criteria.
Time point/frame of measurement for primary variable(s)	The final analysis of phase 1b data will be conducted when all subjects in the phase 1b part have completed 6 doses of radium 223 with the required safety follow up of study treatment, or have discontinued early. For the phase 2 part, the primary analysis of combined CR/VGPR rate will be conducted after all subjects have completed the end of radum-223 dichloride visit and the final analysis of combined CR/VGPR rate will be conducted when all subjects enrolled have completed the end of treatment visit (also including the maintenance therapy). The expected study duration starts with the first study treatment and continues up to 2 years after last patient first treatment (LPFT), followed by an additional 1 month of safety follow-up.
Plan for statistical analysis	All the analyses will be performed separately for the phase 1b part and the phase 2 part of the study. For Phase 1b part, the statistical summary for the safety and efficacy parameters will be provided by dose level cohort. Phase 2 part: Safety variables will be analyzed using frequency tables and descriptive statistics by treatment arm. Fisher's exact test will be used for evaluating response rate difference between treatment groups. Response rate difference and its exact 95% CI will be provided. The descriptive statistics will also be used to summarize response rates (combined CR+VGPR, ORR [CR+VGRP+PR]), and anti-multiple myeloma response assessment, as determined by International Myeloma Working Group (IMWG) uniform response criteria. The number of responders, percentage of responders and 95% confidence interval [CIs]) will be presented by treatment arm. Time to event endpoints (e.g., PFS, OS, DOR, time to SSE, time to pain progression and time to opioid use) will be summarized by treatment arm using Kaplan-Meier estimates. Kaplan-Meier curves will be generated and median survival time together with the 25^{th} and 75^{th} percentiles and associated Brookmeyer-Crowley 95% CIs will be presented. There is no formal interim analysis planned for the primary efficacy endpoint. In the event that enrollment is halted by the IDMC after the review of safety data, an interim analysis may be performed on all randomized subjects during the phase 2.

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List of abbreviations

AE	Adverse event
ADL	Activities of daily living
AL	Light-chain amyloidosis
ALP	Alkaline phosphatase
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AP	Antero-posterior
APEX	Assessment of Proteosome Inhibition for Extending Remissions
AQA	Analgesic Quantification Algorithm
AST	Aspartate aminotransferase
BHA	Bone health agents
BOR	Bortezomib
BPI-SF	Brief Pain Index-Short Form
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
con med	Concomitant medication
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRO	Contract Research Organization
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
ctDNA	Circulating tumor DNA
CTCs	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events; version 4.03
D	Day
DEM	Dose escalation meeting
DES	Dose evaluable set
DEX	Dexamethasone
DK	Decay correction factor
DL	Dose level
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
EAP	Early Access Program
EBRT	External beam radiotherapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture

EMD	Extramedullary disease
EOS	End of study
EOT	End of treatment
EU	European Union
FDA	United States Food and Drug Administration
FEV	Forced expiratory volume
FLC	Free light chain
G-CSF	Granulocyte colony-stimulating factor
GCP	Good clinical practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IC	Investigator's choice
ICF	Informed consent form
ICH	International Conference on Harmonization
ICTP	Type I collagen telopeptide
ID	Identification number
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IF	Immunofixation
IMiDs	Immunomodulatory drugs
IMP	Investigational medicinal product
IMWG	International Myeloma Working Group
INR	International normalized ratio of prothrombin time
IRB	Institutional Review Board
ISS	International Staging System for Multiple Myeloma
ITT	Intent-to-treat
IV	Intravenous
IxRS	Interactive Voice/Web Response System
kBq	KiloBecquerel; SI unit of radioactivity
kg	Kilogram
LDH	Lactate dehydrogenase
LET	Linear energy transfer
mAbs	Monoclonal antibodies
Maint	Maintenance
mCi	Millicurie
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MR	Minimal response

MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIST	National Institute of Standards and Technology
NYHA	New York Heart Association
OME	Oral morphine equivalents
ORR	Objective response rate
OR	Overall response
OS	Overall survival
PA	Postero-anterior
PCP	Pneumocystis carinii pneumonia
PCR	Polymerase chain reaction
PD	Progressive disease
PEP	Protein electrophoresis
PET-CT	Positron emission tomography – computed tomography
PFS	Progression-free survival
PI	Proteasome inhibitor
PINP	Procollagen type I N-propeptide
PK	Pharmacokinetics
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PR	Partial response
PRD	Patient-ready dose
PS	Performance status
PSA	Prostate-specific antigen
PT(-INR)	Prothrombin time(-international normalized ratio)
PTT	Partial thromboplastin time
Q/q	Every
RANKL	Receptor activator for nuclear factor–κB ligand
RAVE	Medidata Rave; electronic data capture tool
RBC	Red blood cell
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RUQ	Resource Utilization Questionnaire
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical analysis plan
SC	Subcutaneous
sCR	Stringent complete response
SCTx	Serum C-terminal cross-linking telopeptide of type-I collagen
SLAM	Signaling lymphocytic activation molecule
SD	Stable disease
SPEP	Serum protein electrophoresis
SRE	Skeletal-related event
SSE	Symptomatic skeletal event

SUMMIT	Study of Uncontrolled Myeloma Management with proteasome Inhibition Therapy
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Drug half-lives
TTP	Time to progression
ULN	Upper limit of normal
UNTx	Urine N-terminal cross-linking telopeptide of type-I collagen
UPEP	Urine protein electrophoresis
US	United States
Vd	Bortezomib, dexamethasone
VGPR	Very good partial response
WBC	White blood cell
wk	Week

Definitions of terms

Radium-223 dichloride	The investigational product, a targeted alpha particle-emitting radiopharmaceutical, is a ready-to-use solution for intravenous (IV) 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. The term "dose" is used to describe the quantity of radioactivity from radium-223 administered.
Line of treatment	A line of treatment is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered 1 line of treatment. A new line of treatment starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of treatment also starts when a planned period of observation off treatment is interrupted by a need for additional treatment for the disease.(1)
Study drug	For this study, the term "study drug" specifically refers to radium-223 dichloride.
Study treatment	For this study, the term "study treatment" can refer to any or all of the drugs being investigated in this study for therapeutic intent: radium-223 dichloride, bortezomib, and dexamethasone.

3. Introduction

3.1 Background

Multiple myeloma (MM) or plasma cell myeloma, globally, resulted in about 74,000 deaths in 2010, up from 49,000 in 1990. In 2014, there were approximately 118,539 people in the United States (US) living with plasma cell myeloma, and according to Surveillance, Epidemiology, and End Results data, an estimated 30,280 new cases of myeloma were diagnosed in 2017 in the US. The age-adjusted incidence rate for plasma cell myeloma is 6.6 per 100,000 per year.(2)

It is the third most prevalent blood cancer after non-Hodgkin's lymphoma and leukemia, and represents approximately 1.8% of all cancers and 2.1% of all cancer deaths.(3) Recent statistics indicate that the incidence has been increasing 0.8% per year based on 2011-2013 data , while 5-year relative survival rates have also increased (from 26.3% in 1973 to 49.6% in 2007-2013).(2)

The median age at diagnosis is 69 years. MM affects more men than women in all racial groups, and Afro-Caribbeans have the highest prevalence rate. The incidence of myeloma is reported to be 1.5 times higher in men than women, and 2 times higher among African-Americans than among Caucasians.(4)

MM is a cancer of plasma cells, differentiated B-cell lymphocytes normally responsible for producing antibodies. In MM, collections of abnormal plasma cells accumulate in the bone marrow, where they interfere with the production of normal blood cells. Most cases of MM also feature the production of a paraprotein, an abnormal antibody which can cause kidney problems. Bone lesions and hypercalcemia are also often encountered.

MM is diagnosed with blood tests (serum protein electrophoresis [SPEP], serum-free kappa/lambda light chain [FLC] assay), bone marrow examination, urine protein electrophoresis (UPEP), and X-rays of commonly involved bones.

MM bone lesions are due to increased osteoclast activity and reduced osteoblast function, resulting from the overexpression of receptor activator for nuclear factor-κB ligand (RANKL) by bone marrow stroma.(5) The RANKL activates osteoclasts, which reabsorbs bone. The resultant bone lesions are lytic in nature (cause breakdown) and are best seen in plain radiographs, which may show "punched-out" reabsorptive lesions (including the "pepper pot" appearance of the skull on radiography). Radiation therapy is sometimes used to reduce pain from bone lesions. Bone pain affects more than 70% of subjects and is the most common symptom. Myeloma bone pain usually involves the spine and ribs, and worsens with activity. Persistent localized pain may indicate a pathological bone fracture. Involvement of the vertebrae may lead to spinal cord compression. The breakdown of bone also leads to release of calcium into the blood, leading to hypercalcemia and its associated symptoms.

The natural history of myeloma is of relapse following treatment. Multiple myeloma is clinically characterized beyond plasma cells abnormalities by infiltration of the bone marrow with differentiated plasma cells that cause lytic lesions in large bones and vertebrae, leading to skeletal-related events (SREs).

MM is considered to be incurable, but treatable. Remissions may be induced with steroids, chemotherapy, proteasome inhibitors (PIs), immunomodulatory drugs (IMIiDs), monoclonal antibodies (mAbs) and stem cell transplants. Radiation therapy is sometimes used to reduce pain from bone lesions. Depending on the patient's condition, the prior treatment modalities used and the duration of remission, options for relapsed disease include re-treatment with the original agent (if relapse >6 months) or use of other alternative agents, alone or in combination. Later in the course of the disease, "treatment resistance" occurs. This may be a reversible effect, and some new treatment modalities may re-sensitize the tumor to standard therapy.

Since 2003, bortezomib (Velcade®), the first generation proteasome inhibitor, is considered an important background therapy for all stages of MM, including new diagnosed subjects, relapsed and relapsed/refractory disease, maintenance therapy, high risk, and renal failure. The thalidomide derivatives, lenalidomide (Revlimid) and pomalidomide (Pomalyst) as well as the proteasome inhibitor carfilzomib (Kyprolis), and a pan-deacetylase inhibitor, panobinostat (Farydak), may be used for relapsed and refractory multiple myeloma. Very recently, positive data have been demonstrated with monoclonal antibodies (mAbs), such as elotuzumab (anti-SLAMF7 antibody) in combination with lenalidomide and dexamethasone and daratumumab (anti-CD38 antibody) in combination with bortezomib and dexamethasone.

Due to the certainty of relapse of nearly 100% subjects, relapsed/refractory MM represent an unmet medical need despite the new treatment options available. An established effective double combination treatment in early relapsed disease was bortezomib/dexamethasone (Assessment of Proteasome Inhibition for Extending Remissions [APEX] study).(5;7;8).

Most recently several phase III trials have demonstrated that triplet combinations are associated with a deeper response and a longer duration of response compared to doublet standard treatments, which may better control the emerging drug resistant clones leading to progression. (9)

Monoclonal antibodies are an important new class of agents with marked activity either as single agent and/or in combination with in relapsed/refractory MM (6). Recently, two phase III trials have demonstrated that adding daratumumab to bortezomib and dexamethasone (DVd) or lenalidomide and dexamethasone (DRd) (8), markedly improved PFS, ORR, CR and VGPR with manageable toxicities (10;11) leading to an approval of these two regimens as primary option for the treatment of relapsed/refractory MM subjects who received at least one prior line of therapy.

Overall despite the introduction of new classes of compounds in the past decade leading to significant PFS improvements, the use of multiple lines of therapy is limited by the overlapping mechanisms of action of the available agents. Therefore, there is a need for new agents with different mechanisms of action for subjects with relapsed or relapsed and refractory MM.

The infiltration of the bone marrow with differentiated plasma cells that cause lytic lesions in large bones and vertebrae, leading to skeletal-related events (SREs) is a characteristic of relapsed MM. The investigation of radium-223 dichloride in an *in vivo* MM model has

shown promising bone-targeting effects as monotherapy and in combination with bortezomib (12).

All together these data support the evaluation of radium-223 dichloride in the clinical myeloma setting

3.2 Study treatments

3.2.1 Radium-223 dichloride (BAY 88-8223, Xofigo)

Radium-223 dichloride solution for injection is a targeted alpha particle-emitting radiopharmaceutical. The bone-targeting property of radium-223 is similar to that of other alkaline earth elements, like calcium or strontium-89. However, the radiation characteristics of an alpha particle-emitting radionuclide appear to be more advantageous than that of a beta-emitting radionuclide. Radium-223, with a physical half-life ($t_{½}$) of 11.4 days, emits high linear energy transfer (LET) alpha radiation, with a range limited to less than 100 micrometers. The high LET of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases.(13)

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.(14;15) Due to increased bone metabolism in skeletal metastases, preferential uptake in these lesions compared to normal bone is observed. Significant radium-223 anti-tumor effects have been demonstrated in experimental osteoblastic prostate cancer in mice (13) and osteolytic breast cancer skeletal metastases models in mice (16), and in rats.(14)

The clinical development of radium-223 dichloride was initiated in 2001 and consists of a total of 26 studies, including two Expanded Access Programs, and two Managed Access Programs in subjects with bone metastases from prostate cancer, breast cancer and other solid tumors or MM, up to the cut-off date of 14 NOV 2016. Nineteen studies, considering also two Expanded Access Programs and two Managed Access Programs, included only subjects with prostate cancer with bone metastases; three studies included only subjects with metastatic breast cancer (MBC) with bone metastases; while one study included subjects with bone metastases from prostate cancer or from breast cancer; one study included subjects with solid tumors and this Study included subjects with Myeloma. Subjects who have completed treatment with radium-223 dichloride in selected clinical studies are included in the long-term follow-up program. The initial focus of development for radium-223 dichloride is metastatic prostate cancer in which eight studies have been conducted.

A phase III study was conducted to evaluate the efficacy and safety of radium-223 dichloride. ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) was a multinational, randomized, double-blind, placebo-controlled study in subjects with symptomatic castration-resistant prostate cancer (CRPC) with bone metastases.(17;18;19). The trial started in 2008 and results have been published in 2013. A total of 922 subjects were randomized 2:1 to receive 6 intravenous (IV) doses of either radium-223 dichloride or placebo every 4 weeks. Subjects were followed until 3 years from the first dose of study drug. The Independent Data Monitoring Committee recommended to unblind the ALSYMPCA trial based on results of a pre-planned interim analysis that evaluated OS.

Based on the positive results of the ALSYMPCA study, radium-223 dichloride was approved in the US in May 2013 and in the European Union (EU) in November 2013 for the treatment of subjects with CRPC with bone metastases, and is currently marketed for this indication.

Radium-223 dichloride is under clinical development for breast cancer with bone metastases. Further detail can be found in the IB, which contains comprehensive information on the study drug.

Based on the data generated in the clinical development program with radium-223 dichloride it appeared that the safety profile of radium-223 dichloride and the treatment effect on bone metastases was consistent throughout the studies.

In this study, it is proposed to investigate radium-223 dichloride for the treatment of relapsed multiple myeloma.

Interaction potential with other medicinal products

Radium-223 is an isotope which decays and is not metabolized by any enzyme. No impact on radium-223 is, therefore, expected by polymorphic enzymes. Radium-223 dichloride is administered intravenously; therefore, absorption-related differences are not applicable for this compound. Given these properties of radium-223 dichloride, it is unlikely that pharmacokinetic (PK) interaction may occur.

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

3.2.2 Bortezomib in combination with dexamethasone

Bortezomib

Bortezomib is a small, cell permeable molecule that specifically and selectively inhibits the proteasome by binding tightly with the enzyme’s active sites. This is the first-in-class of proteasome inhibitors.

Bortezomib is indicated for treatment of subjects with multiple myeloma via subcutaneous (SC) or intravenous (IV) administration routes only.

According to the bortezomib prescribing information, bortezomib is contraindicated in subjects with hypersensitivity to the active substance, to boron, or any of the excipients.

Most commonly reported adverse reactions (incidence ≥20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.

Overall, safety data were similar for the subcutaneous (SC) and intravenous (IV) treatment groups; differences were observed in the rates of some Grade ≥3 adverse reactions. Differences of ≥5% were reported in neuralgia (3% SC versus 9% IV), peripheral neuropathies (6% SC versus 15% IV), neutropenia (13% SC versus 18% IV), and thrombocytopenia (8% SC versus 16% IV). The incidence of Grade ≥2 peripheral neuropathy was 24% for SC versus 39% for IV administration and Grade ≥3 was 6% in the SC treatment group and 15% in the IV group. A local reaction was reported in 6% of

subjects in the SC group, mostly redness, resolved in a median of 6 days. Dose reductions occurred due to adverse reactions in 31% of subjects in the SC treatment group compared with 43% in the IV treatment group. (20;29)

For further details regarding bortezomib please consult specific product labeling.

Dexamethasone

According to the dexamethasone prescribing information, risks for treatment with dexamethasone are summarized as follows: allergic reactions, cardiovascular events, dermatologic events, endocrine events, fluid and electrolyte disturbances, gastrointestinal events, metabolic events, musculoskeletal events, neurologic/psychiatric events, ophthalmic events and other such as decreased resistance to infection. (21)

The safety data of dexamethasone in subjects with relapsed multiple myeloma were reported from a randomized phase III trial comparing bortezomib (n=331) to dexamethasone (n=332) in subjects with relapsed multiple myeloma. (6;20)

Among the bortezomib-treated subjects, the most commonly reported (>20%) adverse reactions overall were nausea (52%), diarrhea (52%), fatigue (39%), peripheral neuropathies (35%), thrombocytopenia (33%), constipation (30%), vomiting (29%), and anorexia (21%). The most commonly reported (>20%) adverse reaction reported among the subjects in the dexamethasone group was fatigue (25%). Eight percent of subjects in the bortezomib-treated arm experienced a Grade 4 adverse reaction; the most common reactions were thrombocytopenia (4%) and neutropenia (2%). Nine percent of dexamethasone-treated patients experienced a Grade 4 adverse reaction. All individual dexamethasone-related Grade 4 adverse reactions were less than 1%. (20)

For further details regarding dexamethasone please consult specific product labeling.

3.2.3 Dosing rationale

3.2.3.1 Radium-223 dichloride

In the completed phase 1 clinical study (ATI-BC-1; Study 15522), safety, tolerability, and PK of radium-223 dichloride have been evaluated in subjects diagnosed with prostate or breast carcinoma and skeletal metastases. Radium-223 dichloride was administered in single doses of 46, 93, 163, 213, or 250 kBq/kg body weight (n=25) or multiple doses of 5 administrations of 50 kBq/kg body weight at 3-week intervals (n=3) or 2 administrations of 125 kBq/kg body weight at 6-week intervals (n=3).

In the completed phase 2 study (BC1-02; Study 15280), 64 subjects with CRPC and painful skeletal metastases received 4 injections of 50 kBq/kg body weight radium-223 dichloride (n=33) or placebo (n=31) 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 3 trial, ALSYMPCA (BC1-06; Study 15245), enrolled 921 subjects diagnosed with CRPC and symptomatic bone metastases who received 6 injections of radium-223 dichloride (50 kBq/kg body weight) in 4-week intervals. Endpoints included OS, time to disease-related events, time to progression (TTP) as measured by serum prostate-specific antigen (PSA), total alkaline phosphatase (ALP) concentrations, pain

palliation, acute and long-term safety profile, and health-related quality of life. (Note: The radium-223 dichloride treatment in the ALSYMPCA CSR was calculated as 50 kBq/kg per NIST 2010, and would be approximately 55 kBq/kg per NIST 2015 standard.)

After discussions with the Steering Committee it was decided to administer radium-223 dichloride every 6 weeks in the proposed trial in order to better align with the 21-day cycles for bortezomib and to synchronize treatment related effects from both agents and to allow the recovery from resulting toxicity. Furthermore, modeling simulations done for exposure to radium-223 in combination with chemotherapy revealed slightly less bone marrow suppression with 6-week intervals compared to 4-week intervals. Finally, the potentially longer treatment duration (6 x 6 weeks instead of 6 x 4 weeks) may be beneficial especially in tumor indications with relatively long time to progression.

Study 18987: Phase 1b

The phase 1b part of the study has the following dose cohorts, which will be implemented sequentially. The initial dose cohort utilizes a dose lower than the dose of radium-223 dichloride monotherapy approved for CRPC (33 kBq/kg body weight) every 6 weeks. The second dose level will be the approved dose 55 kBq/kg body weight).

- **Cohort 1:** 33 kiloBecquerel (kBq)/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses
- **Cohort 2:** 55 kBq/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses (standard dose)

The dose escalation to the next higher dose cohort will follow a '3 + 3' design as described in Section 5.1.2 and decisions regarding dose escalation and the MTD/RP2D will be based on the defined DLT. If no DLTs are experienced in any dose cohort, the MTD/RP2D will be based on a safety data summary review (including, but not limited to, AEs, dose modifications, and laboratory changes) conducted by the Steering Committee, participating Investigators, and Sponsor. All subjects enrolled in the Phase 1b part of the study must be evaluated for occurrence of DLTs during the DLT observation window, which is defined as the time from the first dose of study treatment through 3 weeks after second radium-223 administration. Subjects not evaluable for assessment of DLT due to early discontinuation for reasons other than DLT or subjects who have not completed 2 doses of radium-223 dichloride and 2 cycles of bortezomib will be replaced until the MTD/RP2D has been determined.

Study 18987: Phase 2

The dosing regimen for the phase 2 part of the study will be selected, based on DLT and the safety evaluation as well as a benefit/risk evaluation of the Phase 1 doses, after the last subject in the phase 1b part of the study has received the first 2 doses of radium-223 dichloride in combination with bortezomib and dexamethasone (plus a follow up of at least 3 weeks) as described (Section 5.1.2). In the phase 2 part, subjects will be randomly assigned (1:1) to receive either the selected dose of radium-223 dichloride or matching placebo once every 6 weeks for a total of 6 doses.

3.2.3.2 Bortezomib/dexamethasone

The proposed background treatment for subjects both the Phase 1b and Phase 2 parts of the study is bortezomib (1.3 mg/m2/dose) administered SC on Days 1, 4, 8, and 11 and dexamethasone administered orally at 40 mg, on Days 1, 4, 8, and 11 in a 21-day cycle for 8 cycles. For extended therapy beyond 8 cycles, bortezomib/dexamethasone will be administered on Days 1 and 15 of a 28-day cycle at the same dose for bortezomid and dexamethasone will be administered at 20 mg for up to 2 years after the first dose of study treatment. The maintenance bortezomib injection schedules are based upon dosing schedules cited in the IMWG consensus on maintenance therapy in MM as tolerable and effective. (22;23)

Bortezomib initially received approval in Europe based on the results of the large phase 2 SUMMIT (Study of Uncontrolled Myeloma Management with proteasome Inhibition Therapy) trial, which evaluated bortezomib monotherapy in subjects with multiple myeloma who were refractory to prior therapies. The trial enrolled 202 subjects and bortezomib produced a 35% overall response rate, including 10% complete or near-complete responses. Median TTP was 7 months, and median OS was 16 months.(24) These results gained bortezomib approval for use in third-line treatment or later. The confirmatory phase 3 APEX trial compared bortezomib with dexamethasone in 669 subjects with relapsed/refractory multiple myeloma.(6) More than one-third of these subjects had received only 1 previous regimen. The combined response rate and complete response (CR) rates induced by bortezomib were statistically superior. Median times to disease progression in the bortezomib and dexamethasone groups were 6.2 and 3.5 months, respectively. Median OS for subjects receiving bortezomib was 29.8 months compared with 23.7 months for those receiving dexamethasone; this remained statistically significant despite the fact that 62% of subjects in the dexamethasone arm crossed over to bortezomib upon progression. (25).

Studies comparing bortezomib alone versus bortezomib combined with dexamethasone have shown an advantage for the combined treatment. The addition of dexamethasone to bortezomib treatment in 22 subjects with relapsed and/or refractory MM with less than optimal response to bortezomib treatment alone resulted in improved response without increased AEs.(26) A recent retrospective matched-pairs analysis of 109 pairs of subjects with relapsed MM from 3 trials (MMY-2045, APEX, and DOXIL-MMY-3001) showed significantly higher response rates and longer median TTP and PFS for bortezomib/ dexamethasone combination versus bortezomib-alone.(27)

3.3 Study rationale

Over the last decade, the survival of MM patients has significantly improved due to the autologous stem cell transplantation in younger patients and the introduction of drugs such as the immunomodulatory agents (IMiDs) thalidomide, lenalidomide and pomalidomide, and the proteasome inhibitors (PI) bortezomib, carfilzomib and ixazomib. However, the majority of patients relapse even when intensive therapy is combined with IMiDs and PIs. (28) In patients who had progressive MM after at least one previous treatment the median OS is about 30 months (25). In this population the median time to progression (TTP)/ PFS is in the range of 6 to 9 months with doublet combinations such as: iv bortezomib ± dexamethasone (25), 10.4 months for sc bortezomib ± dexamethasone (29) and 11.1 to

11.3 months for lenalidomide+dexamethasone (30;31). The duration of response (DOR) has been reported to decrease with each relapse from 9.9 months from diagnosis to first relapse, to 3.2 months from diagnosis to sixth relapse. (32)

Recently novel agent-based triplet combinations demonstrated superior response rates and prolonged disease control when compared with two-drug regimens in several randomized clinical trials. (33) The median PFS with triplet PI/IMiDs/dexamethasone combinations was 26 months for lenalidomide/dexamethasone (Rd) ± carfilzomib; (34) 20.6 months for Rd ± ixasomib (35) and with panobinostat/bortezomib/dexamethasone 12 months for Vd± panobinostat. (36)

Most recently monoclonal antibodies (mAbs) emerged as promising therapeutic options in MM. Elotuzumab, (anti-SLAMF7 antibody) is the first mAb approved based on PFS improvement in combination with lenalidomide/dexamethasone (19.4 months) compared to lenalidomide/dex (14.9 months) (37).

The anti-CD38 mAb daratumumab is the second mAb approved in MM. Two phase III trials have demonstrated that adding daratumumab to bortezomib/dexamethasone (DVd) or lenalidomide/dexamethasone (DRd), markedly improved PFS, ORR, complete response (CR) and very good partial response (VGPR) for patients with recurrent/refractory MM with manageable toxicities leading to an accelerate approval. The median PFS was 16.7 months for DVd, while in the control group it was 7.2 months for bortezmib/ dexamethasone. (10;11)

Bone involvement represented by osteolytic bone disease is one of the main characteristics of MM. Bone marrow infiltration by neoplastic plasma cells causes irreversible alteration in structure and function of microenvironment components. Osteolytic bone disease is a consequence of increased osteoclast activation via cytokine deregulation along with osteoblast inhibition, resulting in altered bone remodeling. (5) As a consequence of altered bone remodeling, 80% to 90% of patients with multiple myeloma develop bone lesions that can cause skeletal-related events (SREs) such as bone pain, fractures, spinal cord compression, and hypercalcemia.(38) The occurrence of SREs has been linked to inferior survival, reduced quality of life and increased healthcare costs for MM patients. (5; 39;40; 41;42;43)

Bisphosphonate therapy is the main treatment for bone disease in multiple myeloma for reduction of SREs; however, this treatment comes with risk of decreased renal function in patients with renal impairment and osteonecrosis of the jaw.(44;45)

Therefore an optimal drug targeting the metastatic bone niche would have dual activity, on tumor cells and the microenvironment, leading to both direct and indirect antitumor effects. One such class, a mainstay of myeloma treatment, is proteasome inhibitors; particularly bortezomib has been shown direct toxicity on both tumor and bone cells. Bortezomib-related bone effects are due to enhanced osteoblastogenesis by negatively regulating RANKL, and impaired osteoclast differentiation/ survival by reducing NF-kB. Bortezomib also appears to decrease the serum levels of DKK-1 and RANKL in MM patients. (46;47)

The use of radium-223 dichloride for patients with MM is of interest due to its effects on bone lesions, including in combination with bortezomib as demonstrated in preclinical

study. Radium-223 dichloride has shown significant anti-tumor activity in phase 2 and 3 trials in subjects with bone metastatic CRPC.(48) Data derived from the systemic, syngeneic 5TGM1 mouse model support the development of radium-223 dichloride in combination with bortezomib. Single-agent treatment with radium-223 dichloride, as well as with bortezomib reduced osteolysis, and additive/synergistic effects were observed from combination treatment with bortezomib. In addition, concurrent treatment with bortezomib increased radium-223 dichloride uptake in MM-bearing bone. The strong additive effects of the combined radium-223 dichloride/bortezomib treatment led to an eradication of osteoclasts at the tumor-bone interface, thereby addressing a key pathological mechanism of MM. Furthermore, the combination treatment was well tolerated (12;13).

The potential benefits in radium-223 dichloride treatment in combination with bortezomib/ dexamethasone in MM patients include:

- May increase the response rate
- Long-term local disease control through internal-focused radiation exposure of multiple myeloma lesions, resulting in cellular damage of the tumor and re-activation of antigen exposure and immunological response seen in earlier disease settings
- Improved quality of life through reduced pain and bone structural decompensation as a result of the reversal of bone/bone marrow progressive disease (PD)
- Further follow-up treatment and potentially extended PFS and/or OS

Although both radium-223 dichloride and bortezomib may cause gastrointestinal adverse reactions and myelosuppression, no major overlapping toxicities from the combination are expected. As it is possible that an increase of hematologic toxicities could be also observed due to pre-treatment options and the disease focus in the bone marrow, close monitoring of hematologic parameters (complete blood count, etc.) and the dose-escalation part of the study is planned to identify potential exacerbation of hematologic AEs due to the disease setting and/or co-treatment. Dose modification guidelines for each study agent are provided in Section 7.4.

As an optimal dose of radium-223 dichloride in combination with bortezomib and dexamethasone has not yet been established in MM patients, a dose-escalation part has been included in this study. Two dose levels have been selected: 33 and 55 kBq/kg.

Dose escalation will follow a 3+3 design as described in Section 5.1. The MTD/RP2D dose defined from the review of safety data and DLT events will be implemented in the future phase 2/3 studies.

3.3.1 Benefit-risk assessment

Preclinical data with radium-223 dichloride in combination with bortezomib showed an almost complete eradication of MM-associated osteoclasts in a mouse model. Adding radium-223 dichloride to the established therapy of relapsed MM patients is expected to positively impact patient outcomes (i.e., PFS, pain, SSEs, OS). Transient hematologic Grade 3 or 4 AEs (anemia, leukocytopenia, and thrombocytopenia) are possible due to synergistic effects from the disease setting, pre-treatment options, and radium-223 dichloride and bortezomib-related side effects.

Based on preclinical data and the known safety profile of radium-223 dichloride observed to date in studies for prostate cancer and the need to improve PFS and OS in relapsed multiple myeloma patients, the potential benefits of the combination of radium-223 dichloride with bortezomib exceed the potential risks in this patient population. The expected AE profile for this combination is expected to be within the scope of the current treatments available for this patient population.

Therefore, the sponsor considers the overall benefit-risk profile of the proposed combination to be favorable for this clinical study.

4. Study objectives

Phase 1b part (open-label)

Primary objectives:

- To evaluate the safety of the combination of radium-223 dichloride plus bortezomib (BOR) and dexamethasone (DEX)
- To determine the dose of radium-223 dichloride that will be used in the phase 2 part of the study (maximum tolerated dose [MTD] or recommended phase 2 dose [RP2D])

Secondary objectives:

- To evaluate the combined complete response (CR) + very good partial response (VGPR), as determined by International Myeloma Working Group (IMWG) uniform response criteria

Phase 2 part (double-blind, randomized)

Primary objectives:

- To compare radium-223 dichloride versus placebo in addition to background treatment with BOR plus DEX in terms of CR+VGPR rate in relapsed multiple myeloma subjects, as determined by International Myeloma Working Group (IMWG) uniform response criteria.

Secondary objectives:

- To evaluate safety
- To evaluate the objective response rate (ORR), as determined by IMWG uniform response criteria
- To evaluate overall survival (OS)
- To evaluate progression-free survival (PFS)
- To evaluate duration of response (DOR)

Exploratory objectives:

- To evaluate time to first on-study symptomatic skeletal event (SSE)
- To evaluate bone biomarkers

- To evaluate change in bone lesions
- To evaluate change in MM disease markers
- To evaluate circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs)
- To evaluate time to opioid use for cancer pain in subjects without opioid use at baseline
- To evaluate time to pain progression

5. Study design

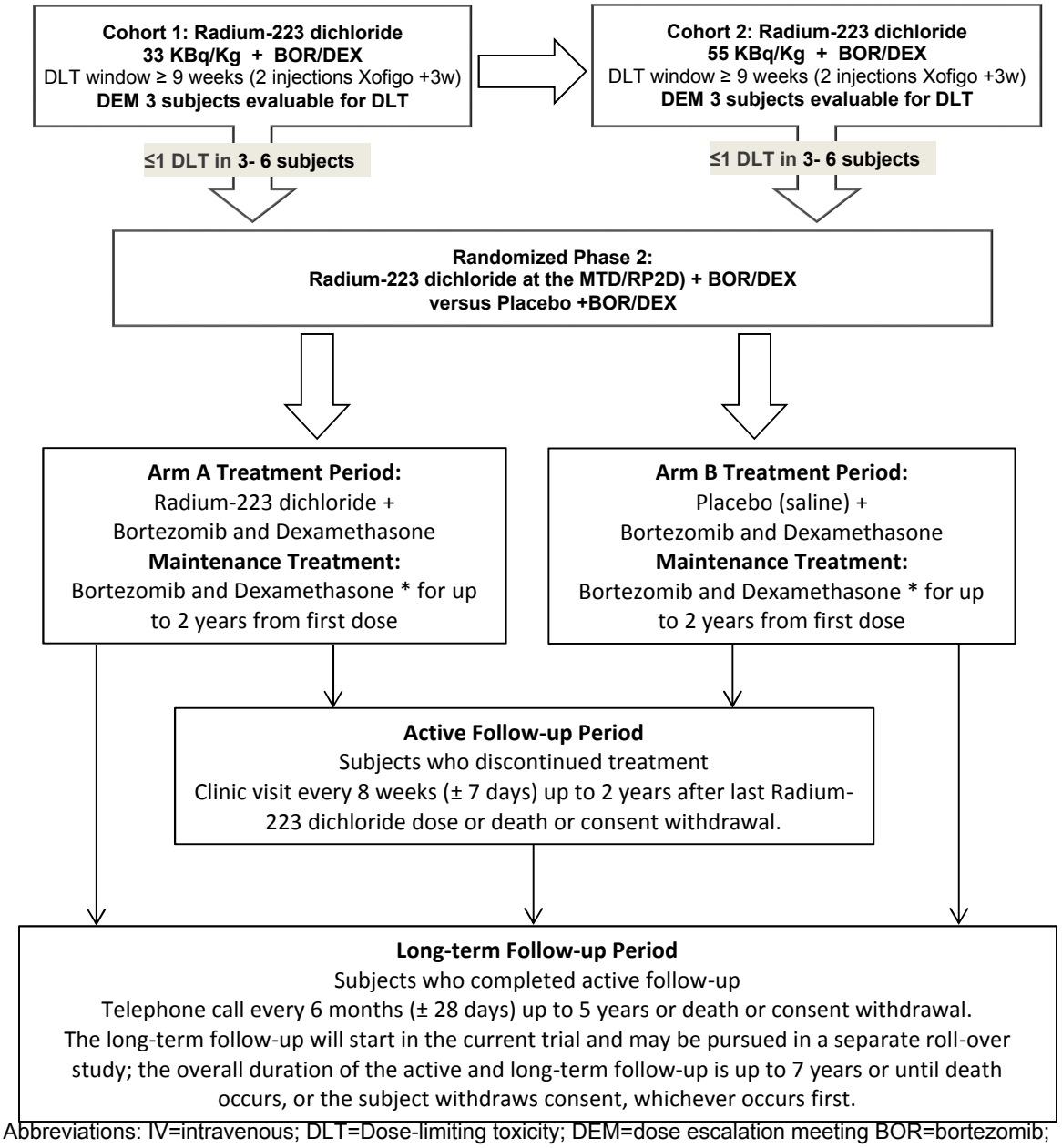
5.1 Design overview

This study will be conducted in 2 parts. The phase 1b part will be an international, phase 1b, open-label, dose-escalation assessment of radium-223 dichloride administered with bortezomib and dexamethasone in subjects with relapsed MM. The phase 2 part will be an international, phase 2, double-blind, randomized, placebo-controlled assessment of radium-223 dichloride versus placebo administered with bortezomib and dexamethasone, in subjects with relapsed MM.

Up to approximately 12 total subjects in the 2 dose cohorts combined will be treated in the phase 1b part of the study and approximately 100 subjects will be enrolled in the phase 2 part of the study.

5.1.1 Study design schematic

Figure 5–1: Study design schematic



Abbreviations: IV=intravenous; DLT=Dose-limiting toxicity; DEM=dose escalation meeting BOR=bortezomib; DEX=dexamethasone; MTD=maximum tolerated dose; RP2D=recommended phase 2 dose; w=weeks

Dose escalation will follow a '3 + 3' design based on defined DLT. The DLT observation window is defined as the time from the first dose of study treatment through 21 days after administration of the second dose of radium-223 dichloride. Decisions on whether to step up to the next dose level will follow the conventional 3 + 3 rules.

*The maintenance treatment for Cohort 1 and Cohort 2 will consist of bortezomib and dexamethasone administered on Days 1 and 15 of a 28-day cycle for up to 2 years after the first dose of study treatment or until a PFS event occurs, unacceptable toxicity develops, or the subject withdraws consent, whichever occurs first.

5.1.2 Study periods and duration

The phase 1b part of the study will evaluate 2 dose levels of radium-223 dichloride in combination with bortezomib and dexamethasone in subjects with relapsed multiple myeloma. Subjects will be treated at the different dose levels of radium-223 dichloride sequentially. The starting dose is 33 kBq/kg body weight every 6 weeks, which is a dose lower than the dose of radium-223 dichloride monotherapy approved for CRPC (55 kBq/kg body weight). The dose of 55 kBq/kg body weight every 6 weeks for up to a total of 6 doses is evaluated in the Cohort 2.

The dose escalation will follow a '3 + 3' design. No intra-subject dose escalation or overlapping recruitment of cohorts will be permitted.

All subjects enrolled in the Phase 1b part of the study must be evaluated for the occurrence of DLTs during the DLT observation window, which is defined as the time from the first dose of study treatment through 3 weeks after second radium-223 administration (approximately 9 weeks). Subjects not evaluable for assessment of DLT due to early discontinuation for reasons other than DLT or subjects who have not completed 2 doses of radium-223 dichloride and 2 cycles of bortezomib will be replaced until the MTD/RP2D has been determined.

Dose-limiting toxicities, using CTCAE version 4.03 for the severity grade, are defined as follows:

1. Grade 4 neutropenia for > 7 days, or febrile neutropenia with or without supportive care*
2. Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with ≥ Grade 2 bleeding, or Grade 3 thrombocytopenia lasting > 2 weeks with or without supportive care*
3. Grade 3 to 4 anemia lasting > 2 weeks with or without supportive care*
4. Grade 3 non-hematological toxicity, except:
    - diarrhea, vomiting, and fatigue that resolve within 72 hours with or without supportive care
    - neuropathy
5. Any Grade 4 non-hematological toxicity (lab abnormalities of any grade will not be considered toxicity unless deemed clinically significant by the investigator)

* Any toxicity can be treated with supportive care according to the institutional guidelines which may include G-CSF, RBC and platelet transfusions. In order to determine the DLT, such supportive care measures should not be given prophylactically during the DLT assessment period but are allowed to start after cycle 3 of BOR/DEX.

Decisions on whether to step up to the next dose level will follow the rules described below:

- If 0 out of 3 subjects experience DLT: proceed to next dose level
- If 1 out of 3 subjects experience DLT: enter 3 more subjects at this dose level
- If 1 out of the 6 subjects experience a DLT: proceed to next dose level
- If 2 or more subjects experience a DLT: do not proceed to next dose level and the current dose will be declared as the non-tolerable dose. The dose level immediately below will be the MTD/RP2D. If this occurs during the first dose cohort, the study will be terminated.

Safety monitoring will occur by telephone conferences between the Investigators and Sponsor on a regular basis. If no DLTs are experienced in any dose cohort, MTD/RP2D will be based on a safety data summary review (including, but not limited to, AEs, dose modifications, and laboratory changes) conducted by the Steering Committee, participating Investigators, and the Sponsor.

All Phase 1b subjects will stay in the study and continue receiving study drug at the assigned dose level until withdrawal criteria are met.

The Phase 2 part of the study will evaluate the activity and safety of radium 223 dichloride in combination with bortezomib and dexamethasone versus placebo in combination with bortezomib and dexamethasone. For the phase 2 part of the study, an Independent Data Monitoring Committee (IDMC) will review the safety data once 20 and 50 subjects have completed 2 doses of radium-223 dichloride or placebo in combination with bortezomib/dexamethasone (plus a follow-up of at least 3 weeks after the second radium 223 dichloride/placebo dose) treatment, and every 6 months thereafter.

After the first IDMC meeting, the following events will initiate ad-hoc IDMC meetings:

- ≥ 33% of subjects discontinue study treatment due to TEAEs or
- ≥ 33% of subjects experience Grade 4 treatment-related hematologic toxicities.

The IDMC members will provide recommendations about the continuation of study with or without any modifications based on safety data and if any of the stopping criteria have been observed with an absolute increase of ≥ 33 percentage points in the active arm over the placebo controlled arm of the study (using CTCAE version 4.03 for the severity grade). Stopping criteria are defined as follows in alignment with the Phase 1b portion of the trial if they occurred within the time from the first dose of study treatment through 2 doses of radium-223 administration + 3 weeks after 2nd radium-223 administration:

- Grade 4 neutropenia for > 7 days, or febrile neutropenia with or without supportive care
- Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with ≥ Grade 2 bleeding, or Grade 3 thrombocytopenia lasting > 2 weeks with or without supportive care
- Grade 3 to 4 anemia lasting > 2 weeks with or without supportive care
- Grade 3 non-hematological toxicity, except:

- diarrhea, vomiting, and fatigue that resolve within 72 hours with or without supportive care
- neuropathy

- Any Grade 4 non-hematological toxicity (lab abnormalities of any grade will not be considered toxicity unless deemed clinically significant by the investigator)

The study participation for each subject in both study parts will comprise 3 periods: screening, treatment, and the follow up period (active follow-up with clinic visits and long-term follow-up with telephone calls). A randomization step is planned for phase 2 only.

Subjects will stay in the study until they completed the 2 year active follow-up period after the last administration of radium-223 dichloride.

Subjects who have completed the 2 year active follow-up will be followed with a telephone call every 6 months (±28 days) for up to 5 years.

A 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. All subjects will be asked to transition into this separate study to complete their long-term follow-up. The long-term follow-up may start in the current trial and subjects will then be asked to transition into the separate roll-over study.

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 21 days starting from the time of ICF signature to ensure that all eligibility criteria are met. Bone marrow biopsy or aspirate, skeletal survey and local blood and urine protein-M tests (as well as any other specific MM tumor assessment blood and urine tests) previously done as part of routine care will be accepted for eligibility confirmation purposes even if done prior to ICF signature, as long as these tests have been performed up to 14 days prior to ICF signature. If logistical reasons require, local lab results for blood and urine protein-M and other specific MM tumor assessment tests ordered after ICF signature can also be used for eligibility assessment only, to ensure that eligibility confirmation timelines are met. If any local lab samples are used to run tumor assessment tests for eligibility confirmation, blood and urine samples for central lab analysis will still be collected and used as the final baseline value for data analysis. Given the complexity of screening assessments, investigators are encouraged to have subjects sign ICF on the same day in which protocol procedures will be undertaken, to avoid starting the screening period too early and reducing the number of screening days actually available in practice.

After eligibility has been confirmed and documented, an additional period of up to a total of 21 days may take place before the administration of the first study drug, to account for all logistical needs related to radium-223 dichloride dose preparation and transportation. All efforts will be made to shorten this period as much as possible.

Randomization step (phase 2 only):

Once eligibility is confirmed and documented, eligible subjects in phase 2 part of the study will be randomized in a ratio of 1:1 to treatment with radium-223 dichloride plus bortezomib and dexamethasone (Arm A) or placebo (isotonic saline) plus bortezomib and dexamethasone (Arm B).

Treatment period:

Treatment consists of:

- Phase 1 b part: up to 6 doses (1 dose every 6 weeks) of radium-223 dichloride at 2 different doses administered to ascending dose cohorts, in combination with 10 cycles (dosing on Days 1, 4, 8, and 11 of a 3-week cycle for the first 8 cycles, then dosing on Day 1 and 15 of a 4-week cycle) of bortezomib and dexamethasone, followed by ongoing maintenance treatment with bortezomib and dexamethasone (dosing on Day 1 and 15 of a 4-week cycle) up to 2 years after the first dose of study treatment or until a PFS event occurs(death or MM progression as per IMWG uniform criteria), unacceptable toxicity develops, or the subject withdraws consent, whichever occurs first.
- Phase 2 part: up to 6 doses (1 dose every 6 weeks) of radium-223 dichloride (Arm A) or placebo (Arm B) in combination with 10 cycles (dosing on Days 1, 4, 8, and 11 of a 3-week cycle for the first 8 cycles, then dosing on Day 1 and 15 of a 4-week cycle) of open label bortezomib and dexamethasone, followed by ongoing maintenance treatment with bortezomib and dexamethasone (dosing on Day 1 and 15 of a 4-week cycle) up to 2 years after the first dose of study treatment or until a PFS event occurs (death or MM progression as per IMWG uniform criteria), unacceptable toxicity develops, or the subject withdraws consent, whichever occurs first.

Subjects will be evaluated for AEs, serious AEs (SAEs), and SSEs at every visit. Subjects will be assessed for response/disease progression and pain endpoints on Day 1 of Cycle 1 and every 3 weeks (±7 days) through Cycle 8 and every 4 weeks thereafter.

Subjects will start treatment with bortezomib and dexamethasone on the same day as the first dose of radium-223 dichloride/placebo. All subjects receive supportive care, as per local standard of practice.

Subjects who experience disease progression per IMWG criteria will discontinue all study treatment. Subjects should not discontinue treatment if they experience a new skeletal event not due to PD (e.g., spontaneous fracture based on existing bone lesion). If, however, the start of a new anti-cancer treatment is required, all study treatment will be permanently discontinued, and the subject should enter the long-term follow-up period.

Subjects who discontinue radium-223 dichloride/placebo treatment prior to experiencing an SSE or a PFS event can continue to receive bortezomib/dexamethasone treatment if considered by the Investigator to be in the subject's best interest and will be followed up for SSEs and response/disease progression.

Subjects who discontinue bortezomib/dexamethasone treatment prior to experiencing an SSE or a PFS event should also discontinue radium-223 dichloride/placebo treatment and be followed up for SSEs and response/disease progression.

Subjects who discontinue only DEX may continue with the other treatment (radium-223 dichloride/placebo and/or BOR).

The treatment period extends from the day of the first dose of radium-223 dichloride/ placebo to 30 days (+7-day window) after the last dose of study treatment (i.e., radium-223 dichloride/placebo, bortezomib, or dexamethasone, whichever occurs last). All subjects must have safety evaluations for 30 days after the last dose of study treatment. If the subject does not return for a 30-day safety follow-up visit regardless of the reason, the site should at a minimum contact the subject for the 30-day safety follow-up by telephone, email, or letter.

Background treatment

Bortezomib will be administered subcutaneous (SC) at 1.3 mg/m2/dose, on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles.

For extended therapy beyond 8 cycles, BOR will be administered on Days 1 and 15 of a 28-day cycle for up to 2 years after the first dose of study treatment, or until a progression-free survival (PFS) event occurs, the subject withdraws consent or unacceptable toxicity develops, whichever occurs first.

Dexamethasone will be administered orally at 40 mg, on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles. DEX administration may be split over 2 days (on the day of BOR administration and the day after BOR administration) at the discretion of the Investigator.

For extended therapy beyond 8 cycles, DEX will be administered orally at 20 mg/dose, on Days 1 and 15 of a 28-day cycle along with BOR for up to 2 years after the first dose of study treatment, or until a progression-free survival (PFS) event occurs, the subject withdraws consent or unacceptable toxicity develops, whichever occurs first.

Radium-223 dichloride/placebo

Radium-223 dichloride/placebo will be administered concomitantly with BOR/DEX. Only for Cycle 1 on Day 1, radium-223 dichloride/placebo will be administered before BOR/DEX.

Subjects with radium-223 dichloride/placebo administration delayed from the date of the intended dose may receive the subsequent cycles of radium-223 dichloride/placebo at another day other than Day 1 of BOR/DEX planned schedule.

All subjects must have safety evaluations for 30 days after the last dose of study treatment. If the subject does not return for a 30-day safety follow-up visit regardless of the reason, the site should at a minimum contact the subject for the 30-day safety follow-up by telephone, email, or letter.

Active follow-up period:

Subjects who have discontinued study treatment for any reason including PD will be followed with a clinic visit every 8 weeks (±7 days) up to 2 years after the last dose of

radium-223 dichloride/placebo treatment or until death occurs or the subject withdraws consent, whichever occurs first.

During active follow-up subjects will be followed for response/disease progression (in case not progressed), treatment-related AEs/SAEs, any anti-cancer treatment and bone health agent (BHA), and SSEs.

Particularly: new primary malignancy (including AML) or hematological conditions (e.g., MDS, aplastic anemia, myelofibrosis) must be reported as SAEs at any time and regardless of the investigator's causality assessment; all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment, through the long-term follow-up. Radium-223 dichloride-related occurrences of febrile neutropenia or hemorrhage will also be collected.

In addition to protocol requirements, subjects will be treated and followed as per the institutional standard of care and/or according to the physician's clinical judgment.

Long-term follow-up period:

Subjects who have completed the 2 year active follow-up will be followed with a telephone call every 6 months (±28 days) up to 5 years.

A 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. All subjects will be asked to transition into this separate study to complete their long-term follow-up. The long-term follow-up may start in the current trial and subjects will then be asked to transition into the separate roll-over study.

During long-term follow-up subjects will be followed for survival status, treatment-related AEs/SAEs, any anti-cancer treatment and bone health agent (BHA). Particularly: new primary malignancy (including AML) or hematological conditions (e.g., MDS, aplastic anemia, myelofibrosis) must be reported as SAEs at any time and regardless of the investigator's causality assessment; all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment, through the long-term follow-up. Radium-223 dichloride-related occurrences of febrile neutropenia or hemorrhage will also be collected.

Subject management, unless defined otherwise in this protocol, will be in accordance with routine clinical practice, at the discretion of the Investigator.

5.1.3 Study endpoints

Phase 1b

Primary endpoint:

- Number of subjects with DLTs treated with radium-223 dichloride in combination with BOR/DEX.
- Maximum tolerated dose/recommended phase 2 dose of radium-223 dichloride in combination with BOR/DEX

Secondary endpoints:

- Combined number of complete response (CR) + very good partial response (VGPR) evaluation

Phase 2

Primary endpoint

- Combined CR+VGPR rate as determined by IMWG uniform response criteria

Secondary endpoints

- Number of subjects with adverse events
- Objective response rate (ORR), as determined by IMWG uniform response criteria
- Overall survival (OS)
- Progression-free survival (PFS)
- Duration of response (DOR)

Exploratory endpoints:

- Time to first on-study SSE
- Bone biomarkers, including but not limited to urine N-terminal cross-linking telopeptide of type-I collagen (UNTx), serum C-terminal cross-linking telopeptide of type-I collagen (SCTx), total alkaline phosphatase (ALP), bone-ALP (B-ALP), procollagen type I N-propeptide (PINP), and type I collagen telopeptide (ICTP)
- Change in the number of active bone lesions (for PET-CT, X-ray, MRI, or low-dose CT) and/or the intensity of PET uptake (for PET-CT) from baseline to the follow-up evaluation.
- Change in MM disease markers:
  - Change in M-protein
  - Evaluate potentially predictive biomarker candidates (ctDNA, CTCs, MM related citokines)
- Time to opioid use for cancer pain in subjects without opioid use at baseline
- Time to pain progression

5.2 Primary variable

Phase 1b:

Safety

- The incidence of DLTs will be used to determine the MTD/RP2D.
- The incidence of treatment-emergent adverse events (TEAEs), drug-related TEAEs, and treatment-emergent serious adverse events.

Phase 2:

- CR/VGPR rate, as per the IMWG uniform response criteria

5.3 End of study

For each participating EU country, the end of study (EOS) according to the EU Clinical Trial Directive will be reached when the last visit of the last subject in any site in the EU has occurred.

The EOS as a whole will be reached as soon as the EOS according to the above definition has been reached in all participating countries (EU and non-EU).

The primary completion of this study will be conducted when all subjects enrolled in Phase 2 part have completed the end of radum-223 dichloride visit and the final analysis will be conducted when all subjects enrolled have completed the end of treatment visit (including the maintenance therapy).

6. Study population

All the inclusion and exclusion criteria below have to be fulfilled

6.1 Inclusion criteria

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

1. Males or females ≥18 years of age
2. Have provided written informed consent. Subjects must be able to understand and be willing to sign the written informed consent, expressing their willingness and ability to comply with protocol-required treatment and assessment schedule, including follow-up visits. A signed informed consent form (ICF) must be appropriately obtained prior to the conduct of any trial-specific procedure.
3. Subject must have documented monoclonal plasma cells in the bone marrow of ≥10%, as defined by their institutional standard at some point in their disease history or the presence of a biopsy proven plasmacytoma.
4. Subjects must have received at least **1 and not more than 3** previous lines of treatment and have had a response to at least 1 prior treatment in the past (i.e., achieved a minimal response [MR] or better) according to the IMWG uniform response criteria Section 16.2.
5. Subject must be non-refractory to bortezomib (Refractory is defined: progression of disease while receiving bortezomib therapy or within 60 days of ending bortezomib therapy)
6. Subjects must have documented evidence of progressive disease according to the IMWG uniform response criteria following the last multiple myeloma treatment.
7. Subjects must have measurable disease defined as at least 1 of the following:
   - Serum M-protein defined by the following:

- IgG multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL (measured by protein electrophoresis [PEP])
- IgA, IgD, IgE, IgM multiple myeloma: serum M-protein level ≥0.5 g/dL (measured by PEP)

- Urine M-protein ≥200 mg/24 hours (any immunoglobulin heavy chain type measured by PEP)
- Serum free light chain (FLC) ≥10 mg/dL with abnormal ratio in subjects with unmeasurable disease by serum or urine PEP.

8. ≥1 bone lesion identifiable by radiograph, computed tomography (CT), positron emission tomography – computed tomography (PET-CT), or magnetic resonance imaging (MRI).
9. Life expectancy of at least 3 months.
10. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2.
11. For subjects experiencing toxicities resulting from a previous therapy (including peripheral neuropathy), the toxicities must be resolved or stabilized to ≤Grade 1.
12. Adequate hepatic function, with total bilirubin ≤1.5 x upper limit of normal (ULN) (except for Gilbert Syndrome: total bilirubin <3.0 x ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x ULN.
13. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L, hemoglobin (Hb) ≥9.0 g/dL, and platelet count ≥75.0 x 10^9/L independent of transfusion of red blood cells (RBC) or platelet concentrates and independent of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF).
Note: Transfusion of RBC or platelet concentrates, use of G-CSF or GM-CSF within 21 days from ICF signature are not allowed.
14. International normalized ratio (INR) ≤1.5 and partial thromboplastin time (PTT) ≤1.5 x ULN. Prothrombine time (PT) may be used instead of INR if ≤1.5 x ULN.
15. Estimated creatinine clearance of ≥30 mL/minute, according to the Cockcroft and Gault formula.
16. Serum potassium levels >3.0 mEq/L
17. Corrected serum calcium <14.0 mg/dL (3.5 mmol/L)
18. Female subjects of child-bearing potential must have a negative urine pregnancy test within 72 hours before the first dose. Postmenopausal females (age ≥55 years and 1 year or more of amenorrhea; or age <55 years and 1 year or more of amenorrhea with an estradiol assay <20 pg/mL; or bilateral oophorectomy) and surgically sterilized females are exempt from a pregnancy test.
    a) Female subjects of child-bearing potential who are sexually active must agree to utilize 2 reliable and acceptable methods of contraception used simultaneously: a barrier method such as (i) condoms (male or female) with spermicidal agent, or (ii) diaphragm or cervical cap with spermicide, combined with a highly effective non hormonal birth control method such as intra-uterine device, during treatment with

and for 6 months following the last dose of radium 223 dichloride/placebo or 3 months after the last administration of bortezomib/dexamethasone, whichever occurs later.

b) Male subjects with partners of child-bearing potential must be willing to use 2 reliable and acceptable methods of birth control (including adequate barrier protection) used simultaneously as determined to be acceptable by the principal investigator and the sponsor during the study and for 6 months following completion of treatment with radium-223 dichloride/placebo or 3 months after the last administration of bortezomib/dexamethasone, whichever occurs later. The contraception measures must be discussed with the subject. Suitable contraception could be, for example, the use of condoms combined with an oral contraceptive taken by the female partner of a study subject.

6.2 Exclusion criteria

Subjects must not meet any of the exclusion criteria listed below:

1. Systemic glucocorticoid therapy (prednisone >10 mg/day orally or equivalent) within the last 4 weeks prior to first dose, unless tapered and on a stable dose (prednisone ≤10 mg/day orally or equivalent) for at least 1 week
2. Subjects with known POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or light chain (AL) amyloidosis
3. Plasma cell leukemia (defined by plasma cell >20%, and/or an absolute plasma cell count of >2 x 10^9/L in peripheral blood)
4. Subject has received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic (PK) half-lives ($t_{1/2}$) of the treatment, whichever is longer, before the date of start of treatment.
5. Radiation therapy in the previous 4 weeks prior to first dose. Note: Subjects treated with local radiotherapy which is recommended to be limited fields for pain control are eligible.
6. Administration of an investigational therapeutic study drug (including investigational vaccines) within 4 weeks or within 5 PK ($t_{1/2}$) of the treatment, whichever time is greater, before the date of start of treatment.
7. Prior treatment with radium-223 dichloride or any experimental radiopharmaceutical.
8. Major surgery within 4 weeks prior to first dose (central line placement and kyphoplasty are not considered major surgery).
9. Congestive heart failure (New York Heart Association [NYHA] class III to IV), symptomatic cardiac ischemia, unstable angina or myocardial infarction in the previous 6 months prior to first dose, or with a known left ventricular ejection fraction (LVEF) <40%, cardiomyopathy, pericardial disease, clinically relevant cardiac arrhythmia (CTCAE version 4.03 Grade 2 or higher), clinically significant ECG abnormalities, or screening 12-lead ECG showing a baseline prolonged QT interval (baseline QT interval as corrected by Fridericia's formula > 470 msec).

Note: LVEF values will not be collected, however the investigator must verify and subjects must be excluded if LVEF < 40% at study entry.

10. Acute diffuse infiltrative pulmonary disease.
11. Acute active infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks prior to first dose.
12. Known HIV infection or subjects who are known to be HIV seropositive.
13. Subjects with active hepatitis B or C infection at screening. Subjects with a known history of occult hepatitis B virus (HBV) infection (defined as positive hepatitis B core antibody [HBcAb] and negative hepatitis B surface antigen [HBsAg]), but who have undetectable HBV DNA at screening may be included. Subjects with a history of positive hepatitis C virus (HCV) antibody must be negative for HCV RNA by polymerase chain reaction (PCR) assessment or similar technology to be included.
14. Any history of malignancy within the past 3 years except adequately treated a) basal cell or squamous cell skin cancer, b) carcinoma in situ of the cervix, c) prostate carcinoma in situ < Gleason Score 6 with stable prostate-specific antigen (PSA), or d) breast carcinoma in situ.
15. Neuropathy ≥Grade 2
16. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis.
17. Subjects with known meningeal and/or extramedullary involvement of MM.
18. Known allergies, hypersensitivity or intolerance to radium-223 dichloride, bortezomib or dexamethasone or their excipients.
19. Any clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.
20. Female subjects who are pregnant or lactating.
21. Serious psychiatric condition that could interfere with compliance of treatment.
22. Close affiliation with the investigational site (e.g., a close relative of the Investigator, dependent person, employee or student of the investigational site).
23. Previous assignment to treatment during this study.

6.3 Withdrawal of subjects from study

6.3.1 Withdrawal

Study treatment 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 treatment for any reason and encourage them to remain in the study for follow up of primary, secondary and other objectives (i.e., continue in safety follow-up, active follow-up and/or long-term follow up for up to 5 years).

Subjects qualifying for follow-up are expected to participate in the follow-up unless they explicitly object. Withdrawal of consent to treatment should be documented in the subject's medical file. If subjects do not wish to be followed up further, they should sign the "Declaration of Objection to Collection of Study Data after Withdrawal of Consent" form as an additional consent withdrawal for follow up.

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

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "dropout" as specified below.

Screening failure

A subject who, for any reason (e.g., failure to satisfy the selection criteria) terminates the study before the first dose of radium-223 dichloride for phase 1b or before randomization for Phase 2 is regarded as a "screening failure".

If one or more screening laboratory tests do not support eligibility, laboratory re-test is permitted only once and after Sponsor approval has been documented. Only the laboratory tests with results which are out of range of eligibility need to be repeated. However absolute neutrophil, hemoglobin, and platelet count must be in the range of eligibility criteria independently of transfusion of red blood cells (RBC) or platelet concentrates and independent of granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF).

- The laboratory re-tests must be completed within 21 days of the original ICF signature. If the tests cannot be performed or their results will not be available within 21 days of the original ICF signature subject is considered a screen failure. These subjects can still undergo a new full re-screening after signing a new ICF.
- The re-testing of blood and urine M-protein, β2 microglobulin, cytogenetic and bone marrow MM assessment due to their original test results being outside of protocol required limits is not allowed.

Re-screening of screen-failed subjects may only be allowed once after discussion with the medical monitor of the Sponsor and after his/her approval. Sponsor approval of re-screening must be documented. Re-screening may be considered under the following circumstances:

- Subjects who underwent screening procedures (i.e., scans and laboratory work) that expired may need the screening procedures to be repeated in order to be within the window required prior to enrollment.
- Re-screening is also permitted when the screening procedures for subject's eligibility expired due to completion of wash-out periods as per protocol, in case of expiry of investigational product that requires replacement, or for extraordinary logistical issues

- Re-screening is also permitted when the screening failure was due to intercurrent infection if not >45 days from date of screen failure AND subject has been off of treatment for infection for at least 7 days or M-protein not meeting the criterion of measurable disease during screening
- Subjects who need to repeat the screening procedures have to sign a new ICF. Screening procedures will be repeated again, as necessary, to meet the timeframe required per protocol and the eligibility criteria. Such subjects will obtain a new subject number after signing their 2nd ICF.

In any case, the Investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk.

Rescreening of a subject as per the rules outlined above can only be attempted once.

Once the number of subjects screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the subjects who screen failed will not be permitted to rescreen.

Information to be collected on screening failures

Subjects who sign an ICF but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a Serious Adverse Event during the Screening Phase.

Dropout

A “dropout” is defined as a subject who has received the first dose of study treatment and discontinues study participation prematurely for any reason.

General procedures

The subject may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12.

6.3.1.1 Withdrawal from study treatment (continue with collection of follow-up data)

The total treatment period is defined from the initiation of treatment until 30 days (+7 days) after the last administration of study treatment (radium-223 dichloride/placebo, BOR and DEX, whichever occurs last).

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 a DLT (phase 1b) defined as follows:
    - •Grade 4 neutropenia for > 7 days, or febrile neutropenia with or without supportive care *
    - •Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with Grade 2 bleeding, or Grade 3 thrombocytopenia lasting > 2 weeks with or without supportive care *
    - •Grade 3 to 4 anemia lasting > 2 weeks with or without supportive care *
    - •Grade 3 non-hematologic toxicity, except:
        - diarrhea, vomiting, and fatigue that resolve within 72 hours with or without supportive care
        - neuropathy
    - •Any Grade 4 non-hematological toxicity (lab abnormalities of any grade will not be considered toxicity unless deemed clinically significant by the investigator) (For laboratory-related Grade 4 toxicities, refer to Section 7.4.4)

  * Any toxicity can be treated with supportive care according to the institutional guidelines which may include G-CSF, RBC and platelet transfusions. In order to determine the DLT, such supportive care measures should not be given prophylactically during the DLT assessment period but are allowed to start after cycle 3 of BOR/DEX.
- Delay in radium-223 dichloride/placebo administration of >28 days due to toxicity from the intended dosing date (maximum of 10 weeks between 2 consecutive doses of radium-223 dichloride/placebo).

  Note: If the delay in radium-223 dichloride/placebo administration of >28 days from the intended dosing date (maximum of 10 weeks between 2 consecutive doses of radium 223 dichloride/placebo) is due to logistics supplying, for subjects with clear benefit (based on the IMWG criteria) the investigator will evaluate on an individual basis whether the study treatment may be continued or discontinued in agreement with the Sponsor.

  Subjects with radium-223 dichloride/placebo administration delayed from the date of the intended dose may receive the subsequent cycles of radium 223 dichloride/placebo at another day other than Day 1 of BOR/DEX planned schedule.

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

- If within the time from the first dose of study treatment through 2 dose of radium-223 administration + 3 weeks after 2nd radium-223 administration the subject

experiences one of the stopping criteria, defined as follows in alignment with the Phase 1b portion of the trial:

- •Grade 4 neutropenia for > 7 days, or febrile neutropenia with or without supportive care **
- •Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with Grade 2 bleeding, or Grade 3 thrombocytopenia lasting > 2 weeks with or without supportive care **
- •Grade 3 to 4 anemia lasting > 2 weeks with or without supportive care **
- •Grade 3 non-hematologic toxicity, except:
  - diarrhea, vomiting, and fatigue that resolve within 72 hours with or without supportive care
  - neuropathy
- •Any Grade 4 non-hematological toxicity (lab abnormalities of any grade will not be considered toxicity unless deemed clinically significant by the investigator) (For laboratory-related Grade 4 toxicities, refer to Section 7.4.4)

* If a subject experiences a clinical benefit from treatment, the subject can continue to receive radium-223 dichloride treatment if considered by the Investigator to be in the subject's best interest.

** Any toxicity can be treated with supportive care according to the institutional guidelines which may include G-CSF, RBC and platelet transfusions. In order to determine the DLT, such supportive care measures should not be given prophylactically during the DLT assessment period but are allowed to start after cycle 3 of BOR/DEX.

The subject can continue to receive bortezomib/dexamethasone treatment if considered by the Investigator to be in the subject's best interest and will continue to be followed as per protocol up to 5 years after the last dose of radium-223 dichloride/placebo, or death, or the subject withdraws consent, whichever occurs first.

Subjects must be withdrawn from **all** study treatment for the following reasons:

- If, in the Investigator's opinion, continuation of study treatment would be harmful to the subject's well-being including unacceptable toxicity related to study treatment
- Delay in BOR administration of >28 days due to toxicity from the intended day of the next scheduled dose.
- If the subject starts a new systemic anti-cancer treatment (Section 8.1.1)
- At her/his own request or at the request of her/his legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- At the specific request of the Sponsor and in liaison with the Investigator (e.g., obvious non-compliance, safety concerns)

6.3.1.2 Withdrawal from active and/or long-term follow-up period (no further data collection)

Subjects must be withdrawn from the follow-up procedures and no further data will be collected for the following reasons:

- Subject withdraws consent from study and objects to any further data collection or study-related procedures. A subject must be removed from the study at her/his own request or at the request of her/his legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result. In this case, the subject has to expressively inform the Investigator and sign the Declaration of Objection to the Collection of Study Data after Withdrawal of Consent as an additional consent withdrawal for follow up. The objection is also valid, if the declaration is not in place for any reason, but the Investigator documented the objection in the files.
- Subject is lost to follow-up
- Death

6.3.2 Replacement

During the phase 1 b part of the study, any subject who terminates treatment before administration of the first 2 doses of radium-223 dichloride, for reasons other than DLT, will be replaced until the MTD/RP2D has been determined. Subjects in the Phase 2 will not be replaced.

Replacement of subjects will ensure collection of data on the safety profile of radium-223 dichloride in combination with BOR/DEX in accordance with the dose escalation ‘3 + 3’ design based on defined DLT.

6.4 Subject identification

A subject number (a unique identification number) will be assigned via an Interactive Voice/Web Response System (IxRS) when a subject signs the ICF and is evaluated for inclusion into the study. When the subject is eligible for the trial, 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.

Subjects who meet re-screening eligibility and are re-screened will be assigned a new subject number in IxRS. See Section 6.3.1.

The subject number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current subject number within the center.

7. Treatment(s)

7.1 Treatments to be administered

Investigational medicinal product (IMP): Radium-223 dichloride at the specified dose will be administered IV as a slow bolus injection for a total of up to 6 doses at intervals of 6 weeks. Please refer to Section 7.4.1 for details regarding radium-223 dichloride dosage and administration. Please refer to Section 7.4.4 for dose reduction, dose interruption, and discontinuation.

For the phase 1b part of the study, up to 2 dose levels of radium-223 dichloride may be administered, following sequential dose escalation using a '3 + 3' design:

- **Cohort 1**: 33 kBq/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses in combination with BOR and DEX
- **Cohort 2**: 55 kBq/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses in combination with BOR and DEX

Phase 2 part (double-blinded, randomized)

- For the phase 2 part of the study, the MTD/RP2D of radium-223 dichloride, as determined by the phase 1b part of the study, will be administered once every 6 weeks for a total of 6 doses.

Reference therapy:

Phase 2 part (double-blinded, randomized)

During the phase 2 part of the study, a placebo 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 6 weeks. The isotonic saline will be provided by the study center. Traceability of the respective manufacturers and batches will be maintained in the respective preparation documentation and drug accountability logs.

It is important to note that, in general (unless otherwise agreed; e.g., for sites using patient-ready dose [PRD] depots [Section 7.4.1.2]), in cases where study drug has been ordered, the time window for administration should be within 3 days of the scheduled treatment visit. If administration must be postponed more than 3 days after the scheduled treatment visit, replacement of the drug order may be required.

Background treatment:

Phase 1b and Phase 2 parts

Bortezomib will be administered subcutaneous (SC) at 1.3 mg/m^2/dose, on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles.

For extended therapy beyond 8 cycles, BOR will be administered on Days 1 and 15 of a 28-day cycle for up to 2 years after the first dose of study treatment, until a progression-free survival (PFS) event occurs, or the subject withdraws consent or unacceptable toxicity develops, whichever occurs first.

Please refer to Section 7.4.2 for details regarding BOR dosage and administration.

Dexamethasone will be administered orally at 40 mg, on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles. DEX administration may be split over 2 days (on the day of BOR administration and the day after BOR administration) at the discretion of the Investigator.

For extended therapy beyond 8 cycles, DEX will be administered orally at 20 mg/dose, on Days 1 and 15 of a 28-day cycle along with BOR for up to 2 years after the first dose of study treatment, or until a progression-free survival (PFS) event occurs, the subject withdraws consent or unacceptable toxicity develops, whichever occurs first.

Please refer to Section 7.4.3 for details regarding DEX dosage and administration.

Radium-223 dichloride/placebo will be administered concomitantly with BOR and DEX. Subjects with radium-223 dichloride/placebo administration delayed from the date of the intended dose may receive the subsequent cycles of radium 223 dichloride/placebo at another day other than Day 1 of BOR/DEX planned schedule.

Only for Cycle 1 on Day 1, radium-223 dichloride/placebo will be administered before BOR/DEX.

Please refer to Section 7.4.4 for dose reduction, dose interruption, and discontinuation for BOR and DEX. Dose modifications and administration of BOR and DEX must be in compliance with the local labels in each of the participating countries and in line with standard practice guidelines.

7.2 Identity of study treatment

The Sponsor will supply radium-223 dichloride, and may supply BOR and DEX which 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 respective local labels will be made available to the study site upon request.

Local sourcing of the background treatments BOR, and DEX might be considered. Locally sourced medication will be handled according to the local procedures and will not be labelled study specific.

For radium-223 dichloride, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study treatment can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the Sponsor's clinical supplies Quality Assurance group.

Placebo (isotonic saline) will be provided by the study site.

A complete record of batch numbers and expiry dates of all centrally or locally sourced study treatment as well as the labels for the centrally supplied study treatments needs to be filed in the Sponsor's study file.

7.3 Treatment assignment (phase 2 only)

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:placebo.

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 isotonic 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 accessing the IXRS from the study site on the date of the previous dose. If, after ordering, the order needs to be cancelled or amended, the Investigator should contact their monitor immediately.

7.4 Dosage and administration

7.4.1 Radium-223 dichloride

The Sponsor will provide radium-223 dichloride, which is manufactured by Bayer AG. Radium-223 dichloride is produced according to GMP and will be delivered 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.

Radium-223 dichloride should be received, used and administered only by authorized personnel in designated clinical settings. The receipt, storage, use, transfer and disposal of radium-223 dichloride is subject to the regulations and/or appropriate licenses of the competent official organization.

The volume per vial is 6 mL, corresponding to 6.6 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 is valid for all climate zones I to IV. In addition, it has been shown that the product quality is not jeopardized upon freezing.

The dose should be ordered through IxRS as soon as possible prior to the planned date of administration. The subject's weight taken 3 to 5 days (for US sites) or within 3 days (for ex-US sites) before radium-223 dichloride dosing will be submitted with the dose request. The site is not required to assess safety labs prior to placing the order.

It is important to note that, in general (unless otherwise agreed; e.g., for sites using PRD depots [Section 7.4.1.2]), in cases where study drug has been ordered, the time window for administration should be within 3 days of the scheduled treatment visit. If administration must be postponed more than 3 days after the scheduled treatment visit, replacement of the drug order may be required.

Written information about radium-223 dichloride and instruction about storage, 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 or vomit. 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 outpatient basis.

To minimize the risk of contamination, the subject and her/his caregivers will be provided with 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 subject's assignment to radium-223 dichloride or placebo doses.

7.4.1.1 Dose calibration

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 may be sent to the study site, if the site is not already a qualified user of radium-223 dichloride.

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 2015, NIST has established an updated standardization for radium-223 dichloride, which indicates that an approximately 10 % difference existed between activity values obtained using the former standard and the updated standardization. The updated standardization was implemented in April 2016. (49)

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.

7.4.1.2 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 trial 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 must be kept by the unblinded person(s) and not shared with the other study site personnel during the conduct of the study.

7.4.1.3 Dose calculation

For this study, two dose levels of radium-223 dichloride are planned:

- 33 kBq/kg body weight
- 55 kBq/kg body weight

The total activity to be injected will be calculated volumetrically using the subject's body weight (kg) within 3 days prior to the dose for ex-US sites or 3 to 5 days prior to the dose for US sites, the dosage level, and the decay correction factor (DK) to correct for physical decay of radium-223 (ex-US sites only). A table with DKs according to physical decay of the study medication will be provided with each vial of radium-223 dichloride (ex-US sites only). 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 for each dose group:

- 33 kBq/kg

$$\frac{\text{Body Weight (kg)} \times 33\ \text{kBq/kg}}{\text{DK} \times 1{,}100\ \text{kBq/mL}} = \text{volume to be injected (mL)}$$

- 55 kBq/kg

$$\frac{\text{Body Weight (kg)} \times 55\ \text{kBq/kg}}{\text{DK} \times 1{,}100\ \text{kBq/mL}} = \text{volume to be injected (mL)}$$

Site specific volume calculation methods are acceptable as well, provided that the subject dose is as indicated above.

For the phase 2 part of the study, the most appropriate dose level will be selected based on the safety results of the phase 1b part of the study. The dosing calculation above that corresponds to the dose level chosen will be used.

Data regarding activity, calculations (ex-US sites only), and volume to be injected must be recorded in the IMP preparation log and in the study electronic data capture (EDC) 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.

In the US, applicable documentation is required for the country PRD depot. The subject's weight will be obtained only once for each dose. To ensure time for the country PRD depot to prepare and deliver the PRDs to the sites:

- The subject's weight will be obtained 3 to 5 days before the planned dosing date
- This weight will be communicated to the country PRD depot for preparation of the current dose along with a prescription and any other details required by the PRD depot; a record of this information transfer will be retained at the site
- Documentation by the PRD depot of the required activity and volume in the syringe will be retained at the depot with a copy provided to the site

Subjects at ex-US sites should be reweighed on the day of dose administration; the final dose to be administered should be determined using that weight. Subjects should not be weighed more than once or at different departments on the day of the administration to avoid the potential use of different weights. Subjects in the US will receive patient-ready doses based on the subject weight 3 to 5 days before the day of administration. Therefore, no other weight measurement is needed.

For subjects randomized to receive placebo, the volume of isotonic saline to be injected will be provided by the IXRS based on the subject's weight and the saline solution will be prepared by the unblinded site staff. Data regarding the isotonic saline batch number and the volume to be injected should be recorded in the eCRF by unblinded staff.

7.4.1.4 Dose preparation

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 physicians. 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.

For subjects in the placebo arm, a syringe with isotonic saline will be prepared in the same way as for the active treatment.

It is important to note that, in general (unless otherwise agreed, e.g., for sites using PRD depots [Section 7.4.1.2]), in cases where study drug has been ordered, the time window for administration should be within 3 days of the scheduled treatment visit. If administration must be postponed more than 3 days after the scheduled treatment visit, replacement of the drug order may be required. The same process must be followed, regardless of treatment arm assignment, to maintain the study blind.

The study drug 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 procedures 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.

7.4.1.5 Dose administration

Every effort will be made to administer the full dosing regimen (6 doses of radium-223 dichloride or placebo). Dose adjustment of radium-223 dichloride/placebo is not permitted. The minimum time window between 2 doses of radium-223 dichloride/placebo must be 6 weeks.

Radium-223 dichloride/placebo administration may be delayed if medically necessary. Preferably, the next dose should be administered within a 2-week delay; however, a maximum of 28 days from the date of the intended dose is allowed (i.e., a maximum of 10 weeks between 2 consecutive doses) for recovery of AEs. If administration is delayed beyond this window due to toxicity, the subject must permanently discontinue radium-223 dichloride/placebo administration. Treatment delays or discontinuations of radium-223 dichloride/placebo may be instituted as described in Section 7.4.4.

Subjects with radium-223 dichloride/placebo administration delayed from the date of the intended dose may receive the subsequent cycles of radium 223 dichloride/placebo at another day other than Day 1 of BOR/DEX planned schedule.

BOR administration may be delayed if medically necessary.

If BOR administration is delayed >28 days from the intended day of the next scheduled dose due to toxicity, the subject must be permanently discontinued from background treatment.

In case BOR have to be permanently discontinued, radium-223 dichloride/placebo will also be discontinued.

7.4.2 Bortezomib

Bortezomib (BOR) is part of background treatment in this study for subjects enrolled in all cohorts and may be provided with appropriate labelling by the Sponsor, where local sourcing is not applicable. Local sourcing might be considered. Locally sourced medication will be handled according to the local procedures and will not be labelled study specific. It is required, at minimum, that the batch numbers and expiry dates are recorded.

In case BOR is supplied centrally the IxRS allocates one vial per treatment to a subject.

Subjects enrolled will start treatment with BOR on the same day as the first dose of radium-223 dichloride/placebo.

BOR is a small, cell permeable molecule that specifically and selectively inhibits the proteasome by binding tightly with the enzyme's active sites. This is the first-in-class of proteasome inhibitors. It is supplied in single use vials of BOR as lyophilized powder for SC injection. Unopened vials may be stored at controlled room temperature 25ºC (77ºF); excursions permitted from 15°C to 30ºC (59°F to 86ºF). Retain in original package to protect from light.

The dose of BOR administered in the study is 1.3 mg/m^2/dose. Subjects previously treated with BOR can receive a starting dose at the last tolerated dose (minimum 0.7 mg/m^2/dose).

- The amount (in mg) of BOR administered will be determined based on body surface area (BSA). Body surface area should be calculated using a standard nomogram (this can be the site's institutional standard formula).
    - To calculate the BSA is recommended to use Gehan and George Equation: BSA (m2) = 0.0235 x height(cm)$^{0.42246}$ x weight(kg)$^{0.51456}$ However, the BSA can be calculated as per standard practice at site.
- The same formula/method should be consistently used for all BSA calculations of a subject.
- The dose should be calculated on Day 1 of each cycle; the dose administered may remain the same throughout each cycle unless the subject experiences a ≥10% change in weight. The Investigator should also assess the cause of any rapid weight change for overall subject management and possible safety reporting.
- It is not required that the BOR dose be corrected for obese subjects.

BOR is administered SC, on Days 1, 4, 8, and 11 in a 21-day cycle for 8 cycles; the route of administration should remain consistent throughout the duration of treatment. For extended therapy beyond 8 cycles (subjects enrolled in Cohort 1 and Cohort 2), BOR will be administered on Days 1 and 15 of a 28-day cycle until disease progression,

unacceptable toxicity or consent withdrawal, whichever occurs first, or for up to 2 years after the first dose of study treatment.

Subjects who experienced severe skin /local toxicity related to the SC administration of BOR and have clinical benefit from study treatment may switch from the SC administration to intravenous maintaining the same dose and schedule of BOR.

The minimum time window between 2 BOR doses is 72 hours. Individual BOR doses can be delayed for a maximum of 3 days from the original scheduled day (calculated from Day 1 of the respective cycle); omit if delay is >3 days. Treatment delays or discontinuations of BOR may be instituted as described in Section 7.4.4.

Follow special handling and disposal procedures for anti-cancer pharmaceuticals as directed in the respective local label. Dosage, administration, and treatment with BOR must be in compliance with the respective local label in each of the participating countries and in line with standard practice guidelines. Treatment will be captured in the eCRFs.

7.4.3 Dexamethasone

Dexamethasone (DEX) is part of background treatment in this study for subjects enrolled in all the cohorts and may be provided with appropriate labeling by the Sponsor, where local sourcing is not applicable. Local sourcing might be considered. Locally sourced medication will be handled according to the local procedures and will not be labelled study specific. It is required at minimum that the batch numbers and expiry dates are recorded.

In case DEX is supplied centrally, the IxRS allocates one kit every other cycle on day 1 to a subject.

Subjects enrolled will start treatment with DEX on the same day as the first dose of radium-223 dichloride/placebo.

DEX is a synthetic adrenocortical steroid, primarily used for anti-inflammatory effects, supplied as tablets for oral administration. Store at 20°C to 25°C (68°F to 77°F). Protect from moisture. Dispense in a well-closed, light-resistant container.

DEX tablets (4 mg or 8 mg, dependent upon participating country) are administered orally. The dose of DEX administered in the study is 40 mg during cycles 1 through 8 (ten 4 mg tablets, or five 8 mg tablets).

DEX is administered on Days 1, 4, 8, and 11 in a 21-day cycle for 8 cycles; however, DEX administration may be split over 2 days (on the day of BOR administration and the day after BOR administration) at the discretion of the Investigator. For subjects who are older than 75 years, underweight (BMI<18.5), have poorly controlled diabetes mellitus or prior intolerance/adverse event (AE) to steroid therapy, the DEX dose may administered at a dose of 20 mg weekly.

During extended therapy beyond 8 cycles, DEX will be administered 20 mg/dose, on Days 1 and 15 of a 28-day cycle along with BOR until disease progression, unacceptable toxicity or consent withdrawal, whichever occurs first, or for up to 2 years after the first dose of study treatment. Treatment will be captured in the eCRFs.

7.4.4 Dose modification, delays and treatment discontinuation guidance

7.4.4.1 Dosing criteria to administer radium-223 dichloride/placebo:

After first radium-223 dichloride/placebo administration, prior to each subsequent dose of radium-223 dichloride/placebo, subjects must meet the following criteria for study treatment administration:

- Hb level ≥8.0 g/dL
- Platelet count ≥75 × 10^9/L
- ANC ≥1 x 10^9/L
- All non-hematological toxicities resolved to Grade ≤1 or baseline

Radium-223 dichloride/placebo is recommended to be given on Day 1 of a cycle of BOR/DEX.

Radium-223 dichloride/placebo administration may be delayed by no more than 28 days from the date of the intended dose (maximum of 10 weeks between 2 consecutive doses) for recovery of AEs.

Subjects with radium-223 dichloride/placebo administration delayed from the date of the intended dose may receive the subsequent cycles of radium-223 dichloride/placebo at another day other than Day 1 of BOR/DEX planned schedule.

If administration is delayed beyond 28 days due to toxicity, permanently discontinue radium-223 dichloride/placebo administration.

Continuation of BOR/DEX after stopping radium-223 dichloride/placebo can be considered after consultation with the medical monitor, if this is considered by the Investigator to be in the best interest of the subject.

7.4.4.2 Dosing criteria to administer bortezomib and dexamethasone at the start of a bortezomib cycle

Prior to initiating any cycle of BOR, subjects must meet the following criteria for study treatment administration on Day 1 of any BOR cycle:

- Hb level ≥8.0 g/dL
- Platelet count ≥75 x 10^9/L
- ANC ≥1 x 10^9/L
- All non-hematological toxicities resolved to Grade ≤1 or baseline

Initiation of a new cycle of BOR may be delayed up to 28 days to allow recovery of all toxicities.

If BOR administration is delayed beyond 28 days from the intended day of the next scheduled due to toxicity, the subject should be permanently discontinued.

Supportive care per institutional guidelines, including blood product transfusions or growth factor support is allowed for treatment criteria to be met.

Management of toxicities during a cycle

Grade 1 to 2 AEs (excluding neuropathy)

No pre-specified dose modifications are required except for neurological toxicities (see below); however, an Investigator may interrupt, delay, or reduce BOR and/or DEX more conservatively if deemed medically necessary according to his or her clinical judgment.

Grade 3 non-hematological AEs (excluding neuropathy)

For Grade 3 non-hematological toxicities, hold the BOR until the toxicity has resolved to Grade ≤1 or baseline. Restart at a reduced dose.

Grade 4 non-hematological AEs

For Grade 4 non-hematological toxicities, discontinue study treatment (Note: decisions concerning laboratory-related Grade 4 toxicities should be based on the Investigator's clinical judgment in discussion with the medical monitor).

Grade 3 hematological AEs

For Grade 3 hematological toxicities, except febrile neutropenia and thrombocytopenia with bleeding (see below), no pre-specified dose modifications are required. Institutional guidelines for supportive care and BOR dosing can be applied.

Grade 4 hematological AEs

For Grade 4 hematological toxicities or thrombocytopenia with bleeding or febrile neutropenia, hold the BOR until the toxicity has resolved to Grade ≤2. Restart at reduced dose.

Dose Reductions

If BOR is re-initiated, it will be at a 25% reduced dose. The first dose reduction is to 1 mg/m^2/dose; a second dose reduction is to 0.7 mg/m^2/dose. If a third dose reduction is required for any toxicity, permanently discontinue all study treatment. If a dose delay of BOR lasts longer than 28 days, permanently discontinue BOR treatment. A table for recommended dose modification for management of toxicities is presented in Table 7–1.

Table 7–1: Dose modification for management of toxicities

Toxicity	Dose modification
Hematological toxicity Grade 1, 2, or 3	Continue dosing and apply supportive care according to institutional guidelines; (For Day 1 of each cycle, please follow minimum dosing criteria)
Grade 3 or 4 febrile neutropenia, thrombocytopenia with bleeding Grade 4 neutropenia, thrombocytopenia, anemia	Hold treatment until Grade 2 or less; restart at reduced dose (reduce 1 dose level); (For Day 1 of each cycle, please follow minimum dosing criteria)
Grade 1 or 2 non-hematological toxicity	Continue dosing and apply supportive care per institutional guidelines;
Grade 3 Non-hematological toxicity (except neuropathy)	Hold treatment until Grade 1 or less; restart at reduced dose (reduce 1 dose level)

Grade 4 non-hematological toxicity	Permanently discontinue bortezomib treatment

Source: adapted from Velcade - EMEA/H/C/000539 -IB/0083 Summary of product characteristics

Hepatic Impairment (for starting dose of bortezomib only)

In subjects with hepatic impairment, for moderately elevated levels (>1.5 x to 3 x ULN) or severely elevated levels (>3 x ULN) of bilirubin, reduce BOR to 0.7 mg/m^2/dose. Subsequent dose escalation to 1.0 mg/m^2/dose or further dose reduction to 0.5 mg/m^2/dose is allowed based on subject tolerability. Note: this dose level of 0.5 mg/m^2 is only applicable to hepatic impairment.

Modify BOR as indicated in Table 7–2.

Table 7–2: Recommended starting dose of bortezomib for hepatic impairment

	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose
Mild	Less than or equal to 1.0x ULN	More than ULN	None
Mild	More than 1.0x−1.5x ULN	Any	None
Moderate	More than 1.5x−3x ULN	Any	Reduce bortezomib to 0.7 mg/m2 in the first cycle. Consider dose escalation to 1.0 mg/m2 or further dose reduction to 0.5 mg/m2 in subsequent cycles based on subject tolerability.
Severe	More than 3x ULN	Any	

Abbreviations: AST = aspartate aminotransferase; SGOT = serum glutamic oxaloacetic transaminase; ULN = upper limit of the normal range
Source: adapted from Velcade - EMEA/H/C/000539 -IB/0083 Summary of product characteristics

Neuropathy

Modify BOR as indicated in Table 7–3.

Table 7–3: Dose modifications for neuropathy

Neuropathic pain and/or peripheral neuropathy	Dose modification
CTCAE Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
CTCAE Grade 2 (moderate symptoms; limiting instrumental ADL [preparing meals, shopping for groceries or clothes, using telephone, managing money, etc.])	Reduce bortezomib to 1 mg/m^2/dose
CTCAE Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL [bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden])	Withhold bortezomib until toxicity resolves. When toxicity resolves, re-initiate with reduced dose of bortezomib at 0.7 mg/m^2/dose
CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib permanently

Abbreviations: ADL=activities of daily living; CTCAE=Common Terminology Criteria for Adverse

events, version 4.03.
Source: adapted from Velcade - EMEA/H/C/000539 -IB/0083 Summary of product characteristics

Other considerations

Delay of an individual BOR dose administration on Days 4, 8, or 11 is allowed up to 3 days to investigate possible toxicity or to allow recovery from rapidly reversible toxicity or for logistical reasons (e.g., bank holiday); alternatively the dose may be omitted. There must be at least 72 hours between each injection of BOR. If toxicity has not resolved within a 3-day delay, the dose should be omitted.

As there have been reports of cardiopulmonary adverse reactions associated with BOR administration, in the event of new or worsening cardiopulmonary symptoms, a prompt comprehensive diagnostic evaluation should be conducted, per the Investigator's clinical judgment.

Diarrhea should be managed aggressively as a Grade 2 may progress to Grade 3, necessitating interruption in therapy. Consideration regarding the use of prophylactic and/or supportive care should be made upon the first observation of diarrhea. Consider giving the subject a prescription for anti-diarrheals (e.g., loperamide) to be used as needed and to maintain hydration.

For subjects that experience any Grade 3 or 4 infection, therapy with BOR must be interrupted till resolved to Grade ≤1. For subjects with suspected infection, the subject should undergo work-up for possible infection (e.g., chest XR, blood cultures, urinalysis, etc. as applicable) and dosing with BOR may be delayed for the work-up to occur.

For situations where dose modification guidance is ambiguous or conflicting, the more conservative approach will be used.

Dexamethasone considerations

DEX can be adjusted as needed per standard of care. Subjects who cannot tolerate DEX are permitted to continue study treatment without DEX.

7.4.5 Supportive care guidelines

Supportive treatment should be provided as deemed necessary by the treating Investigator. Recommendations for supportive treatment are provided in the IMWG supportive care guidelines for multiple myeloma.(50)

Supportive treatment may include anti-emetics, antidiarrheal medications, fluid and electrolyte replacement, anti-pyretics, antihistamines, analgesics, antibiotics, blood products, growth factors, focal external radio therapy if given for pain management, and others.

Adequate hydration is recommended for the prevention of myeloma-related kidney disease.

During treatment with bisphosphonates, the subjects may be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily

Antiviral prophylaxis to prevent herpes zoster infection or re-activation is recommended.

If surgery is required, the subject should continue with study treatment, if this is considered safe in the treating Investigator's opinion. The surgeon needs to be notified that the subject has been given radioactive drug and needs to follow the guidelines for radioactive protection. The subject should continue with study treatment if it is considered safe in the treating Investigator's opinion.

7.5 Blinding

Every effort will be made to keep the phase 2 part of the study blinded. In the phase 2 part, subjects will be randomized to receive radium-223 dichloride or placebo in a double-blind fashion. All subjects will also receive bortezomib and dexamethasone; this treatment will be provided by the Sponsor or locally sourced and will be administered in an open-label format.

All treating physicians, clinical staff, subjects, Contract Research Organization (CRO), 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. Blinded and unblinded roles are not interchangeable during the study. Unblinded personnel must only perform unblinded tasks; blinded personnel must only perform blinded tasks.

Study personnel from the sponsor and the CRO responsible for drug supply and monitoring, who are not otherwise involved in the conduct of the study, will also be unblinded to study treatments.

Due to the nature of radium-223 dichloride, there must be at least 2 people 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. 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/placebo (isotonic 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.

Treatment with bortezomib and dexamethasone is not blinded.

In compliance with applicable regulations, in the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR; see Section 9.6.1.4) related to the blinded treatment, the subject's treatment code will usually be unblinded before reporting to the health authorities and ethic committees.

Emergency unblinding by the Investigator

Investigators may only unblind subjects under emergency conditions. If a subject is unblinded by the Investigator, the subject must discontinue treatment with radium-223 dichloride or placebo. The subject may continue treatment with bortezomib and dexamethasone if the Investigator considers continued treatment to be in the subject's best interest.

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 system (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 1 working day of unblinding to discuss the rationale for the premature unblinding. It is the investigator's responsibility to notify the medical monitor before placing a call to IXRS to unblind the subject.

7.6 Drug logistics and accountability

All study treatments will be stored at the investigational site in accordance with national regulations on radioactive materials, Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the Sponsor (or its affiliate/CRO), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the Sponsor's study file. All documents regarding drug logistics need to be filed in the Investigator Site File.

On the day of receipt, the responsible site personnel will confirm receipt of study drug via IxRS. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor´s agreed and specified procedures. Written instructions on medication destruction will be made available to affected parties as applicable. If performing drug accountability implies a potential risk of contamination, a safety process/guidance for handling returned drug will be provided. Locally sourced medication, is to be handled by the local standards. It is required at minimum that the batch numbers by subject and expiry dates are recorded.

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. 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.

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 1 day before the planned treatment at the latest. The responsible unblinded study site personnel will confirm receipt of Sponsor-supplied study drug via IxRS system.

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. Drug accountability for isotonic 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 study treatment bortezomib and dexamethasone

In case BOR and DEX is supplied centrally, the medication will be shipped to the study center upon IxRS shipment request. The responsible site personnel will confirm receipt of Sponsor-supplied study treatment in writing and via IxRS.

Locally sourced medication will be handled according to the local procedures and will not be labelled study specific. It is required, at minimum, that the batch numbers and expiry dates are recorded.

An accountability log of all study medication must be maintained and signed by the appropriately trained site personnel for drug handling at each site. All study treatment packages provided by the sponsor must be stored until drug accountability has been completed by the monitor.

7.7 Treatment compliance

Subjects will receive treatment with radium-223 dichloride/placebo 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 30 days after last study treatment administration must be recorded in the eCRF.

The option of starting a bone health agent (BHA) including bisphosphonates or denosumab should be considered, taking into consideration applicable guidelines. Thereafter, until the end of the follow-up period, only medications given to treat any grade AEs related to the

study treatment, 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 protocol-specified radiological procedures (CT or PET-CT) 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

Other cancer treatment with established efficacy in multiple myeloma 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 and BOR/DEX administrations must be discontinued.

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

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

The following concomitant therapy is prohibited during the treatment phase:

- Any marketed therapy with anti-myeloma effect including, but not limited to, chemotherapy, immunotherapy, and stem cell transplant
- Radiopharmaceuticals with anti-cancer properties such as strontium-89, samarium-153, rhenium-186, or rhenium-188
- Hemibody external radiotherapy
- Any investigational drugs
- All medications that are prohibited as per the local label instructions for BOR and DEX and the supportive treatment
- Per FDA recommendation, biotin supplements over 30 mcg per day should be avoided as they may interfere with biomarker assays.

It is the site's responsibility to ensure that the study treatment with BOR and DEX is administered in line with standard practice and local label instructions.

8.1.2 Permitted concomitant therapy

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 bone health agents (BHA) including bisphosphonates or denosumab before the start of study treatment and to continue on this therapy without change during the course of the study, unless

unable to tolerate or contraindicated. If not already on treatment, the option of starting a BHA, including bisphosphonates or denosumab should be considered during or after study drug treatment, taking into consideration applicable guidelines. Injection of bisphosphonates should be done at least 2 hours before or after study treatment administration.

- Focal external radiotherapy if given for pain management
- Blood transfusions and use of biologic response modifiers, such as G-CSF or GM-CSF, are allowed during the study per institutional guidelines, at the discretion of the Investigator, except during the DLT observation window when they are allowed only in a curative setting.
- Analgesic use will be captured via the eCRF (analgesic concomitant medication, 24-hour analgesic use and opioid use, see Table 9–1) , and the subject should be asked to record any pain medication they 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. The Brief Pain Index-Short Form (BPI-SF; Section 16.7) will also be dispensed according to the schedule of assessments.
- External beam radiotherapy (EBRT) treatment should be recorded in the eCRFs until end of the active follow-up period.
- Antiviral prophylaxis is recommended as per the local standard of care.
- Pneumocystis carinii pneumonia (PCP) prophylaxis is recommended as per the local standard of care.

8.1.3 Interaction potential of bortezomib with other medicinal products

BOR is a substrate of cytochrome P450 enzyme 3A4, 2C19, and 1A2. Subjects taking BOR in combination with the below medicinal products should be closely monitored.

CYP3A4 inhibitors

Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure of BOR by 35% in 12 subjects. Monitor subjects for signs of BOR toxicity and consider a BOR dose reduction if BOR must be given in combination with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir).

CYP2C19 inhibitors

Co-administration of omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of BOR in 17 subjects.

CYP3A4 inducers

Co-administration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of BOR by at least 45%. Because the drug interaction study (n=6) was not designed to exert the maximum effect of rifampin on BOR PK, decreases greater than 45% may occur.

Efficacy may be reduced when BOR is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in subjects receiving BOR.

St. John's Wort (hypericum perforatum) may decrease BOR exposure unpredictably and should not be used.

For more details on strong, moderate, and weak CYP3A4 inhibitors and inducers please refer to Section 16.8

8.2 Post-study therapy

Treatment with radium-223 dichloride/placebo will be halted following completion of the full assigned treatment (6 doses) or at early termination. Treatment with BOR or DEX will be terminated for disease progression or unacceptable toxicity or other reasons (Section 6.3.1.1).

Following discontinuation of all study treatments (radium-223 dichloride/placebo, BOR and DEX), subjects will be treated and followed as per the institutional standard of care and/or according to the physician's clinical judgment. The option of starting bone health agent (BHA) including bisphosphonates or denosumab should be considered, taking into consideration applicable guidelines.

Once a subject enters the follow-up period, all protocol-related treatments must be stopped; all standard anti-cancer treatments a subject might receive during the follow-up period will be recorded as follow-up anti-cancer therapy.

If possible, cytotoxic chemotherapy, other systemic radioisotope, hemibody external radiotherapy, or other investigational drug should not be given prior to completing a 4-week wash-out period after last administration of radium-223 dichloride/placebo, provided the subject is eligible for such therapy according to local physician's assessment.

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

All disease response analyses will be conducted by central laboratory (Section 9.4.2). Safety evaluations will be conducted locally (Section 9.6).

Safety measurements and data from the evaluation of the early signal of anti-MM activity obtained during the course of the study are summarized in the schedule of assessments (Table 9–1).

A diagram of dosing for is presented in Figure 9–1.

Table 9–1: Schedule of assessments for screening and treatment period for Phase 1b and Phase 2

Study Period	**Screening [a] D-21 to D-1**	**Randomization (Phase 2 only)**	**Treatment [b,c]**																**End of Radium-223 dichloride/placebo visit [d] (Placebo option for Phase 2 only)**
			Radium-223 dichloride or placebo (Placebo option for Phase 2 only) + BOR/DEX												**Radium-223 dichloride or placebo (Placebo option for Phase 2 only) + Maintenance BOR/DEX**				
Cycle			**1**			**2**			**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**		
Week			**0**	**1**	**2**	**3**	**4**	**5**	**6-8**	**9-11**	**12-14**	**15-17**	**18-20**	**21-23**	**24**	**26**	**28**	**30**	
BOR/DEX [e]		**D 0**	**D 1,4**	**D 8, 11**		**D 1,4**	**D 8, 11**		**D 1,4, 8, 11**	**D 1, 4, 8, 11**	**D 1,4 D 8, 11**	**D 1,4, 8, 11**	**D 1,4 D 8, 11**	**D 1,4 D 8, 11**	**D 1**	**D 15**	**D 1**	**D 15**	
Radium-223 dichloride / placebo dosing [f] (Placebo option for Phase 2 only)			**Dose 1 (D1 only)[gg]**						**Dose 2 (D1 only)**		**Dose 3 (D1 only)**		**Dose 4 (D1 only)**		**Dose 5**			**Dose 6**	
Informed consent [h]	X																		
Subject ID Assignment	X																		
Review of eligibility [a]	X	X																	
Demographics	X																		
Disease history	X																		
Medical history	X																		
Prior SRE [i]	X																		
Randomization (Phase 2 only)		X																	
BPI-SF [j] (Day 1)	X		X						X		X		X		X		X		
RUQ [j] (Day 1)	X		X						X		X		X		X		X		
24-hr analgesic use [j] (Day 1)	X		X						X		X		X		X		X		X
Opioid use	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs, SAEs [k]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLT assessment (Phase 1 only)			X	X	X	X	X	X	X	X [gg]									
Prior and con meds (+anti-cancer treatments) [l,m]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 9–1: Schedule of assessments for screening and treatment period for Phase 1b and Phase 2

Study Period	**Screening [a] D-21 to D-1**	**Randomization (Phase 2 only)**	**Treatment [b,c]**																**End of Radium-223 dichloride/placebo visit [d] (Placebo option for Phase 2 only)**
			Radium-223 dichloride or placebo (Placebo option for Phase 2 only) + BOR/DEX												**Radium-223 dichloride or placebo (Placebo option for Phase 2 only) + Maintenance BOR/DEX**				
Cycle			**1**			**2**			**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**		
Week			**0**	**1**	**2**	**3**	**4**	**5**	**6-8**	**9-11**	**12-14**	**15-17**	**18-20**	**21-23**	**24**	**26**	**28**	**30**	
BOR/DEX [e]		**D 0**	**D 1,4**	**D 8, 11**		**D 1,4**	**D 8, 11**		**D 1,4, 8, 11**	**D 1, 4, 8, 11**	**D 1,4 D 8, 11**	**D 1,4, 8, 11**	**D 1,4 D 8, 11**	**D 1,4 D 8, 11**	**D 1**	**D 15**	**D 1**	**D 15**	
Radium-223 dichloride / placebo dosing [f] (Placebo option for Phase 2 only)			**Dose 1 (D1 only)[g]**						**Dose 2 (D1 only)**		**Dose 3 (D1 only)**		**Dose 4 (D1 only)**		**Dose 5**			**Dose 6**	
Vital signs [n]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [o]	X																		
Weight [p]	X		X			X	X		X	X	X	X	X	X	X	X	X	X	
Height	X																		
Physical examination [q]	X		X			X			X	X	X	X	X	X	X		X	X	
ECOG-PS [r]	X		X			X			X	X	X	X	X	X	X		X		
Hematology [s, t]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test and estradiol assay [u]	X		X						X		X		X		X			X	X
Clinical chemistry [v]	X		X	X		X	X		X	X	X	X	X	X	X		X		
Coagulation panel [w]	X																		
Assessment for hepatitis B and C [x]	X																		
Blood and urine biomarkers [y]	X		X						X		X		X		X			X	X
Plasma for ctDNA analysis [z]	X		X						X		X		X		X			X	X
Whole blood for CTCs analysis [aa]			X						X		X		X		X			X	X

Table 9–1: Schedule of assessments for screening and treatment period for Phase 1b and Phase 2

Study Period	**Screening [a] D-21 to D-1**	**Randomization (Phase 2 only)**	**Treatment [b,c]**																**End of Radium-223 dichloride/placebo visit [d] (Placebo option for Phase 2 only)**
			Radium-223 dichloride or placebo (Placebo option for Phase 2 only) + BOR/DEX												**Radium-223 dichloride or placebo (Placebo option for Phase 2 only) + Maintenance BOR/DEX**				
Cycle			**1**			**2**			**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**		
Week			**0**	**1**	**2**	**3**	**4**	**5**	**6-8**	**9-11**	**12-14**	**15-17**	**18-20**	**21-23**	**24**	**26**	**28**	**30**	
BOR/DEX [e]		**D 0**	**D 1,4**	**D 8, 11**		**D 1,4**	**D 8, 11**		**D 1,4, 8, 11**	**D 1, 4, 8, 11**	**D 1,4 D 8, 11**	**D 1,4, 8, 11**	**D 1,4 D 8, 11**	**D 1,4 D 8, 11**	**D 1**	**D 15**	**D 1**	**D 15**	
Radium-223 dichloride / placebo dosing [f] (Placebo option for Phase 2 only)			**Dose 1 (D1 only)[g]**						**Dose 2 (D1 only)**		**Dose 3 (D1 only)**		**Dose 4 (D1 only)**		**Dose 5**			**Dose 6**	
Bone marrow biopsy [bb]	X		Performed according to IMWG criteria																
EMD assessments [cc]	X		Performed according to IMWG criteria																
M-protein measurements by SPEP, UPEP, Freelite essay IF (central lab) [dd]	X		X			X			X	X	X	X	X	X	X		X		
β_2-microglobulin	X																		
Disease assessment [dd]	X		X			X			X	X	X	X	X	X	X		X		
SSEs [i,dd,ee]	X		X			X			X	X	X	X	X	X	X		X		
Radium-223 dichloride / placebo dosing [g] (Placebo option for Phase 2 only)			X						X		X		X		X			X	
Skeletal survey [ff]	X																		X

Abbreviations: AE=adverse event; BOR=bortezomib; BPI-SF=Brief Pain Index-Short Form; con med=concomitant medication; CT=computed tomography; CTCs= circulating tumor cells; ctDNA= circulating tumor DNA; D=Day; DEX=dexamethasone; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG-PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic case report form; EMD=extramedullary disease; EOT=end of treatment; Hb=hemoglobin; HBcAb=hepatitis B core antibody; HBV=hepatitis B virus; HCV-hepatitis C virus; HIV=human immunodeficiency virus; ID=identification number; IF=Immunofixation; IMWG=International Myeloma Working Group; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PET=positron emission tomography; PFS=progression-free survival; PRD=patient-ready dose; q=every; RBC=red blood cell; RNA= ribonucleic acid; RUQ=Resource Utilization Questionnaire; SAE=serious adverse event; SPEP=serum protein electrophoresis; SRE= skeletal-related event, SSE=symptomatic skeletal event; UPEP=urine protein electrophoresis; US=United States; WBC=white blood cell; wk=week

a. All screening evaluations must be complete and reviewed prior to confirmation of eligibility (phase 1b) or randomization (phase 2). Screening evaluations must be complete within 21 days starting from the time of ICF signature. Bone marrow biopsy or aspirate, skeletal survey and local blood and urine protein-M tests (as well as any other specific multiple myeloma tumor assessment blood and urine tests) previously done as part of routine care will be accepted for eligibility confirmation purposes even if done prior to ICF signature, as long as these tests have been performed up to 14 days prior to ICF signature. If logistical reasons require, local lab results for blood and urine protein-M and other specific multiple myeloma tumor assessment tests ordered after ICF signature can also be used for eligibility assessment only, to ensure that eligibility confirmation timelines are met. If any local lab samples are used to run tumor assessment tests for eligibility confirmation, blood and urine samples for central lab analysis will still be collected and used as the final baseline value for data analysis.
b. All assessments at treatment visits should be performed before study treatment administration.
c. Subjects will continue in the treatment period until the occurrence of a PFS event, unacceptable toxicity develops, or the subject withdraws consent, whichever occurs first (Section 9.4.2).
d. The End of radium-223 dichloride/placebo visit should occur 30 days (+7 days) after radium-223 dichloride/placebo treatment is completed or discontinued.
e. Bortezomib/dexamethasone will be given for eight 21-day cycles on Days 1, 4, 8, and 11. The minimum time window between 2 BOR injections is 72 hours; if an injection is delayed, this can be for a maximum of 3 days from original scheduled day (calculated from Day 1 of the respective cycle). Omit injection if delay is >3 days. DEX may be administered over 2 days, at the discretion of the Investigator.
f. A total 6 radium-223 dichloride/placebo doses are planned at 6-week intervals. The minimum time window between 2 doses of radium-223 dichloride/placebo must be 6 wks. Radium-223 dichloride/placebo administration may be delayed if medically necessary. A maximum of 28 days from the date of the intended dose is allowed (i.e., a maximum of 10 weeks between 2 consecutive doses) for recovery of AEs is allowed. If administration is delayed beyond the 10 weeks window due to toxicity, the subject must permanently discontinue radium-223 dichloride/placebo administration. Subjects with radium-223 dichloride/placebo administration delayed from the date of the intended dose may receive the subsequent cycles of radium 223 dichloride/placebo at another day other than Day 1 of bortezomib/dexamethasone planned schedule.
g. On Cycle 1 Day 1 only, radium-223 dichloride/placebo must be administered before BOR or DEX. Samples for M-protein must be collected before administration of radium-223 dichloride/placebo. The IxRS must be accessed for drug re-supply in preparation for the next study visit. 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.
h. Informed consent is to be collected before the initiation of any study related procedures.
i. Bone fractures / pathological fractures will be collected regardless disease relationship.
j. Analgesic use (24-hr), BPI-SF, and RUQ will be provided to the subject at Screening, on Cycle 1 Day 1, and every 6 weeks thereafter until the end of Cycle 6 of radium-223 dichloride/placebo with a window of ±7 days. During the Maintenance Period and until EOT visit, they will be provided at Day 1 every 28 days with a window of ±7 days and during active follow-up, they will be provided every 8 weeks with a window of ±7 days. Pain medication will also be assessed at each visits and analgesic use will be recorded in the appropriate eCRF page.
k. Window ±1 day for AEs. Adverse events will be collected through 30 days post-last study treatment administration. Investigator should check for occurrences of any new malignancy: new primary malignancy (including AML) or hematological conditions (e.g., MDS, aplastic anemia, myelofibrosis) must be reported as SAEs at any time and regardless of the investigator's causality assessment. All AEs and SAEs considered related to any agent of study treatment (radium-223 dichloride/placebo,

bortezomib, or dexamethasone) occurring during the active follow-up period will be collected. 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.

l. Window ±7 days. At baseline screening, all prior medications, including analgesics, are to be recorded. Thereafter, collect all medications, including analgesics, up to 30 days post last study treatment administration. Thereafter, until the end of the active follow-up period, only collect medications used to treat any grade adverse drug reaction and analgesics. Analgesic use has to be recorded via the analgesic concomitant medication eCRF. The initiation of bone health agent (BHA) such as bisphosphonates or denosumab should be considered by investigators taking into consideration applicable guidelines

m. Record any cancer-related and prior multiple myeloma treatments. The option of starting bone health agent (BHA) including bisphosphonates or denosumab should be considered, taking into consideration applicable guidelines.

n. Window ±1 day. The measurement of vital signs will include: blood pressure, heart rate, respiratory rate, and temperature.

o. Required at screening, otherwise as clinically indicated. Hypokalemia should be corrected prior to ECG collection. Twelve-lead ECG should be obtained when serum potassium is ≥3.5 mmol/L.

p. Window ±1 day. Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. At all sites (US and ex-US), weight is to be taken before each Day 1 bortezomib dose AND 3 to 5 days before each radium-223 dichloride/placebo dose (for US sites) or 72 hours before each radium-223 dichloride/placebo dose (for ex-US sites). The weight measurements prior to radium-223 dichloride/placebo dose must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits. Body weight can be obtained at the local healthcare provider on a calibrated scale and the results sent by fax to the Principal Investigator with advanced notice and agreement from the Covance Medical Monitor for each subject.

q. Window ±1 day. A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems. The physical exam is to be performed before every radium-223 dichloride dose/placebo and before every Day 1 BOR injection.

r. Window ±1 day. The ECOG-PS is to be assessed every Day 1 of BOR before injection.

s. The screening hematology values are recommended to be measured within 2 weeks before the first dose of radium-223 dichloride/placebo and the first radium-223 dichloride/placebo dose should be done as soon as possible after enrollment. The same sample can be used for dosing radium-223 dichloride/placebo if taken within 72 hours before dosing, otherwise a repeat sample within 72 hours before dosing will be required. Hematology parameters will include hematocrit, Hb, platelet counts, RBC counts, WBC counts, WBC differential. Subjects with platelet counts $<75x10^9$/L and/or absolute neutrophil count $<1.0x10^9$/L should undergo repeat weekly hematology examination until resolution.

t. Window ±1 day. Hematology will be collected a minimum of once weekly. Sites may collect hematology assessments more often, if that is the standard of care at that site. In addition, hematology must also be collected 72 hours before radium-223 dichloride/placebo dosing. A complete blood count must be performed before every radium-223 dichloride/placebo and BOR dosing during combination therapy. Analysis and evaluation of hematology samples must be completed within 72 hours before radium-223 dichloride/placebo dosing. During maintenance treatment, within 3 days prior to each dose of BOR/DEX, hematology, must be assessed and the Investigator must confirm that the subject meets dosing criteria for bortezomib. Hematology assessments will also be performed at the EOT visit. Additional laboratory assessments should be performed according to the institutional guidelines.

u. Window ±1 day. Pregnancy tests will be administered at screening and 72 hours before radium-223 dichloride/placebo dosing. After the last radium-223 dichloride/placebo dose, pregnancy tests will be administered on Day 1 of the BOR-only cycle through the EOT. Women of child-bearing potential must have a negative urine pregnancy test performed within 72 hours before the first dose of radium-223 dichloride/placebo. Postmenopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. An estradiol assay is required within 72 hours before the first dose of radium-223 dichloride/placebo in premenopausal women with radiotherapy ovarian ablation or medical ovarian suppression and postmenopausal women age <55 years and 1 year or more of amenorrhea and no ovarian suppression.

v. Window ± 1 day. The screening clinical chemistry values are recommended to be measured within 2 weeks before the first dose of radium-223 dichloride/placebo and

the first radium-223 dichloride/placebo dose should be done as soon as possible after enrollment. The same sample can be used for dosing radium-223 dichloride/placebo if taken within 72 hours before dosing, otherwise a repeat sample within 72 hours before dosing will be required. Clinical chemistry samples will be taken at screening and on Days 1 and 11 for the first 2 cycles, then Day 1 of BOR dosing from Cycle 3 onwards. Sodium, potassium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total alkaline phosphatase, serum creatinine, bilirubin (total), glucose, phosphate, and albumin. Blood urea nitrogen or urea will also be collected, according to each site's standard of care.

w. Required at screening, otherwise as clinically indicated.

x. Subjects are not eligible if they have active hepatitis B or C infection requiring treatment; subjects with occult or prior HBV infection (defined as positive HBcAb and negative HBsAg) may be included if HBV-DNA is undetectable at screening. Subjects positive for HCV antibody must be negative for HCV-RNA by PCR assessment.

y. Window ±7 days. Blood and urine samples for biomarkers will be collected at screening, before radium-223 dichloride/placebo doses 1 to 6 and then 30 days after the last dose of radium-223 dichloride/placebo, or disease progression, whichever occurs first.

z. Window ±7 days. For ctDNA, plasma samples will be collected at screening, before radium-223 dichloride/placebo doses 1 to 6 and then 30 days after the last dose of radium-223 dichloride/placebo, or disease progression, whichever occurs first.

aa. Whole blood will be collected prior to every dosing with radium-223 dichloride/placebo for dose 1 through 6 and end of radium-223 dichloride treatment.

bb. At baseline screening and repeated to confirm complete response per IMWG criteria. A bone marrow aspirate is acceptable. After the percentage of plasma cells is determined by the local laboratory, the remaining bone marrow sample will be sent to the central laboratory for biomarker testing.

cc. At screening if EMD present at baseline as per IMWG criteria subject is not eligible. To repeat if suspicion of new EMD lesion.

dd. M-protein samples will be drawn , disease response assessments, and SSEs will be performed on Cycle 1 Day 1 and every 21 days (±7 days) thereafter through Cycle 8 of BOR/DEX, and then every 28 days thereafter (±7 days) through the end of treatment. These assessments should be based on laboratory results provided by the central lab and according to IMWG criteria.

ee. All bone fractures, or any relevant bone event (e.g., osteoporosis) should be reported as SSE and need to be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

ff. Window ±7 days. The skeletal survey should be conducted at EITHER 30 days after last dose of radium-223 dichloride/placebo OR at the end of all study treatment, whichever occurs first). Magnetic resonance imaging, low-dose CT, or PET-CT are allowed as alternatives to the skeletal survey at sites where this is considered the institutional standard; the same methodology (MRI, low-dose CT, PET-CT, or skeletal survey) should be used at baseline and all subsequent assessments.

gg. The final DLT assessment should occur prior to bortezomib dosing on Cycle 4, Day 1.

Table 9–2: Schedule of assessments for maintenance period and follow-up periods (Phase 1b and Phase 2)

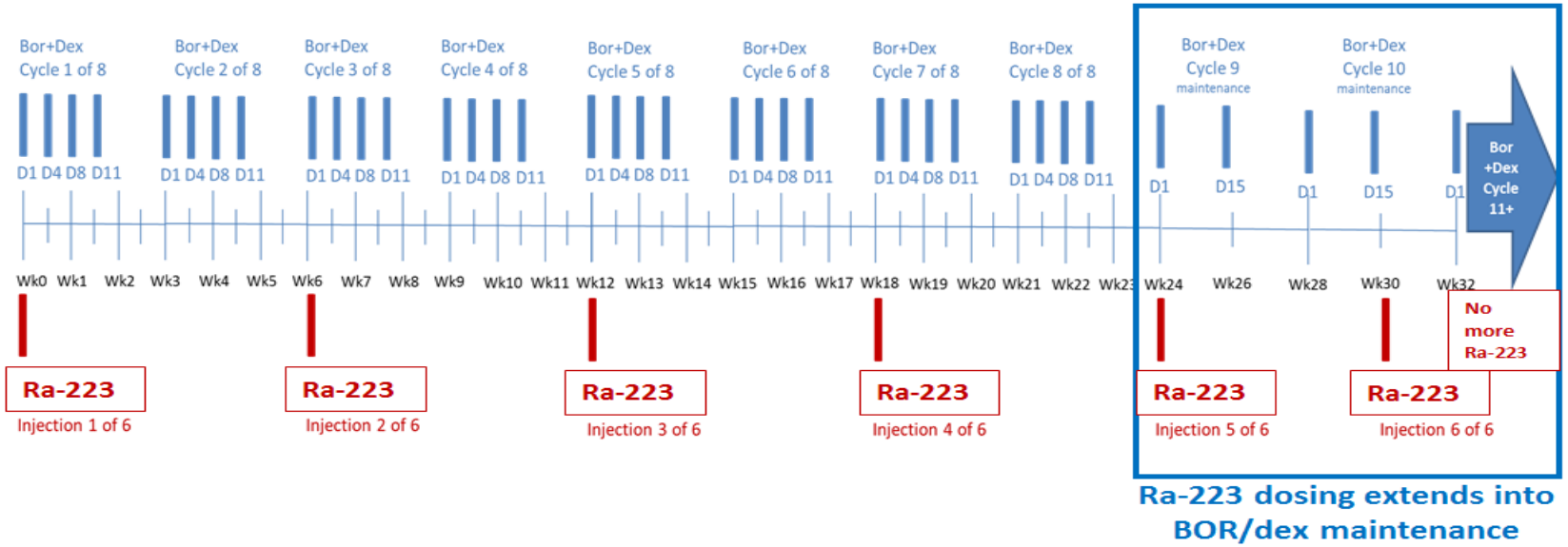
Study Period	Treatment [a,b]		Follow-up Periods	
	Maint (BOR/DEX)	EOT [c]	Active Follow-up	Long-term Follow-up [x]
Cycle	11+			
Weeks		30 days post last dose	Q8 wk for 2 years after last radium-223 dichloride dose	Every 6 months for up to 5 years
BOR/DEX dosing [d]	X			
BPI-SF [e]	X	X	X	
RUQ [e]	X	X	X	
24-hr analgesic use [e]	X	X	X	
Opioid use	X	X	X	
AEs, SAEs [f]	X	X	X	X
Prior and con meds [g,h]	X	X	X	X
Vital signs [i]	X	X	X	
Weight [j]	X			
Physical examination [k]	X			
ECOG-PS [l]	X	X		
Hematology [m,n]	X	X		
Pregnancy test and estradiol assay [o]	X	X		
Clinical chemistry [p]	X	X		
Bone marrow biopsy [q]	Performed according to IMWG criteria			
EMD assessments [r]	Performed according to IMWG criteria			
M-protein measurements by SPEP, UPEP, Freelite assay IF (central lab) [s]	X	X	X	
Disease response assessment [s,t]	X	X	X	
SSEs/other relevant bone events [s]	X	X	X	X
Blood biomarkers [u]	X	X	X	
Urine biomarkers [u]	X	X		
Plasma for ctDNA analysis [v]	X	X	X	
Whole blood for CTCs analysis [w]	X	X	X	
Survival status				X

Abbreviations: AE=adverse event; BOR=bortezomib; BPI-SF=Brief Pain Index-Short Form; con med=concomitant medication; CT=computed tomography; CTCs= circulating tumor cells; ctDNA= circulating tumor DNA; DEX=dexamethasone; ECOG-PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic case report form; EMD=extramedullary disease; EOT=end of treatment; Hb=hemoglobin; IC=Investigator's choice; IF=Immunofixation; IMWG=International Myeloma Working Group; maint=maintenance; MRI=magnetic resonance imaging; PET=positron emission tomography; PFS=progression-free survival; Q=every; RBC=red blood cell; RUQ=Resource Utilization Questionnaire; SAE=serious adverse event; SPEP=serum protein electrophoresis; SSE=symptomatic skeletal event; UPEP=urine protein electrophoresis; US=United States; WBC=white blood cell; wk=week

a. All assessments at treatment visits should be performed before study treatment administration.
b. Subjects treated with BOR/DEX will continue in the treatment period up to 2 years after the first dose of study treatment, until a progression-free survival (PFS) event occurs, the subject withdraws consent or an unacceptable toxicity develops, whichever occurs first.
c. The EOT visit will be conducted 30 days (+7 days) after last dose of study treatment (radium-223 dichloride/placebo, BOR/DEX, , whichever is last).
d. Bortezomib will be administered on Days 1 and 15 of a 28-day cycle. Dexamethasone will be administered 20 mg/dose, on Days 1 and 15 of a 28-day cycle along with bortezomib.
e. Window ±7 days. Analgesic use (24-hr), RUQ, and BPI-SF will be dispensed to the subject every 28 days through the end of the Maintenance Period, at the EOT visit, and at active follow-up clinic visits. Pain medication will also be assessed at each 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.
f. Window ±1 day for AEs. Adverse events will be collected through 30 days post-last study treatment administration. Investigator should check for occurrences of any new malignancy: new primary malignancy (including AML) or hematological conditions (e.g. MDS, aplastic anemia, myelofibrosis) must be reported as SAEs at any time and regardless of the investigator's causality assessment. All AEs and SAEs considered related to any agent of study treatment (radium-223 dichloride/placebo, bortezomib, dexamethasone) occurring up to 30 days after the last study treatment administration will be collected. During the follow-up (either active or long-term follow up). All bone fractures, or any relevant bone event (e.g., osteoporosis) should be reported as SSE and need to be collected as either AE(s) or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. Any occurrence of febrile neutropenia and hemorrhage considered related to radium-223 dichloride will also be reported until end of follow-up period.
g. Window ±7 days. Collect all medications, including analgesics, up to 30 days post last study treatment administration. Thereafter, until the end of the follow-up period, only collect medications used to treat any grade adverse drug reaction and analgesics. Analgesic use has to be recorded via the analgesic concomitant medication eCRF.
h. Record any cancer-related treatments and bone health agent (BHA) therapy. The option of starting BHA including bisphosphonates or denosumab should be considered, taking into consideration applicable guidelines.
i. Window ±1 day. The measurement of vital signs will include: blood pressure, heart rate, respiratory rate, and temperature.
j. Window ±1 day. Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. At all sites (US and ex-US), weight is to be taken every 28 days, at minimum, or according to the Investigator's standard of care, whichever is more frequent. Body weight can be obtained at the local healthcare provider on a calibrated scale and the results sent by fax to the Principal Investigator with advanced notice and agreement from the Covance Medical Monitor for each subject.
k. Window ±1 day. A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems. The physical exam is to be performed every 28 days (at minimum), or according to the Investigator's clinical judgment.
l. Window ±1 day. The ECOG-PS is to be assessed every 28 days (at minimum), or according to the Investigator's clinical judgment.

m. Hematology parameters will include hematocrit, Hb, platelet counts, RBC counts, WBC counts, WBC differential. Subjects with platelet counts <75x10^9/L and/or absolute neutrophil count <1.0x10^9/L should undergo repeat weekly hematology examination until resolution.
n. Within 3 days prior to Day 1 of each cycle, safety laboratory assessments, including hematology and clinical chemistry, must be assessed and the Investigator must confirm that the subject meets dosing criteria for bortezomib, as applicable. Additional laboratory assessments should be performed according to the institutional guidelines.
o. If the End of radium-223 dichloride/placebo visit occurs at the same time as the EOT visit, the pregnancy test only needs to be performed once. Postmenopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
p. Window ± 1 day. Clinical chemistry samples will be taken every 28 days, beginning at the start of the Maintenance Period. Sodium, potassium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total alkaline phosphatase, serum creatinine, bilirubin (total), glucose, phosphate, and albumin. Blood urea nitrogen or urea will also be collected, according to each site's standard of care.
q. To confirm complete response per IMWG criteria. Bone marrow aspirate is acceptable. After the percentage of plasma cells is determined by the local laboratory, the remaining bone marrow sample will be sent to the central laboratory for biomarker testing.
r. To perform if suspicion of new EMD lesion
s. Window ±7 days. Beginning at the start of the Maintenance Period, collection will occur every 28 days through the end of treatment. During active follow-up, M protein will be evaluated according to the site procedures but not less frequently than every 8 weeks. During the follow-up (either active or long-term follow up) all bone fractures, or any relevant bone event (e.g., osteoporosis) should be reported as SSE and need to be collected as either AEs) or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
t. Window ±7 days. Response/disease progression assessments will be performed on Cycle 1 Day 1, and every 28 days thereafter through the end of the Maintenance Period. During active follow-up, disease response will be assessed according to the site procedures but not less frequently than every 8 weeks. These assessments should be based on laboratory results provided by the central lab and according to IMWG criteria.
u. Window ±7 days. Blood and urine samples for biomarkers will be collected before radium-223 dichloride/placebo doses 1 to 6 and then 30 days after the last dose of radium-223 dichloride/placebo, or disease progression, whichever occurs first. During the maintenance period, samples will be collected every 4 cycles (every 16 weeks). During active follow up visits, samples will be drawn every other visit (every 16 weeks).
v. Window ±7 days. Plasma samples for circulating tumor DNA will be collected before radium-223 dichloride/placebo doses 1 to 6 and then 30 days after the last dose of radium-223 dichloride/placebo, or disease progression, whichever occurs first.
w. Whole blood for CTC analysis will be collected prior to every dosing with radium 223 dichloride/placebo then 30 days after the last dose of radium-223 dichloride/placebo, or disease progression, whichever occurs first. During maintenance period, samples will be collected every 4 cycles (every 16 weeks).
x. Subjects who have completed the 2 year active follow-up, will be followed with a telephone call every 6 months (±28 days) up to 5 years. A 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. All subjects will be asked to transition into this separate study to complete their long-term follow-up. The long-term follow-up may start in the current trial and subjects will then be asked to transition into the separate roll-over study.

Figure 9–1: Schedule of drug administration for radium-223 dichloride/placebo, bortezomib, and dexamethasone



A maximum delay of 28 days is allowed for starting the next cycle of bortezomib + dexamethasone (See Sections 6.3.1.1 and 7.4.4 for further details).

A maximum delay of 28 days due to toxicity (maximum time between two consecutive doses is 10 weeks) is allowed for administering the next dose of radium-223 dichloride/placebo (See Sections 6.3.1.1 and 7.4.4 for further details). Subjects with radium-223 dichloride/placebo administration delayed from the date of the intended dose may receive the subsequent cycles of radium 223 dichloride/placebo at another day other than Day 1 of bortezomib/dexamethasone planned schedule.

In case bortezomib is permanently discontinued, radium-223 dichloride/placebo will also be discontinued. (See Section 7.4.4.2 for further details).

9.2 Visit description

Computed tomography, magnetic resonance, or other imaging conducted at any time during the study should be collected and stored.

9.2.1 Screening period

Pre-treatment evaluations will only be performed after the subject has agreed to participate and has signed and dated the ICF. No treatment- or trial-related procedures will be initiated before the signed consent has been obtained. Skeletal survey, bone marrow specimens (bone marrow aspirate or biopsy) and blood and urine protein-M tests (as well as any other specific multiple myeloma tumor assessment blood and urine tests) may be done before obtaining informed consent if done as part of local standard of care routine and only when performed up to 14 days prior to ICF signature. After the percentage of plasma cells is determined by the local laboratory, the remaining bone marrow sample will be sent to the biorepository for retrospective biomarkers testing. Details of the sample handling will be summarized in the biosample management report.

The same skeletal survey imaging method (magnetic resonance imaging [MRI], low-dose computed tomography [CT], or positron emission tomography CT [PET-CT] are acceptable if it is the institutional standard) should be used for the baseline measurement and throughout the study. Subjects will not be required to undergo skeletal survey or bone biopsy/aspirate if suitable images/samples taken up to 14 days prior to ICF signature are available.

If logistical reasons require, only for eligibility confirmation, local lab results of blood and urine specific multiple myeloma tumor assessment tests can be used. If indeed any local lab samples are used for eligibility confirmation, blood and urine samples for central lab analysis will still be collected and used as the final baseline value for data analysis.

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.

After eligibility has been confirmed and documented, an additional period of up to a total of 21 days will take place before the administration of the first study drug, to account for all logistical needs related to radium-223 dichloride dose preparation and transportation. All efforts will be made to shorten this period as much as possible.

9.2.1.1 Study Procedures

Screening Procedures

The following procedures and evaluations will be performed within 21 days after the time of ICF signature.

- Sign informed consent
- Subject registration and subject number assignment via IxRS
- Review of inclusion and exclusion criteria and confirm eligibility
- Demographics

- Record disease history
- Record medical history
- Record prior SRE
- Administer the BPI-SF questionnaire
- Administer the Resource Utilization Questionnaire (RUQ)
- Record analgesics on the eCRF. Subjects will be asked to record 24-hour analgesic use. Pain medication will also be assessed at each visit by study site; subjects should be requested to bring all pain medication to each visit.
- Record opioid use
- Record AEs and SAEs

  Note: 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
- Record concomitant medications/therapy including bone health agent (BHA) (e.g., bisphosphonates, denosumab) and any anti-cancer treatments

  Note: The initiation of BHA such as bisphosphonates or denosumab should be considered by investigators taking into consideration applicable guidelines.
- Record prior multiple myeloma-related treatment
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- 12-lead ECG; hypokalemia should be corrected prior to ECG collection. ECG should be obtained when serum potassium is ≥3.5 mmol/L.
- Record height and weight. Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. Body weight can be obtained at the local healthcare provider on a calibrated scale and the results sent by fax to the Principal Investigator with advanced notice and agreement from the Covance Medical Monitor for each subject. At all sites (US and ex-US), weight is to be taken 3 to 5 days before each radium-223 dichloride/ placebo dose (for US sites) or 72 hours before each radium-223 dichloride dose (for ex-US sites). The weight measurements prior to radium-223 dichloride/placebo dose must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days).
- Perform full physical examination
- ECOG-PS
- Blood draw for hematology: hematocrit, Hb, platelet counts, RBC counts, white blood cell (WBC) counts, and WBC differential. Hematology should be measured within 2 weeks before the first radium-223 dichloride/placebo dose. The same sample can be used for dosing radium-223 dichloride/placebo if taken within

72 hours before dosing, otherwise a repeat sample within 72 hours before dosing will be required.

- Pregnancy test and estradiol assay: women of child-bearing potential must have a negative urine pregnancy test performed at screening and within 72 hours before the first dose of radium-223 dichloride/placebo. Postmenopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. An estradiol assay is required within 72 hours before the first dose of radium-223 dichloride/placebo in premenopausal women with radiotherapy ovarian ablation or medical ovarian suppression and postmenopausal women age <55 years and 1 year or more of amenorrhea and no ovarian suppression.
- Blood draw for clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, lactate dehydrogenase (LDH), total ALP, serum creatinine, blood urea nitrogen (BUN; or urea), bilirubin (total), glucose, phosphate, and albumin; clinical chemistry should be measured within 2 weeks before the first radium-223 dichloride/placebo dose. The same sample can be used for dosing radium-223 dichloride/placebo if taken within 72 hours before dosing, otherwise a repeat sample within 72 hours before dosing will be required.
- A coagulation panel: PT, PTT, and INR of PT
- Hepatitis B and C assessment: Subjects are not eligible if they have an active Hepatitis B or C infection requiring treatment. Subjects with occult or prior HBV infection (defined as positive HBcAb and negative HBsAg) may be included if HBV-DNA is undetectable at screening. Subjects positive for HCV antibody must be negative for HCV-RNA by PCR assessment.
- Collect blood for serum and plasma as well as urine samples for exploratory evaluation of biomarkers
- Plasma for ctDNA analysis
- Bone marrow evaluation for assessment of percentage plasma cells if no suitable sample is available that was taken as part of local routine standard of care up to 14 days prior to ICF signature; repeat assessment is required to confirm CR per IMWG criteria. Samples must be sent to the local laboratory for evaluation.
- Extramedullary disease (EMD; i.e., soft-tissue plasmacytoma) assessment: the method of assessment will be recorded in the eCRF; if EMD is present at screening as per IMWG criteria subject is not eligible, if suspicion of new lesion then see Section 9.4.2 for additional details.
- Blood draw and 24-hour urine collection for M-protein and β_2-microglobulin assessments by SPEP, 24-hour UPEP, and Free lite assay. Serum and urine immunofixation (IF) is only performed at study entry and to confirm a CR (conducted on the first observation of a CR in the SPEP and/or UPEP sample and repeated every 28 days until disease progression). These measurements will be performed at the Central Laboratory. These samples should be collected and sent to Central Laboratory even in the case that local lab samples are used for the purpose of eligibility confirmation.

- Disease assessments should be based on laboratory results provided by the central lab and according to IMWG criteria.
- Record SSEs during the screening period. 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
- Skeletal survey (MRI, low-dose CT, or PET-CT are acceptable if it is the institutional standard): if no suitable images are available that were taken as part of local routine standard of care up to 14 days prior to ICF signature. Skeletal survey should include chest (postero-anterior [PA] or antero-posterior [AP]; lateral), skull (lateral), upper extremities (shoulder to elbow; AP), lower extremities (hip to knee; AP), pelvis (AP), and cervical/thoracic/lumbar spine (AP and lateral). The same skeletal survey imaging method should be used for the baseline measurement and throughout the study. All digitized images (both baseline and post-baseline) will be collected and stored for potential retrospective analysis.

Important note: If re-screening is indicated, approval from the Sponsor's medical monitor is required. No more than 1 re-screening attempt will be allowed for each subject. Please refer to Section 6.3.1 for further guidance on cases in which re-screening is allowed and the time window for re-screening.

9.2.2 Randomization

Phase 2 only

Randomization in the IXRS may occur only after the completion of the screening evaluations and re-confirmation of subject eligibility and weight. 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. Once the subject is registered in IXRS, the initial drug shipment will be triggered.

9.2.3 Treatment period

Treatment consists of the following:

Phase 1b: up to 6 doses of radium-223 dichloride (1 dose every 6 weeks) at 2 different planned dose levels administered to ascending dose cohorts, in combination with 10 cycles (3 weeks per cycle for the first 8 cycles, then every 4 weeks) of BOR and DEX (Cohort 1 and Cohort 2), followed by ongoing maintenance treatment with BOR and DEX (4 weeks per cycle) up to 2 years after the first dose of study treatment or until a PFS event occurs (death or MM progression as per IMWG uniform criteria), unacceptable toxicity develops, or the subject withdraws consent, whichever occurs first.

Phase 2: up to 6 doses of radium-223 dichloride/placebo (1 dose every 6 weeks) at the MTD/RP2D in combination with 10 cycles (3 weeks per cycle for the first 8 cycles, then

every 4 weeks) of BOR and DEX followed by ongoing maintenance treatment with BOR and DEX (4 weeks per cycle) up to 2 years after the first dose of study treatment or until a PFS event occurs (death or MM progression as per IMWG uniform criteria), unacceptable toxicity develops, or the subject withdraws consent, whichever occurs first.

All subjects must have safety evaluations for 30 days after the last dose of study treatment. If the subject does not return for a 30-day safety follow-up visit regardless of the reason, the site should at a minimum contact the subject for the 30-day safety follow-up by telephone, email, or letter.

The treatment period extends from the day of the first dose of radium-223 dichloride/ placebo to 30 days after last dose of study treatment (radium-223 dichloride/placebo, BOR, or DEX, whichever is last) or after discontinuation from study treatment.

During the treatment period, the subject will visit the study center at regular intervals. Radium-223 dichloride/placebo will be injected once every 6 weeks for a total of 6 doses. The minimum time window between 2 doses of radium-223 dichloride/placebo must be 6 weeks (Section 7.1).

Bortezomib will be administered subcutaneous (SC) at 1.3 mg/m^2/dose, on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles.

For extended therapy beyond 8 cycles (Cohort 1 and Cohort 2), BOR will be administered on Days 1 and 15 of a 28-day cycle for up to 2 years after the first dose of study treatment.

Dexamethasone will be administered orally at 40 mg, on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles. DEX administration may be split over 2 days (on the day of BOR administration and the day after BOR administration) at the discretion of the Investigator.

For extended therapy beyond 8 cycles (Cohort 1 and Cohort 2), DEX will be administered orally at 20 mg/dose, on Days 1 and 15 of a 28-day cycle along with BOR for up to 2 years after the first dose of study treatment, or until a progression-free survival (PFS) event occurs, the subject withdraws consent or unacceptable toxicity develops, whichever occurs first.

Omit BOR if delay is >3 days. Maintenance BOR and DEX is administered on Days 1 and 15 of a 28-day cycle beginning at the start of the Maintenance Period for up to 2 years after the first dose of study treatment, or until a progression-free survival (PFS) event occurs, the subject withdraws consent or unacceptable toxicity develops, whichever occurs first (Section 7.1).

Note: Subjects who experience improvement of disease symptoms from the study treatment may continue radium-223 dichloride/placebo plus BOR-DEX at the investigator discretion and with sponsor agreement.

On Cycle 1 Day 1 only, radium-223 dichloride/placebo must be administered before BOR or DEX and the sample collection for M-protein must be completed before administration of radium-223 dichloride/placebo.

Weight is to be assessed 3 to 5 days before each radium-223 dichloride/placebo dose (for US sites) or 72 hours before each radium-223 dichloride/placebo dose (for ex-US sites). The weight measurements prior to radium-223 dichloride/placebo dose must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery

(approximately 2 days). It is the responsibility of the unblinded site staff to calculate the required volume of radioactivity for the subject's radium-223 dichloride dose based on the subject's body weight before the dosing day, and the reference date of the received study medication (Section 7.4).

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

The blood samples for clinical chemistry and hematology should be taken within 72 hours before each radium-223 dichloride/placebo dose, and the hematology parameters, including a complete blood count (CBC), must be evaluated before each radium-223 dichloride/placebo dose.

Pregnancy test and estradiol assay: women of child-bearing potential must have a negative urine pregnancy test performed within 72 hours before each radium-223 dichloride/placebo dose. Postmenopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. An estradiol assay is required within 72 hours before the first radium-223 dichloride dose in premenopausal women with radiotherapy ovarian ablation or medical ovarian suppression and postmenopausal women age <55 years and 1 year or more of amenorrhea and no ovarian suppression.

Laboratory parameters will be checked before dosing of study treatment per Section 7.4.4.

If there is more than a 28 day delay in the next dose (i.e., more than 10 weeks between doses), radium-223 dichloride/placebo doses should be permanently discontinued. Subjects who discontinue radium-223 dichloride/placebo treatment prior to experiencing an SSE or a PFS event can continue to receive BOR/DEX if considered by the Investigator to be in the subject's best interest and be followed up for SSEs and response/disease progression.

Subjects with radium-223 dichloride/placebo administration delayed from the date of the intended dose may receive the subsequent cycles of radium 223 dichloride/placebo at another day other than Day 1 of BOR/DEX.

9.2.3.1 Day of administration of radium-223 dichloride/placebo (total of 6 doses to be given once every 6 weeks)

Assessments to be performed BEFORE radium-223 dichloride/placebo administration:

- Ensure radium-223 dichloride/placebo dosing criteria have been met

Please note: For Cycle 10, Day 15 (dose # 6) not all assessments below are required (see Table 9–1).

- Review and ensure subjects complete:
  - The BPI-SF questionnaire
  - The RUQ
  - 24-hour analgesic use; subjects should bring all pain medications to each visit. Record analgesic use on the eCRF.
- Record opioid use

- Record AEs, SAEs and DLTs

  Note: All bone fractures and bone related 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.

- Record concomitant medications/therapy including bone health agent (BHA, e.g., bisphosphonates, denosumab) and any anti-cancer treatments

  Note: The initiation of BHA such as bisphosphonates or denosumab should be considered by investigators taking into consideration applicable guidelines.

- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Record weight. Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg. The same scale should be used for a given subject throughout the study. Body weight can be obtained at the local healthcare provider on a calibrated scale and the results sent by fax to the Principal Investigator with advanced notice and agreement from the Covance Medical Monitor for each subject. At all sites (US and ex-US), weight is to be taken 3 to 5 days before each radium-223 dichloride dose (for US sites) or 72 hours before each radium-223 dichloride/placebo dose (for ex-US sites). The weight measurements prior to radium-223 dichloride/placebo dose must be reported to the country PRD depot to allow adequate time for PRD preparation and delivery (approximately 2 days).
- Perform full physical examination
- ECOG-PS
- Blood draw for hematology: hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential. The blood sample for hematology must be taken, analyzed, and evaluated within 72 hours before each radium-223 dichloride/placebo dose.
- Pregnancy test: women of child-bearing potential must have a negative urine pregnancy test performed within 72 hours before each radium-223 dichloride/placebo dose. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Blood draw for clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, lactate dehydrogenase (LDH), total ALP, serum creatinine, blood urea nitrogen (BUN; or urea), bilirubin (total), glucose, phosphate, and albumin; clinical chemistry should be measured within 72 hours before each radium-223 dichloride/placebo dose.

- Collect blood for serum and plasma as well as urine samples for exploratory evaluation of biomarkers
- Plasma for ctDNA analysis
- Whole blood for CTCs analysis
- Blood draw and 24-hour urine collection for M-protein assessments by SPEP, 24-hour UPEP, and Freelite assay. Serum and urine IF is only performed to confirm a CR (conducted on the first observation of a CR in the SPEP and/or UPEP sample and repeated every 21 days (±7 days) through Cycle 8 and then every 28 days (±7 days) thereafter until disease progression). These measurements will be performed at the Central Laboratory.
- Record disease assessment according to IMWG criteria based on central laboratory results
- Record SSEs (in accordance with the schedule of procedures (see Table 9–1). 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
- Administer radium-223 dichloride/placebo. One of 2 different doses of radium-223 dichloride (33 or 55 kBq/kg) will be administered in the phase 1b, then the MTD/RP2D in the phase 2.

Assessments to be performed AFTER each dose of radium-223 dichloride/placebo:

- The IxRS must be accessed for drug re-supply in preparation for the next study visit. 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.

9.2.3.2 Day 1 of bortezomib/dexamethasone Cycles 1 through 8 (±7 days)

- Review and ensure subjects complete:
  - 24-hour analgesic use; subjects should bring all pain medications to each visit. Record analgesic use on the eCRF
- Record opioid use
- Record AEs, SAEs and DLTs

  Note: All bone fractures and bone related 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.

- Record concomitant medications/therapy including bone health agent (BHA, e.g., bisphosphonates, denosumab) and any anti-cancer treatments

  Note: The initiation of BHA such as bisphosphonates or denosumab should be considered by investigators taking into consideration applicable guidelines.
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Record body weight
- Perform full physical examination
- ECOG-PS
- Blood draw for hematology: hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential. Hematology samples must be drawn a minimum of once weekly, or according to the site's standard of care, whichever is more frequent. A CBC must be performed before each BOR injection.
- Pregnancy test: women of child-bearing potential must have a negative urine pregnancy test performed within 72 hours before each radium-223 dichloride dose. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Blood draw for clinical chemistry on Day 1 of each cycle: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, serum creatinine, BUN (or urea) bilirubin (total), glucose, phosphate, and albumin.
- Blood draw and 24-hour urine collection for M-protein assessments by SPEP, 24-hour UPEP, and Freelite assay. Serum and urine IF is only performed to confirm a CR (conducted on the first observation of a CR in the SPEP and/or UPEP sample and repeated every 21 days (±7 days) through Cycle 8 and then every 28 days (±7 days) thereafter until disease progression). These measurements will be performed at the Central Laboratory.
- Bone marrow evaluation for assessment of percentage of plasma cells: only to confirm CR after CR was observed at 2 consecutive visits based on M-protein results
- Record response/disease progression according to IMWG criteria based on central laboratory results
- Record SSEs in accordance with the schedule of procedures (see Table 9–1). 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
- Administer BOR plus DEX

9.2.3.3 Days 4, 8, and 11 of bortezomib/dexamethasone Cycles 1 through 8 (±3 days)

- Record opioid use
- Record AEs, SAEs and DLTs

  Note: All bone fractures and bone related 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.
- Record concomitant medications/therapy including bone health agent (BHA, e.g., bisphosphonates, denosumab) and any anti-cancer treatments

  Note: The initiation of BHA such as bisphosphonates or denosumab should be considered by investigators taking into consideration applicable guidelines.
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Record body weight
- Blood draw for hematology: hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential. Hematology samples must be drawn a minimum of once weekly, or according to the site's standard of care, whichever is more frequent. A CBC must be performed before each BOR injection.
- Blood draw for clinical chemistry on Day 11 of Cycles 1 and 2: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, serum creatinine, BUN (or urea) bilirubin (total), glucose, phosphate, and albumin.
- Administer BOR plus DEX

9.2.3.4 End of radium-223 dichloride/placebo visit

The End of radium-223 dichloride/placebo visit will be conducted 30 days (+7 days) after the last dose of radium-223 dichloride/placebo.

- 24-hour analgesic use; subjects should bring all pain medications to each visit. Record analgesic use on the eCRF
- Record opioid use
- Record AEs and SAEs

  Note: All bone fractures and bone related 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.
- Record concomitant medications/therapy including bone health agent (BHA, e.g., bisphosphonates, denosumab) and any anti-cancer treatments

  Note: The initiation of BHA such as bisphosphonates or denosumab should be considered by investigators taking into consideration applicable guidelines.
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature

- Blood draw for hematology: hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential.
- Pregnancy test. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Collect blood for serum and plasma as well as urine samples for exploratory evaluation of biomarkers
- Plasma for ctDNA analysis
- Whole blood for CTCs analysis
- A skeletal survey (MRI, low-dose CT, or PET-CT are acceptable if it is the institutional standard) will be completed and should include the chest (PA or AP; lateral), skull (lateral), upper extremities (shoulder to elbow; AP), lower extremities (hip to knee; AP), pelvis (AP), and cervical/thoracic/lumbar spine (AP and lateral).

9.2.3.5 Maintenance treatment with bortezomib/dexamethasone

For extended therapy beyond 8 cycles, BOR and DEX will be administered on Days 1 and 15 of a 28-day cycle as maintenance therapy for up to 2 years after the first dose of study treatment, or until a progression-free survival (PFS) event occurs, the subject withdraws consent or unacceptable toxicity develops, whichever occurs first.

Note: For cycles 9 and 10, radium-223 dichloride/placebo may be administered (see Table 9–1).

- Review and ensure subjects complete (every 28 days):
  - The BPI-SF questionnaire
  - The RUQ
  - 24-hour analgesic use; subjects should bring all pain medications to each visit. Record analgesic use via the analgesic concomitant medication eCRF.
- Record opioid use
- Record AEs and SAEs

  Note: all bone fractures and bone related events (e.g., osteoporosis) need to be reported as either AE(s) or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- Record concomitant medications/therapy including bone health agent (BHA, e.g., bisphosphonates, denosumab) and any anti-cancer treatments

  Note: The initiation of BHA such as bisphosphonates or denosumab should be considered by investigators taking into consideration applicable guidelines.
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Perform full physical examination every 28 days (at minimum), or according to the Investigator's clinical judgment

- Record weight at least every 28 days, or per the Investigator's standard of care, whichever is more frequent
- ECOG-PS every 28 days (at minimum), or according to the Investigator's clinical judgment
- Blood draw for hematology: hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential to be done within 3 days prior to each dose of BOR and the Investigator must confirm that the subject meets dosing criteria for BOR. Additional laboratory assessments should be performed according to the institutional guidelines.
- Pregnancy test will be administered 72 hours before radium-223 dichloride/placebo dosing. After the last radium-223 dichloride/placebo dose, pregnancy tests will be administered on Day 1 of the BOR-only cycle through the EOT.
- Blood draw for clinical chemistry every 28 days: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, serum creatinine BUN (or urea), bilirubin (total), glucose, phosphate, and albumin.
- Blood draw and 24-hour urine collection every 28 days for M-protein assessments by SPEP, 24-hour UPEP, and Freelite assay. Serum and urine IF is only performed to confirm a CR (conducted on the first observation of a CR in the SPEP and/or UPEP sample and repeated every 28 days until disease progression). These measurements will be performed at the Central Laboratory.
- Record disease assessment
- Record SSEs every 28 days. 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
- Collect blood for serum and plasma as well as urine for exploratory evaluation of biomarkers every 4 cycles during maintenance
- Plasma for ctDNA analysis every 4 cycles during maintenance
- Whole blood for CTCs analysis every 4 cycles during maintenance
- Administer BOR plus DEX

9.2.3.6 End of treatment visit (30 days[+7 days] post-last study treatment administration)

All subjects must have safety evaluations for 30 days after the last dose of study treatment. If the subject refuses to return for a 30-day safety follow-up visit, the site should at a minimum contact the subject for the 30-day safety follow-up by telephone, email, or letter.

This visit will occur 30 days (+7 days) after the last dose of study treatment administration (radium-223 dichloride/placebo, BOR, DEX; whichever is last) or after discontinuation from study treatment. Subjects whose last dose of radium-223 dichloride/placebo coincides with the last dose of BOR and DEX should complete all procedures noted for both the End of radium-223 dichloride/placebo visit and the EOT visit; however, overlapping procedures from the 2 visits only need to be completed once.

- Review and ensure subjects complete:
  - The BPI-SF questionnaire on the day of the visit
  - The RUQ
  - 24-hour analgesic use; subjects should bring all pain medications to each visit. Record analgesic use via the analgesic concomitant medication eCRF.
- Record opioid use
- Record AEs and SAEs

  Note: all bone fractures and bone related 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.
- Record concomitant medications/therapy including bone health agent (BHA, e.g., bisphosphonates, denosumab) and any anti-cancer treatments

  Note: The initiation of BHA such as bisphosphonates or denosumab should be considered by investigators taking into consideration applicable guidelines.
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- ECOG PS
- Blood draw for hematology: hematocrit, Hb, platelet counts, RBC counts, WBC counts, and WBC differential.
- Pregnancy test. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Blood draw for clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, serum creatinine, BUN (or urea), bilirubin (total), glucose, phosphate, and albumin.
- Blood draw and 24-hour urine collection for M-protein assessments by SPEP, 24-hour UPEP, and Freelite assay. Serum and urine IF is only performed to confirm a CR (conducted on the first observation of a CR in the SPEP and/or UPEP sample and repeated every cycle until disease progression). These measurements will be performed at the Central Laboratory.
- Record disease assessment
- 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

- Collect blood for serum and plasma as well as urine samples for exploratory evaluation of biomarkers
- Plasma for ctDNA analysis
- Whole blood for CTCs analysis

9.2.4 Active follow-up period

Subjects who have discontinued study treatment for any reason including progressive disease (PD) will be followed with a clinic visit every 8 weeks (±7 days) up to 2 years after the last dose of radium-223 dichloride/placebo treatment, death or consent withdrawal, whichever occurs first.

The maximum duration of the active follow-up period is 2 years from last dose of radium 223 dichloride/placebo treatment.

- Review and ensure subjects complete:
  - The BPI-SF questionnaire on the day of the visit
  - The RUQ
  - 24-hour analgesic use; subjects should bring all pain medications to each visit. Record analgesic use on the eCRF
- Record opioid use
- Record treatment-related AEs/SAEs

  Note: all bone fractures and bone related 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.

  Note: Record all occurrences of leukemia, MDS, aplastic anemia, myelofibrosis, or any other new primary malignancy. All occurrences of leukemia, MDS, aplastic anemia, myelofibrosis, or any other new primary malignancy must be reported as SAEs regardless of the Investigator's causality assessment. If a subject is unable to provide required details, this information may need to be obtained from the primary provider.

  Note: Record any occurrence of febrile neutropenia and hemorrhage related to radium-223 dichloride
- Record any anti-cancer treatments and bone health agent (BHA) such as bisphosphonates or denosumab

  Note: The initiation of BHA such as bisphosphonates or denosumab should be considered by investigators taking into consideration applicable guidelines.
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature

- Blood draw and 24-hour urine collection for M-protein assessments by SPEP, 24-hour UPEP, and Freelite assay for subjects who ended study treatment for reasons other than disease progression. Serum and urine IF is only performed to confirm a CR (conducted on the first observation of a CR in the SPEP and/or UPEP sample and repeated every cycle until disease progression). These measurements will be performed at the Central Laboratory.
- 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
- Record response/disease progression

  Note: Only for subjects who ended study treatment for reasons other than disease progression.
- Collect serum, plasma and urine samples samples for exploratory evaluation of biomarkers every 2 visits (every 16 weeks)
- Plasma for ctDNA analysis
- Whole blood for CTCs analysis

9.2.5 Long-term follow-up (telephone call every 6 months [±28 days])

Subjects who have completed the 2 year active follow-up will be followed with a telephone call every 6 months (±28 days) for up to 5 years.

A 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. All subjects will be asked to transition into this separate study to complete their long-term follow-up. The long-term follow-up may start in the current trial and subjects will then be asked to transition into the separate roll-over study.

- Record treatment-related AEs/SAEs

  Note: all bone fractures and bone related 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.

  Note: Record all occurrences of leukemia, MDS, aplastic anemia, myelofibrosis, or any other new primary malignancy. All occurrences of leukemia, MDS, aplastic anemia, myelofibrosis, or any other new primary malignancy must be reported as SAEs regardless of the Investigator's causality assessment. If a subject is unable to provide required details, this information may need to be obtained from the primary provider.

Note: Record any occurrence of febrile neutropenia or hemorrhage related to radium-223 dichloride

- Record any anti-cancer treatments and bone health agent (BHA) such as bisphosphonates or denosumab

  Note: The initiation of BHA such as bisphosphonates or denosumab should be considered by investigators taking into consideration applicable guidelines.

- Record survival status

  Note: As this information will be collected from the subject over the telephone, it is the clinical site's responsibility to obtain and make available the source documentation for the information collected and document it in the eCRF.

9.3 Population characteristics

9.3.1 Demographic

The following demographic characteristics will be collected:

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

9.3.2 Medical history

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

- Not pertaining to the study indication (e.g., bone related events such as osteoporosis)
- Start before signing of the informed consent
- Considered relevant for the subject's study eligibility

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

The following other baseline characteristics will be collected:

- Date of multiple myeloma diagnosis
- International Staging System for multiple myeloma (ISS) at diagnosis
- ISS for multiple myeloma at baseline
- Treatment of multiple myeloma before enrollment (e.g., chemotherapy, stem cell transplantation, radiotherapy)
- Date of latest multiple myeloma relapse

- Weight and height
- Vital signs: blood pressure, heart rate, respiratory rate, and temperature
- ECOG-PS
- Cancer pain assessment
- Laboratory assessments:
  - Hematology: hematocrit, Hb, platelet counts, RBC count, WBC count, WBC differential
  - Clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, serum creatinine, BUN (or urea), bilirubin (total), glucose, phosphate, and albumin
- LVEF
  - LVEF values will not be collected, however the investigator must verify that subjects meet all inclusion/exclusion criteria at study entry

9.4 Anti-multiple myeloma activity (phase 2)

9.4.1 Anti-multiple myeloma activity endpoints (phase 2)

Primary endpoint

- Combined CR+VGPR rate as determined by IMWG uniform response criteria, defined as the proportion of subjects in the analysis population who have complete response (CR), and very good partial response [VGPR]) during the course of the study

Secondary endpoints:

- Objective response rate (ORR), as determined by IMWG uniform response criteria, defined as the proportion of subjects in the analysis population who have complete response (CR), partial response (PR) and very good partial response [VGPR]) during the course of the study
- Progression-free survival, as defined as the time (in months) from the date of randomization to the date of disease progression or death, whichever occurs first.
- Duration of response (DOR), as determined by IMWG response criteria, is defined as the time (in months) from the date of first response to treatment (CR, VGPR or PR) to the date of disease progression or death. Duration of response is only applied to subjects with a disease response of at least PR.
- Overall survival as defined as the time (in months) the date of randomization to the date death.

Exploratory endpoints:

- Time to first on-study SSE, defined as the time (months) from the date of the first dose of radium-223 dichloride to the date of the first on-study SSE.
    - An on-study SSE is defined as:
        - Use of EBRT to relieve skeletal symptoms
        - Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)
        - Occurrence of spinal cord compression
        - Tumor-related orthopedic surgical intervention
- Time to pain progression, defined in subjects evaluable for pain progression at baseline (i.e., subjects with a worst pain score of ≤8 at the baseline assessment). Pain intensity is measured using the Brief Pain Index-Short Form (BPI-SF) (Section 16.7).

  Pain progression is defined as the occurrence of either a pain increase or an increase in pain management with respect to baseline, whichever occurs first.

  A pain increase 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 ≥28 days apart.

  An increase in pain management is defined as follows:

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

  - The time to pain progression is defined for applicable subjects as the time (in days) from date of the first dose of radium-223 dichloride/placebo until occurrence of the first post-baseline pain progression event. Subjects without pain progression as of the last post-baseline pain assessment, whether or not surviving, will be censored at the last post-baseline pain assessment. Subjects with insufficient baseline assessment(s) or without adequate post-baseline assessment(s) will be censored at the baseline date.
- Change in MM disease markers:
    - Change in M-protein

- Evaluate potentially predictive biomarker candidates (ctDNA, CTCs, MM related cytokines)

- Time to opioid use for cancer pain in subjects without opioid use at baseline, defined as the interval from date of the first dose of radium-223 dichloride to the first date of opioid use.
- Bone biomarkers, including UNTx, SCTx, total ALP and B-ALP, PINP, and ICTP.
- Change in the number of active bone lesions (for PET-CT, X-ray, MRI, or low-dose CT) and/or the intensity of PET uptake (for PET-CT) from baseline to the follow-up evaluation. The number of active bone lesions and the intensity of PET uptake at baseline will be evaluated in comparison to the follow-up PET-CT. For conventional skeletal surveys based on x-ray, MRI, or low-dose CT, the number of bone lesions at baseline and at the end of radium-223 dichloride treatment, as specified, will be evaluated.

9.4.2 Anti-multiple myeloma activity evaluation

Disease Assessment

Response and disease progression will be assessed by Investigators based on central laboratory results and according to the IMWG uniform response criteria every 21 days during the first 8 cycles of BOR for all cohorts and afterwards every 28 days (±7 days) from the first dose of radium-223 dichloride/placebo and BOR/DEX to the EOT, and at each visit during the active follow-up period. The assessments will include SPEP, 24-hour urine collection for UPEP, and Freelite assay at all visits for all subjects. Bone marrow specimen (bone marrow aspirate or biopsy) and EMD evaluation will be performed at baseline and thereafter as clinically indicated according to IMWG criteria.

For subjects obtaining a CR, this will also include IF, a bone marrow biopsy (or aspirate) at the time of second consecutive CR. After the percentage of plasma cells is determined by the local laboratory, the remaining bone marrow sample will be sent to the central laboratory for biomarker testing.

The anti-multiple myeloma activity endpoint of combined CR+VGPR rate and ORR (proportion of subjects with PR or better) will be assessed by Study Investigators. The responses of sCR, CR, VGPR, and PR require 2 consecutive assessments (according to IMWG criteria) at any time before progression or initiation of any new therapy.

Disease progression requires any 1 of the following criteria:

- Increase in serum M-protein by ≥25% above the lowest response level and an absolute increase of ≥ 5 g/L
- Increase in urine M-protein by ≥25% above the lowest remission value and an absolute increase in excretion by ≥200 mg/24 hours
- Appearance of soft-tissue plasmacytoma (extramedullary disease, EMD)
- Appearance of new bone lesion or increase in size of existing bone lesions by ≥50%
- Unexplained hypercalcemia (>2.875 mM or >11.5 g/dL)

Progression must be confirmed according to IMWG criteria.

9.5 Pharmacokinetics / pharmacodynamics

No PK measurements will be performed in this study. No PK interaction is expected between radium-223 dichloride and the co-administered BOR and DEX therapy or with BOR and DEX. Radium-223 dichloride 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 dichloride 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 dichloride on the PK of the co-administered products is expected.

9.6 Safety

The primary objective of the phase 1b part of the study is to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) and the safety of radium-223 dichloride in combination with bortezomib (BOR) and dexamethasone (DEX).

One of the secondary objectives of phase 2 is to evaluate the safety of radium-223 dichloride in combination with BOR and DEX compared to the safety of placebo in combination with BOR and DEX.

The Investigator(s) and the Sponsor's representative will review the safety data throughout the course of the study. Additional safety reviews will be conducted by the Steering Committee, IDMC and Sponsor as appropriate.

In phase 1 b, radium-223 dichloride at 2 dose levels in combination with BOR/DEX will be evaluated in subjects with relapsed multiple myeloma. Subjects will be treated sequentially at two dose levels (33 kBq/kg body weight and 55 kBq/kg body weight). The starting dose is 33 kBq/kg body weight every 6 weeks, which is a dose lower than the dose of radium-223 dichloride monotherapy approved for CRPC (55 kBq/kg body weight) and will be evaluated in combination with BOR/DEX. The dose of 55 kBq/kg body weight is evaluated in the second cohort.

The decision to move from one cohort to the next higher dose cohort will be made following a 3 + 3 design as described in Section 5.1.2.

All subjects enrolled in this Phase 1b study must be evaluated for the occurrence of DLTs during the DLT observation window, which is defined as the time from the first dose of study treatment through 21 days after administration of the second dose of radium-223 dichloride.

A safety data summary review (including, but not limited to, AEs, dose modifications, and laboratory changes) will be conducted by the Steering Committee and Sponsor to determine whether dosing into the next higher cohort may proceed.

For the phase 2 part of the study, an Independent Data Monitoring Committee (IDMC) will conduct safety reviews in accordance with the appropriate Charter. The IDMC will review the safety data once 20 and 50 subjects have completed 2 doses of radium-223 dichloride or placebo in combination with bortezomib/dexamethasone (plus a follow-up of at least

3 weeks after the second radium-223 dichloride/placebo dose) treatment, and every 6 months thereafter. The first evaluation will be performed in order to evaluate the safety and to confirm the MTD/RP2D.

The following safety variables will be evaluated in this study:

- 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 count, WBC count, WBC differential
    - Clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, serum creatinine, BUN (or urea), bilirubin (total), glucose, phosphate, and albumin
    - A coagulation panel: PT, PTT, and INR

All AEs will be reported according to MedDRA coding and graded for severity according to 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

Definition of adverse event

In a clinical study, an AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a 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).

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 recorded 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 recorded 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 **AEs**

Definition of serious adverse event

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria:

- Results in death
- 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least 1 of the following exceptions is met:
    - The admission results in a hospital stay of less than 12 hours
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study)
    - 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.
- Results in persistent or significant disability/incapacity

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

- Is a congenital anomaly/birth defect
- Is another serious or important medical event as judged by the Investigator

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 ICH 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 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 decision to be made by the Investigator, who is a qualified physician, based on all information available at the time of the completion of the eCRF.

Causality should be assessed separately for each study treatment as detailed in the eCRF. If the Investigator feels that the event cannot be firmly attributed to 1 of the study treatments (e.g., owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

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

Possible answers are "yes" or "no".

An assessment of "no" would include:

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

or

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

An assessment of "yes" indicates that the AE is reasonably associated with the use of 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 re-challenge should be considered in 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 might have caused the event in question
- Known response pattern for this class of drug: clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and 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
- The assessment is not possible

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. The study treatment action should be recorded separately for each study treatment as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- 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

The Investigator has to record on the respective eCRF pages all AEs occurring in the period from the signing of the ICF until 30 days after the last dose of study treatment administration; during follow-up, all bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AE(s)s or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. Radium-223 dichloride-related occurrences of febrile neutropenia or hemorrhage will also be collected during follow-up. After the end of the follow-up period there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the Investigator for each AE is listed in Section 9.6.1.2.

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

For all SAEs the Sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study treatment.

9.6.1.4 Reporting of serious adverse events

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 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 "alternative explanation".

Reporting of additional malignancies / hematological conditions

During study treatment and follow-up periods, all occurrences of any additional malignancies including AML, or hematological conditions such as MDS, aplastic anemia, and 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.

The Investigator must report immediately (within 24 hours of the Investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the eCRF must be completed for each SAE.

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

Additionally, all occurrences of MDS, aplastic anemia, myelofibrosis, 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 9.6.1.1). 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 Investigators are in doubt about the applicable reporting obligations, they should consult with the medical monitor.

For subjects who die >28 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 AG Pharmacovigilance Department if the death is considered related to study treatment.

Notification of the IECs/IRBs

Notification of the Independent Ethics Committees (IECs)/Institutional Review Boards (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 site

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

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the Investigator's Brochure/Summary of Product Characteristics for radium-223 dichloride and the current local product labels for BOR and DEX.

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

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

9.6.3 Further safety

9.6.3.1 Laboratory safety assessments

The blood samples for clinical chemistry and hematology should be taken at Screening, within 72 hours before each radium-223 dichloride dose, and during active follow-up. The hematology parameters, including a complete blood count (CBC), must be evaluated before each radium-223 dichloride dose.

Clinical chemistry:

Sodium, potassium, chloride, calcium (and albumin-adjusted calcium), ALT, AST, lactate dehydrogenase (LDH), total ALP, serum creatinine, blood urea nitrogen (BUN; or urea), bilirubin (total), alkaline phosphatase, glucose, phosphate, and albumin.

Coagulation panel:

PT, PTT, and INR of PT

Hematology:

Hematocrit, Hb, platelet counts, RBC counts, white blood cell (WBC) counts, and WBC differential.

9.6.3.2 Vital signs

Blood pressure, heart rate, respiratory rate, and temperature should be recorded.

9.6.3.3 Body weight

Body weight should be obtained without shoes, using a calibrated electronic physician (column) scale with digital display, measurement units 0.1 kg.

9.6.3.4 Physical examination

Abnormal physical examination findings are recorded either as medical history or as adverse events.

9.7 Other procedures and variables

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 16.6).

9.7.2 Biomarkers

Radium-223 dichloride may work in subjects with multiple myeloma and tumor biomarkers circulating in plasma or, if available, in biopsies either collected prior to study entry or at disease progression. The biomarker assessment will be performed as exploratory objective to investigate whether prognostic and /or predictive biomarkers of MM response can be identified.

Biomarker status will be correlated with clinical outcome to evaluate whether any biological targets appear to define subject populations that are particularly sensitive or resistant to radium-223 dichloride. Details of the biomarker analyses will be described in a separate statistical analysis plan (SAP) and the results of these analyses will be provided as a separate biomarker report.

Tumor biomarkers may be categorized as “nonor bioma” (involving protein) or “genetic” (involving ribonucleic acid [RNA] or deoxyribonucleic acid [DNA]). In the current study, analyses of both ribonucleic acid [RNA] and deoxyribonucleic acid [DNA]) will be performed. Tumor biomarker studies will be performed to investigate the mechanisms by which the drug combinations may exert their therapeutic activity.

In the current study genetic markers by tumor DNA sequencing and/or gene expression studies with tissue samples taken from the primary tumor and metastases may support identification of biomarkers contributing to clinical benefit to therapy. Utmost care will be taken to protect subject identity during biomarker analyses.

9.7.2.1 Circulating Bone Biomarkers

Bone biomarkers, including UNTx, SCTx, total ALP and B-ALP, PINP, and ICTP will be analyzed from plasma serum and urine.

9.7.2.2 Circulating DNA

Circulating tumor DNA will be analyzed from plasma collected at baseline and each cycle of radium-223 dichloride treatment prior to dosing with radium-223 dichloride.

9.7.2.3 Circulating Tumor Cells

Circulating Tumor Cells (CTCs) may serve as source of tumor metastases circulating in blood and may reflect the tumor phenotype or genotype. Enumeration of CTCs may serve

as description of tumor burden. Circulating tumor cells will be analyzed in detail from whole blood samples collected at various time points to assess the effect of radium-223 dichloride in decreasing numbers of CTCs as well as to characterize the phenotype and genotype of CTCs.

9.7.2.4 Tumor biomarkers

Archival or freshly collected tumor tissue will be used to determine the presence of somatic mutations in order to identify biomarker which may have potential to confer to sensitivity or resistance to drug treatment. This analysis may contain the identification of DNA Damage Repair deficiency by analyzing mutations in genes involved in the DNA repair.

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 trials of oncology drugs.

10. Statistical methods and determination of sample size

10.1 General considerations

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

All analyses will be performed for phase 1b and phase 2, separately. All data will be listed, and descriptive summary tables will be provided by dose level cohort for phase 1b, and by treatment arm for phase 2.

10.2 Analysis sets

10.2.1 Phase 2

Phase 2 Safety Set (SAF): All subjects who received at least one dose of study treatment. Subjects will be included in the analyses according to the treatment they actually received.

Phase 2 Intent-to-treat (ITT): All randomized subjects in phase 2. The phase 2 ITT population will be the primary analysis set for all efficacy endpoints. Subjects will be included in the analyses according to the treatment to which they are randomized. The definition of the ITT population is identical to that of the FAS (Full Analysis Set) population.

10.3 Variables and planned statistical analyses

10.3.1 Phase 1b

The following populations are defined:

Phase 1b Safety Set (SAF): All subjects who received at least one dose of study treatment. Subjects will be included in the analyses according to the treatment they actually received.

Phase 1b Dose Evaluable Set (DES): Subjects in dose escalation cohorts who meet the minimum drug exposure criterion (at least 2 doses of radium-223 dichloride plus a follow-up of 21 days after the second radium-223 dichloride dose) or experience a DLT (during the DLT observation window). Subjects not evaluable for assessment of DLT due to early discontinuation for reasons other than DLT or subjects who have not completed 2 doses of radium-223 dichloride and 2 cycles of BOR will be replaced and will not be included in the DES.

10.3.2 Variables

The primary, secondary, and exploratory endpoints are defined in Sections 9.4, 9.5 and 9.6.

10.3.3 Statistical and analytical plans

The details of all statistical analyses will be provided in the SAP.

10.3.3.1 Demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized by dose level cohorts for Phase 1b and by treatment arm for Phase 2 part. Continuous data will be summarized by arithmetic mean, standard deviation, median, minimum, and maximum. Frequency tables (number of data available and missing, and percent of available data) for categorical data will be provided.

Medical history findings will be summarized using MedDRA terms.

10.3.3.2 Safety analysis

Safety variables will be analyzed using frequency tables and descriptive statistics by dose level cohort for Phase 1b part and by treatment arm for Phase 2 part. The primary safety assessment period is from the first dose of study treatment until 30 days after the last dose of radium-223 dichloride. After study treatment has completed, subjects will be followed for related AEs. All bone fractures and bone associated events (e.g., osteoporosis) as well as new primary malignancies/hematological conditions will be reported regardless of the investigator's causality assessment. Radium-223 dichloride-related occurrences of febrile neutropenia or hemorrhage will also be collected during follow-up. Adverse events will be coded using MedDRA.

The incidence of treatment-emergent AEs, drug related AEs and Serious AEs will be summarized using coding by MedDRA and grading of severity by NCI-CTCAE version 4.03 terms by dose level cohort for Phase 1b part and by treatment arm for Phase 2 part. The bone fractures and bone-associated events (e.g., osteoporosis) will be summarized using descriptive statistics.

Laboratory values and changes from baseline will be summarized by visit and by dose level cohort for phase 1 part and by treatment arm for phase 2 part using descriptive statistics. The incidence of laboratory toxicities will be summarized by worst CTCAE grade and by dose level cohort for phase 1 part and by treatment arm for phase 2 part. Frequency tables will also be provided for the changes of worst CTCAE grade after start of treatment versus baseline.

Vital signs will be summarized by visit and by dose level cohort for phase 1 part and by treatment arm for phase 2 part for observed values and changes from baseline using descriptive statistics.

10.3.3.3 Maximum tolerated dose (MTD)/Recommended phase 2 dose (RP2D)

MTD/RP2D will be evaluated by the sponsor in consultation with the investigators during the conduct of the dose escalation part of the study. MTD/RP2D will be determined using the incidence of DLTs during the DLT observation window, which is defined as the time from the first dose of study treatment through 21 days after administration of the second dose of radium-223 dichloride. The decision about MTD/RP2D will be made after all subjects in last dose escalation cohort are treated with at least 2 doses for radium-223 dichloride and observed for 21 days after second dose. If no DLT is observed in Phase 1b part, a RP2D will be selected based on safety and efficacy data obtained during the phase 1b part.

Individual listings of DLTs will be presented by dose level cohort for phase 1 part with treatment cycle of onset, serious or nonserious, CTCAE v4.03 grade and term, and MedDRA terms provided for each DLT. Dose Evaluable Set (DES) will be used for the analyses.

10.3.3.4 Anti-multiple myeloma activity analysis

Phase 1b

Anti-multiple myeloma response assessment (CR, VGPR, PR, etc.) will be summarized using descriptive statistics (i.e., number and percentage of subjects) by dose level cohort.

Phase 2

Fisher's exact test will be used for evaluating response rate difference between treatment groups. Response rate difference and its exact 95% CI will be provided. The descriptive statistics will also be used to summarize response rates (combined CR+VGPR, ORR [CR+VGRP+PR]), and anti-multiple myeloma response assessment The number of responders, percentage of responders and 95% confidence interval (CIs) will be presented by treatment arm.

Time to event endpoints (e.g., DOR, PFS, OS, time to SSE, time to pain progression, and time to opioid use) will be summarized by treatment arm using Kaplan-Meier estimates. Kaplan-Meier curves will be generated, and median survival time together with the 25th and 75th percentiles and associated Brookmeyer-Crowley 95% CIs will be presented. Details on these analyses will be provided in the SAP.

Descriptive statistics will also be provided for DOR only for subjects with an objective response (OR) (PR or higher).

10.3.3.5 Biomarker analysis

Interest in this study is taken in identifying predictive biomarkers for radium-223 dichloride anti-multiple myeloma activity in subjects with relapsed multiple myeloma. Subjects' key biomarker status at baseline will be correlated with response (OR [PR or

better]) to explore which biomarkers may be important in defining the appropriate therapeutic population for the agent.

Biomarker analyses will be performed on urine, plasma or serum samples collected at various time points as well as from bone biopsies collected at study entry.

Biomarkers from plasma or serum will include the determination of changes in circulating cytokines or proteins as well as circulating microRNAs, ctDNA and CTCs.

Additional exploratory analyses such as examination of the relationship between post-treatment change in biomarker levels and various clinical endpoints may be considered.

Additionally for subjects who signed the optional genetic consent form, genetic biomarkers may be determined from bone marrow specimens (bone marrow aspirate or biopsy) such as gene amplifications or somatic mutations in oncogenes using Next Generation Sequencing.

Data from the biomarker studies will be reported in a separate biomarker report.

10.3.4 Missing data / drop outs

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 and long-term follow up periods).

Missing data will generally not be imputed in this study. Any further details will be described in the SAP if there is any imputation performed.

10.4 Determination of sample size

Phase 1b

To evaluate the MTD/RP2D for radium-223 dichloride in combination with BOR/DEX in subjects with relapsed multiple myeloma, two cohorts with up to 12 subjects are planned for dose escalation part. The sample size was based on feasibility, not formal statistical calculation. Subjects not evaluable for assessment of DLT for dose escalation part due to early discontinuation for reasons other than DLT will be replaced until the MTD/RP2D has been determined. These subject numbers are considered to be sufficient for a 3 + 3 dose escalation design to determine whether to start the next dose level, using DLT definitions and the 3 + 3 dose escalation rules (see Section 5.1.2).

Phase 2

The primary endpoint is combined CR+VGPR rate in phase 2 part of the study. Approximately 100 subjects will be randomized at a 1:1 ratio to two treatment arms: radium-223 dichloride + BOR/DEX (study arm), and placebo + BOR/DEX (control arm). The placebo + BOR/DEX arm is anticipated to have combined CR+VGPR rate of 35%. The radium-223 dichloride + BOR/DEX arm will be considered promising if true combined CR+VGPR rate will be 55% or higher. Assuming one-sided alpha of 0.2 and 50 randomized subjects in each arm, there will be 87% of power to detect the treatment difference of 0.2 in combined CR+VGPR rate between two arms.

10.5 Planned interim analyses

No formal interim analysis will be performed.

In the event that enrollment is halted by the Steering Committee after the review of safety data, an interim analysis may be performed on all evaluable subjects during the phase 1. See Section 13.1.2.1 for further details.

In the event that enrollment is halted by the IDMC after the review of safety data, an interim analysis may be performed on all randomized subjects during the phase 2. See Section 13.1.2.2 for further details.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be a validated EDC system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (SAS®).

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

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigative site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

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

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

Source documentation

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

Study-specific data not needed for the subject's routine medical care (e.g., scores or questionnaires) may be entered directly into the eCRF, without availability of corresponding source documentation.

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

Data recorded from screening failures

Data of 'only screened subjects' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, the following data should be recorded in the eCRF:

- Demographic information (subject number; year of birth/age; sex; if applicable race/ethnicity)
- Date of informed consent
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the eCRF in addition to the data specified above:

- 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 site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

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

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- 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

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable Sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g., IxRS, laboratory, ECG, adjudication committees).

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

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 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 notifies the Sponsor if the archival arrangements change (e.g., relocation or transfer of ownership).

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

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

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; centers]) at any time, which may be due, but not limited, to the following reasons:

- If 2 or more subjects experience a DLT during the 33 kBq/kg dose cohort (Cohort 1) , the study will be terminated. (see Section 5.1.2)
- Criteria for stopping the study will be provided to the IDMC (see Section 5.1.2). In the Phase 2 portion of the study, the IDMC will meet to review the safety data once 20 and 50 subjects in the phase 2 portion of the study have completed 2 doses of radium-223 dichloride or placebo + bortezomib/dexamethasone therapy (plus a follow-up of at least 3 weeks after the second radium-223 dichloride dose), and every 6 months thereafter. The IDMC may recommend stopping the study based on the stopping criteria.
- If risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study (e.g., SAEs)
    - Results of any interim analysis
    - Results of parallel clinical studies
    - Results of parallel animal studies
      (e.g., toxicity, teratogenicity, carcinogenicity, or reproduction toxicity).
- If the study conduct (e.g., recruitment rate, dropout rate, data quality, protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame

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

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g., IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law
- All study materials (except documentation that has to remain stored at site) must be returned to the Sponsor. The Investigator will retain all other documents until notification is given by the Sponsor for destruction.

- In the event of a partial study closure, ongoing subjects, including those in post-study follow-up, must be taken care of in an ethical manner

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

13. Ethical and legal aspects

13.1 Investigator(s) 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 centers will be available in each center's Investigator Site File.

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

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

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

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

13.1.1 Sponsor's medical expert

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	Viale Certosa 210
	20156 Milano, Italy
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13.1.2 External data evaluation bodies

13.1.2.1 Steering Committee

The Steering Committee, participating Investigators, and Sponsor will review available safety data (including, but not limited to, AEs, dose modifications, and laboratory changes), and using defined DLT criteria will determine dose escalation, dose de-escalation, cohort expansion, and will determine an appropriate radium-223 dichloride dose level for use in phase 2.

The Steering Committee may include external experts in the treatment of multiple myeloma and hemato-oncologists familiar with the existing treatment paradigm in multiple myeloma and are involved in current development research in this disease area as well as study investigators.

After 3 subjects in each sequentially enrolled cohort have received the first 2 doses of radium-223 dichloride in combination with BOR and DEX (plus a follow-up of at least 21 days), the Steering Committee and Sponsor will review all available safety data to determine, based on defined DLTs, whether enrollment in phase 2 may proceed, and will determine the MTD/RP2D (see Section 5.1.2).

13.1.2.2 Independent Data Monitoring Committee

For the phase 2 part of the study, an IDMC will be established to review accumulating safety data at regular intervals throughout the study and monitor overall study conduct. The IDMC will include experts in oncology, biostatistics, and safety who are not participating in this trial and do not have affiliation with the investigators or the Sponsor or other significant conflicts of interest. Their main objective will be to protect the interests of the subjects in the study and of those still to be entered. They will do this by monitoring the study periodically for safety, study progress, and protocol compliance, as well as assessing the risk/benefit of the trial. The IDMC meetings will be held as per the IDMC Charter. Ad hoc meetings will take place if needed.

Specific areas of concern for the IDMC are:

- Subject safety (unblinded safety data will be reviewed at each meeting and any cases of unexpected AEs will be considered)
- Accrual factors that may potentially impact on randomization balance
- Subject eligibility and adequacy of follow-up
- Protocol compliance (deviations from outcome assessment schedules which may lead to biases will be evaluated)

The specific duties of the IDMC, as well as statistical monitoring guidelines and procedures, are described in the IDMC Charter. The IDMC will review the safety data once 20 and 50 subjects in the phase 2 portion of the study have completed 2 doses of radium-223 dichloride or placebo + bortezomib/dexamethasone treatment (plus a follow up of at least 3 weeks after the second radium-223 dichloride dose), and every 6 months thereafter.

After the first IDMC meeting the following events will initiate ad-hoc IDMC meetings:

- ≥ 33% of subjects have discontinued study treatment due to treatment-related adverse events or
- ≥ 33% of subjects experience Grade 4 treatment-related hematologic toxicities.

The IDMC members will provide recommendations about the continuation of study with or without any modifications based on safety data and if any of the following criteria has been observed with an absolute increase of ≥ 33 percentage points in the active arm over the placebo controlled arm of the study (using CTCAE version 4.03 for the severity grade). Stopping criteria are defined as follows in alignment with the Phase 1b portion of the trial

if they occurred within the time from the first dose of study treatment through 2 doses of radium-223 administration + 3 weeks after 2nd radium-223 administration:

1. Grade 4 neutropenia for > 7 days, or febrile neutropenia with or without supportive care
2. Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with ≥ Grade 2 bleeding, or Grade 3 thrombocytopenia lasting > 2 weeks with or without supportive care
3. Grade 3 to 4 anemia lasting > 2 weeks with or without supportive care
4. Grade 3 non-hematological toxicity, except:
    a. diarrhea, vomiting, and fatigue that resolve within 72 hours with or without supportive care
    b. neuropathy
5. Any grade 4 non-hematological toxicity (lab abnormalities of any grade will not be considered toxicity unless deemed clinically significant by the investigator)

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 the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the Sponsor. The responsible unit (e.g., IEC/IRB, head of the study center/medical institution) must supply to the Sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

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

Modifications to the study protocol will not be implemented by either the Sponsor or the Investigator without agreement by both parties. However, the Investigator or the Sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/Sponsor approval/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 center. A sample subject information and ICF is provided as a document separate to this protocol.

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

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

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

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit description described in Section 9.2.3.6 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the SAP.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine, or tissues); these data would also be retained and statistically analyzed in accordance with the SAP. The subject has the right to object to the generation and processing of this post-withdrawal data. For this, she/he needs to sign a corresponding declaration of objection; alternatively, the subject's oral objection may be documented in the subject's source data.

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

Only if the subject/legal representative or proxy consenter voluntarily agrees to sign the ICF and has done so, may she/he enter the study. Additionally, the Investigator will personally sign and date the form. The subject/legal representative or proxy consenter will receive a copy of the signed and dated form.

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

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

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/his own will. Her/his refusal or the withdrawal of her/his consent may not be disregarded.

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

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 her/his 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 trial 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 eCRF, and if the subject name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the Sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

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

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

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15. Protocol amendments

15.1 Amendment 1 - 08 AUG 2017

15.1.1 Overview of changes to the study

Section 3.1 Background

The current Multiple Myeloma treatment landscape is evolving fast and several new treatment agents have recently been brought to the market. The background treatment offered in the currently approved protocol was no longer considered among the therapies of choice for MM patients previously treated with 1 to 3 prior therapies.

Feedback from investigators confirmed that enrolling patients in the phase II part of the trial would be challenging because patients in the placebo arm would only receive bortezombib + dexamethasone. Therefore, the study background treatment was updated with the recently approved triplet therapy of daratumumab + bortezomib + dexamethasone

In order to address this decision, significant changes to the study design have been introduced throughout the protocol.

Section 3.2 Study treatment

Information regarding daratumumab based on the specific product labeling has been introduced. In addition, clarifications of radium 223 dichloride and bortetzomib/ dexamethasone administration have been updated.

Section3.3 Study rationale

Recent results from animal models of radium 223 dichloride in combination with bortezomib have been updated and clinical data of daratumumab/ bortezomib/ dexamethasone have been added.

Section 3.3.1 Benefit-risk assessment

Benefit-risk assessment has been updated with corresponding information for daratumumab/ bortezomib/ dexamethasone.

Section 4. Study objectives

The objectives of the study have been revised according to the new study design.

Section 5 Study design

The design overview has been revised as follows:

- The dose level of 88kBq/kg body weight has been removed
- The randomized phase 2 part of the study has been removed
- Two new cohorts of radium 223 dichloride at 33kBq/kg body weight and 55kBq/kg body weight in combination with daratumumab/ bortezomib/ dexamethasone have been introduced
- An expansion cohort of up to 15 subjects treated with radium 223 dichloride at MTD in combination with daratumumab/ bortezomib/ dexamethasone have been added to confirm the MTD and to detect the early signal of anti-MM activity.

Section 5.1.1 Study design schematic

The schematic of study design has been modified in order to reflect the modifications of the study design.

Section 5.1.2 Study periods and duration

Study periods have been updated with clarifications of radium-223 dichloride and bortezomib/dexamethasone information. Information regarding the daratumumab/ bortezomib/ dexamethasone regimen has been introduced.

Section 5.1.3 Study endpoints

Primary and secondary endpoints have been modified according to the new study design and exploratory endpoints have been updated.

Section 6 Study population

Study population has been updated as follow:

- Clarifications of inclusion/ exclusion criteria and new criteria specific to daratumumab have been added
- Clarification of screen failures and subject rescreening
- Clarification of study withdrawal
- Clarification of subject replacement.

Section 7.1 Treatments

Information related to the treatments administered in the new cohorts exploring radium-223 in combination with daratumumab/ bortezomib/ dexamethasone and clarifications of the existing cohorts have been added.

Section 7.4 Dosage and administration

Dosage and administration has been modified including:

- Clarifications of dose calculation of each study drug
- Dose modification has been updated with daratumumab/ bortezomib/ dexamethasone combination and clarifications related to treatment interruptions and permanent discontinuation of each study drug has been added
- Drug logistics and accountability was updated considering central and local supply.

Section 9 Procedures and variables

Visits description and study procedures have been updated including:

- Visit description was updated with the daratumumab/ bortezomib/ dexamethasone combination
- Clarification of screening and study procedures
- Clarifications related to treatment periods of radium -223 in combination with bortezomib/ dexamethasone and with daratumumab/ bortezomib/ dexamethasone combinations
- Clarifications related to the active follow up period
- Clarifications to anti-MM activity, exploratory and safety endpoints.

Section 16 Appendices

Appendices updated with the interaction potential of bortezomib with other medicinal products.

15.1.2 Changes to the protocol text

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

15.2 Amendment 2 - 18 MAY 2018

15.2.1 Overview of changes to the study

Rationale of the amendment

The current multiple myeloma treatment landscape is evolving fast with daratumumab emerging as a potent compound in MM. We had amended the protocol to add daratumumab to the backbone, but this change was considered too complex by some authorities, who required a separate protocol for this new combination.

While no daratumumab cohort had been started yet, we consequently return to the original backbone with a randomized expansion cohort in order to obtain more robust data on the anti-multiple myeloma activity of radium-223 dichloride in combination with bortezomib/dexamethasone. This is also in agreement with feedback from advisory board experts.

Therefore, the current phase 1b study has been amended in order to evaluate whether radium-223 dichloride may increase the activity of bortezomib/dexamethasone in an expansion randomized phase 2 trial as clinical proof of concept for the next steps of development.

In order to address this decision, significant changes to the study design have been introduced throughout this version of the study protocol.

Section 1 Synopsis

Changes in the synopsis included:

- Change from a phase 1b study to a phase 1b/2 study with corresponding changes to add the randomized phase 2 part of the study to all applicable sections of the synopsis including: dosing information, study design, methodology, reference drug/type of control (addition of matching placebo, isotonic saline), addition of an Independent Data Monitoring Committee, number of subject, primary variables and statistical analysis.
- Changes to the phase 1b study objectives to remove information related to daratumumab administration during the study, change of the safety evaluation from secondary to primary objectives and removal of partial response (PR) and overall response rate (ORR) evaluations from the phase 1b part of the study. Addition of phase 2 study objectives.
- Removal of daratumumab administration during the study from all applicable sections of the synopsis including: dosing information, descriptions of Cohort 3, Cohort 4 and Expansion Cohort (as defined in protocol amendment 1), background treatment, inclusion/exclusion criteria, study design, methodology
- Clarification of inclusion and exclusion criteria (inclusion criteria 5, 7, 15 and 18; exclusion criteria 17 and 18 and removal of exclusion criteria specific to daratumumab (exclusion criteria 24, 25, 26, 27)

Section 3.1 Background

Update of background information and removal of some study data already contained in the Investigator Brochure.

Section 3.2 Study treatment

Study treatment sections were updated as follows:

- Update of radium-223 dichloride and bortetzomib/dexamethasone background information and removal of some radium-223 dichloride study data already contained in the Investigator Brochure. Removal of background information related to daratumumab.
- Update of dosing rationale for radium-223 dichloride and bortetzomib/dexamethasone administration, addition of phase 2 details and removal of daratumumab dosing information.

Section 3.3Study rationale

Update of rationale for the study and benefit-risk assessment information for bortezomib/dexamethasone and removal of information related to daratumumab.

Section 4 Study objectives

The objectives of the study have been revised according to the new study design.

- Changes to the phase 1b study objectives to remove reference to daratumumab administration during the study, change of the safety evaluation of radium-223 dichloride in combination from secondary to primary objectives and removal of partial response (PR) and overall response rate (ORR) evaluations from the phase 1b part of the study.
- Addition of phase 2 study objectives.

Section 5 Study design and Section 5.1.1 Study design schematic

The study design overview and study design schematic have been revised as follows:

- A randomized phase 2 part of the study with 100 subjects has been added
- All information related to daratumumab administration during the study was removed
- Safety follow-up information has been updated.

Section 5.1.2 Study periods and duration

Study periods and duration were updated as follows:

- Added the randomized phase 2 part of the study
- Removed all information related to daratumumab administration during the study
- Added randomization step for the phase 2 part of the study
- Added clarifications to the safety follow up for the collection of bone fracture and bone associated events

Section 5.1.3 Study endpoints

Primary and secondary endpoints have been modified and exploratory endpoints have been updated according to the new study design (addition of the randomized phase 2 part of the study).

Section 5.2 Primary variable and Section 5.3 End of study

Sections updated to reflect new study design (addition of the randomized phase 2 part of the study).

Section 6 Study population

Study population has been updated as follow:

- Section 6.1: Clarifications of inclusioncriteria 5, 7, 15 and 18
- Section 6.2: Clarifications of exclusion criteria 17 and 18 and removal of exclusion criteria specific to daratumumab administration (exclusion criteria 24, 25, 26, 27)
- Section 6.3: Update of withdrawal and replacement sections to reflect new study design (addition of the randomized phase 2 part of the study and removal of all information for daratumumab administration during the study), update of safety follow-up information and clarification added for the use of an additional consent form for the objection of the collection of study data after withdrawal of consent.

Section 7 Treatments

Information related to the treatments administered in the new phase 2 expansion cohorts exploring radium-223 in combination with bortezomib/dexamethasone and clarifications of the existing cohorts have been added (removal of Cohorts 3 and 4).

Additional changes to subsections of Treatments (Section 7) included:

- Section 7.1: Adding reference drug information for matching placebo (isotonic saline) to be used in the phase 2 part of the study.

- Section 7.3: Update of treatment assignment and IXRS/drug delivery information for the phase 2 part of the study.
- Section 7.4: Update of dosage and administration sections to reflect new study design (addition of the randomized phase 2 part of the study and removal of all information related to daratumumab administration during the study) and to ensure the blinding and the use of reference placebo in the phase 2 part of the study. Additional changes to subsections of Section 7.4 included:
    - Section 7.4.1: Detailed instructions for handling, storage and administration of radium-223 dichloride were removed from the protocol. This information is provided separately to the sites in a standardized handling instruction document.
    - Section 7.4.1.4: Details of tolerance limits required for the actual amount of radioactivity per dose.
- Section 7.5: Added sections describing blinding procedures and procedures for emergency unblinding for the phase 2 part of the study
- Section 7.6: Added section to drug logistics and accountability describing the procedures for locally provided isotonic saline (placebo) and removed all information related to daratumumab administration during the study
- Section 7.7: Update information for collection of treatment compliance while ensuring the blinding in the phase 2 part of the study.

Section 8 Non-study therapy

Changes to the non-study therapy subsections were as follows:

- All information related to daratumumab administration during the study was removed
- Clarification about recommended use of bone health agents

Section 9 Procedures and variables

All subsections of procedures and variables were updated to reflect new study design (addition of the randomized phase 2 part of the study and removal of all information related to daratumumab administration during the study).

Changes to visit description, schedule of evaluations and study procedures were as follows:

- Removal of daratumumab administration during the study from all applicable sections
    - Removal of Table 9-2 and Figure 9-2 and update of Maintenance Table (Table 9-3 amendment 1 / Table 9-2 amendment 2)

    - Removal of Cohort 3, Cohort 4 and Expansion Cohort as defined in protocol amendment 1

- All applicable sections were updated to reflect new study design (addition of the randomized phase 2 part of the study and use of matching placebo in the phase 2 part of the study)
    - Clarifications related to the active and long-term follow up periods
    - Clarifications related to anti-MM activity, exploratory and safety endpoints.
- Clarifications were added related to MM and bone biomarker exploratory endpoints.
- Clarification about recommended use of bone health agents
- Notes added details regarding the collection of all bone fractures and bone related events.

Section 10 Statistical methods and determination of sample size

All subsections of statistical methods were updated to reflect new study design (addition of the randomized phase 2 part of the study and removal of all information related to daratumumab administration during the study).

- Removal of daratumumab administration during the study from all applicable sections
- Added details regarding the collection of all bone fractures and bone related events.
- Clarifications related to anti-MM activity, exploratory and safety variables and endpoints

Other changes in Section 10 Statistical methods and determination of sample size were:

- Section 10.2: Changes to analysis sets (removal of mITT analysis set and addition of Phase 2 Safety Set [SAF] and Phase 2 Intent-to-treat)
- Section 10.4: Changes to sample size calculation information (removal of daratumumab cohorts and addition of the phase 2 part of the study
- Section 10.5: Addition of details regarding the termination of the study during phase 2 by the IDMC in regards to performing an interim analysis.

Section 12 Premature termination of the study

Addition of details regarding the termination of the study during phase 2 by the IDMC.

Section 13 Ethical and legal aspects

All applicable subsections of ethical and legal aspects were updated to reflect new study design (addition of the randomized phase 2 part of the study and removal of all information related to daratumumab administration during the study).

Other changes in Sections 13 Ethical and legal aspects were:

- Section 13.1.1: Change of sponsor's medical expert
- Section 13.1.2.2: Addition of details regarding the use of an IDMC in the phase 2 part of the study.

15.2.2 Changes to the protocol text

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

16. Appendices

16.1 National Cancer Institute-Common Terminology Criteria, version 4.03

This study will utilize the CTCAE v4.03 for grading of severity 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 International Myeloma Working Group (IMWG) uniform response criteria

Disease response and progression will be evaluated in this study using the recently revised IMWG uniform response criteria.(51)

IMWG uniform response criteria

Response	Criteria
Complete response (CR)	Negative immunofixation of serum and urine, disappearance of any soft-tissue plasmacytomas, and <5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum free light chain (FLC) level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; 2 consecutive assessments are needed
Stringent complete response (sCR)	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry; 2 consecutive assessments of laboratory parameters are needed
Very good partial response (VGPR)	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-component plus urine M-component <100 mg/24 hours (hrs); in patients for whom only measurable disease is by serum FLC level, >90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; 2 consecutive assessments are needed
Partial response (PR)	≥50% reduction of serum M-protein and reduction in 24-hr urinary M-protein by ≥90% or to <200 mg/24 hrs If serum and urine M-protein are not measurable, ≥50% decrease in difference between involved and uninvolved FLC levels is required in place of M-protein criteria If serum and urine M-protein and serum FLC assay are not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30% In addition, if present at baseline, ≥50% reduction in size of soft-tissue plasmacytomas is required Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed
Minimal response (MR)	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hr urine M-protein by 50% to 89% In addition, if present at baseline, 25% to 49% reduction in size of soft-tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed

IMWG uniform response criteria

Response	Criteria
Progressive disease (PD)	Increase of 25% from lowest response value in any of following: Serum M-component with absolute increase ≥0.5 g/dL; serum M-component increases ≥1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL and/or;
	Urine M-component (absolute increase must be ≥200 mg/24 hrs) and/or;
	Only in patients without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL);
	Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥10%)
	Development of new or definite increase in size of existing bone lesions or soft-tissue plasmacytomas
	Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder
	Two consecutive assessments before new therapy are needed

Source: 51

16.3 Calculation for glomerular filtration rate

Calculation of estimated glomerular filtration rate (Cockcroft-Gault formula, 52):

Glomerular filtration rate [mL/min per 1.73 m^2]

= (140 – age) x weight (kg) [x 0.85 if female] / (72 x mean serum creatinine [mg/dL])

16.4 New York Heart Association (NYHA) functional classification

Class	NYHA 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 Eastern Cooperative Oncology Group (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 Resource Utilization Questionnaire

Resource Utilization Questionnaire

Visit number: ☐☐

Subject number: ☐☐☐☐☐☐☐☐☐

Date of completion: ☐☐ DD ☐☐☐ MMM ☐☐☐☐ YYYY

Since the last study visit:

1. Has the subject been living in a Nursing Home? ☐ No ☐ Yes

If yes: how long has the subject been living in a Nursing Home during this period? ☐☐ Weeks

---

2. Has the subject been attending a Day Care Centre? ☐ No ☐ Yes

If yes:

1) How long has the subject been attending a Day Care Centre during this period? ☐☐ Weeks

2) On average, how many days per week has the subject been attending a Day Care Centre? ☐☐ Days

---

3. Has the subject received home health care services?

☐ No

☐ Yes

If yes:

1) In total, how long has the subject received home health care services during this period? ☐☐ Weeks

2) On average, how many hours per week has the subject received home health care services? ☐☐☐ Hours

---

4. Has the subject been hospitalized?

☐ No

☐ Yes

If yes: Please complete the reason for hospitalization(s) (or the main diagnosis received in connection with the hospitalization(s)) and the number of days the subject was in hospital in connection with (each of) the hospitalization(s) below:

Hospitalization Number	Reason/Diagnosis	Number of days in hospital
1		
2		
3		
4		

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5. Has the subject visited or been visited by a physician?

☐ No

☐ Yes

If yes: how many times? ☐☐

16.7 Brief Pain Index-Short Form (BPI-SF)

STUDY ID #: 18987 DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

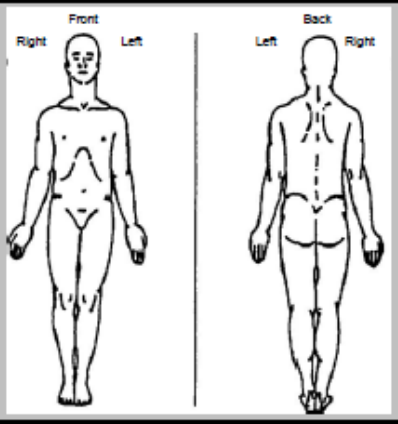
Date: ___/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Page 1 of 2

STUDY ID #: 18987 DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Date: ___/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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16.8 Interaction potential of bortezomib with other medicinal products

16.8.1 CYP3A clinical inhibitors for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (9/26/2016)

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP3A	boceprevir, cobicistat[h], conivaptan[h], danoprevir and ritonavir[j], elvitegravir and ritonavir[j], grapefruit juice[k], indinavir and ritonavir[j], itraconazole[h], ketoconazole, lopinavir and ritonavir[h,j], paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[j], posaconazole, ritonavir(h,j), saquinavir and ritonavir[h,j], telaprevir[h], tipranavir and ritonavir[h,j], troleandomycin, voriconazole	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone[h], erythromycin, fluconazole[f], fluvoxamine[a], imatinib, tofisopam, verapamil[h]	chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor[h], lomitapide, ranitidine, ranolazine[h], tacrolimus, ticagrelor[h]
	clarithromycin[h], diltiazem[h], idelalisib, nefazodone, nelfinavir[h]		

16.8.2 CYP2C19 clinical inhibitors or P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (9/26/2016)

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP2C19	fluconazole[f], fluoxetine[g], fluvoxamine[a], ticlopidine	-	omeprazole, voriconazole

16.8.3 CYP3A inducers for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (9/26/2016)

	Strong inducers	Moderate inducers	Weak inducers
CYP3A	carbamazepine[d], enzalutamide[f], mitotane, phenytoin[b], rifampin[a], St. John's wort(g)	bosentan, efavirenz, etravirine, modafinil	armodafinil, rufinamide

This is not a comprehensive list of medications which may inhibit CYP3A4/5. The above list was compiled by using information listed under "draft guidance for industry, drug interaction studies, CDER 2006", Indiana University School of Medicine drug interaction

tables at http//medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp and “drug interaction database” from University of Washington.