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Cover Page of the Integrated Clinical Study Protocol

A phase III randomized, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)

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

- Original protocol, Version 1.0, dated 05 NOV 2013
- Amendment 1 (global amendment described in Section 13.1) forming integrated protocol Version 2.0, dated 26 AUG 2014
- Amendment 2 (global amendment described in Section 13.2) forming integrated protocol Version 3.0, dated 12 JUN 2015
- Amendment 3 (local for Brazil only), dated 10 JUN 2016
- Amendment 4 (global amendment described in Section 13.3) forming integrated protocol Version 4.0, dated 13 SEP 2016
- Amendment 5 (local for Japan only), dated 21 SEP 2016
- Amendment 6 (global amendment described in Section 13.4) forming integrated protocol Version 5.0, dated 03 APR 2018
- Amendment 7 (global amendment described in Section 13.6) forming integrated protocol Version 6.0, dated 26 NOV 2019
- Amendment 8 (global amendment described in Section 13.6) forming integrated protocol Version 7.0, dated 08 FEB 2023

This document integrates the original protocol and all global amendments.

Title page

A phase III randomized, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)

Short title: **E**valuation of **R**adium-223 dichloride in combination with **A**biraterone in CRPC - ERA 223

Test drug:	BAY 88-8223 / Radium-223 dichloride and abiraterone and prednisone / prednisolone		
Study purpose:	To compare the symptomatic skeletal event-free survival of subjects with asymptomatic or mildly symptomatic chemotherapy-naïve bone predominant metastatic castration-resistant prostate cancer treated with radium-223 dichloride or placebo, in combination with abiraterone and prednisone / prednisolone		
Clinical study phase:	III	Date:	08 FEB 2023
EudraCT no.:	2013-003438-33	Version no.:	7.0
Study no.:	BAY 88-8223 / 15396		
Sponsor:	Bayer AG, D-51368 Leverkusen, Germany Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, US		
Sponsor's medical expert:	PPD PPD Bayer AG Muellerstr. 178 13342 Berlin, Germany PPD		

The study will be conducted in compliance with the protocol, International Council on Harmonisation and Good Clinical Practice and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

This document is electronically signed. The eSignature is archived in the trial master file (TMF) and can be provided upon request.

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

Name: PPD

Role: PPD

Date: .....

Signature: .....

Signature of principal investigator

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

Name:

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

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

Synopsis

Title	A phase III randomized, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)
Short title	**E**valuation of **R**adium-223 dichloride in combination with **A**biraterone in CRPC - ERA 223
Clinical study phase	Phase III
Study objectives	The **primary objective** is to compare, in subjects with asymptomatic or mildly symptomatic chemotherapy-naïve bone predominant metastatic castration-resistant prostate cancer (CRPC), the clinical benefit of radium-223 dichloride versus placebo in combination with abiraterone and prednisone / prednisolone, with the primary efficacy endpoint being: • Symptomatic skeletal event free survival (SSE-FS) The **secondary objectives** are to compare the radium-223 dichloride and placebo treatments to establish additional clinically relevant improvements in subjects with CRPC bone predominant metastasis using the variables below: • Overall survival (OS) • Time to opiate use for cancer pain • Time to pain progression • Time to cytotoxic chemotherapy • Radiological progression-free survival (rPFS) • Safety, acute and long-term, including new primary malignancies and hematopoietic reserve for tolerability of subsequent chemotherapy The study will also include the following **exploratory endpoints**: • Time to first on-study symptomatic skeletal event (SSE) • Percentage change in total alkaline phosphatase (ALP) from baseline • Time to ALP progression • Time to prostate specific antigen (PSA) progression • ALP response • PSA response

	• Bone scan specific rPFS • Time to increase in physical symptoms of disease based on the functional assessment of cancer therapy / National Comprehensive Cancer Network prostate cancer symptom index 17 item questionnaire disease related symptoms - physical (FPSI-DRS-P) subscale score measured during the treatment period • Time to increase in physical symptoms of disease based on the FPSI-DRS-P subscale score measured during the period between start of treatment and end of active follow-up with clinic visits • Assessment of pharmacokinetics of abiraterone (see Section 7.4) • Resource utilization • Biomarker assessments An explorative objective is to evaluate the impact of baseline total body weight and ideal body weight on SSE-FS and adverse events (AEs). Note: Evaluation of efficacy and exploratory endpoints, except for SSE and OS, will be discontinued following the final OS analysis.
Test drug	BAY 88-8223, administered in combination with oral abiraterone acetate and prednisone / prednisolone
Name of active ingredient	Radium-223 dichloride
Dose	50 kBq/kg (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight every 4 weeks for 6 cycles
Route of administration	Intravenous (IV) injection (slow bolus)

Duration of treatment	6 cycles
Reference drug	Matching placebo (normal saline), administered in combination with oral abiraterone acetate and prednisone / prednisolone
Name of active ingredient	Not applicable
Dose	Every 4 weeks for 6 cycles
Route of administration	IV injection (slow bolus)
Duration of treatment	6 cycles
Background treatment	All study subjects will receive treatment with oral abiraterone acetate (1000 mg once daily) and oral prednisone / prednisolone (5 mg twice daily), with best supportive care
Indication	Radium-223 dichloride in combination with abiraterone acetate and prednisone / prednisolone is indicated for the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic CRPC
Diagnosis and main criteria for inclusion	Subjects must meet the following criteria for inclusion in the study: 1. Have provided written informed consent. Subjects must be able to understand and be willing to sign the written informed consent form (ICF). A signed, written ICF must be appropriately obtained prior to the conduct of the any trial-specific procedure. 2. Histologically confirmed adenocarcinoma of the prostate. 3. Male subjects of age ≥ 18 years. The lower limit may be higher if legally required in the participating country. 4. Prostate cancer progression documented by prostate specific antigen according to the Prostate Cancer Working Group 2 criteria or radiological progression according to Response Evaluation Criteria in Solid Tumors, version 1.1. 5. Two or more bone metastases on bone scan within 4 weeks prior to randomization with no lung, liver, other visceral, and / or brain metastasis. 6. Asymptomatic or mildly symptomatic prostate cancer. A worst pain score (WPS) of 0 on the Brief Pain Inventory-Short Form Question #3 (worst pain in last

24 hours) will be considered asymptomatic, and a WPS of 1 to 3 will be considered mildly symptomatic. This is to be assessed once during the screening period.

7. Subjects who received combined androgen blockade with an anti-androgen must have shown PSA progression after discontinuing the anti-androgen prior to enrollment (≥ 4 weeks since last flutamide, ≥ 6 weeks since last bicalutamide or nilutamide).
8. Maintenance of medical castration or surgical castration with testosterone less than 50 ng/dL (1.7 nmol/L). If the subject is being treated with luteinizing-hormone-releasing hormone agonists or antagonists (subject who has not undergone orchiectomy), this therapy must have been initiated at least 4 weeks prior to randomization and must be continued throughout the study.
9. Eastern Cooperative Oncology Group Performance Status 0 or 1
10. Life expectancy ≥ 6 months
11. Laboratory requirements:
    a. Absolute neutrophil count ≥ 1.5 x 10^9/L
    b. Platelet count ≥ 100 x 10^9/L
    c. Hemoglobin ≥ 9.0 g/dL (90 g/L; 5.6 mmol/L)
    d. Total bilirubin level ≤ 1.5 x institutional upper limit of the normal (except for subjects with documented Gilbert's disease)
    e. Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x upper limit of the normal (ULN)
    f. Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2
    g. International normalized ratio (INR) of prothrombin time (PT; PT-INR) and partial thromboplastin time (PTT) ≤ 1.5 x ULN. Subjects treated with warfarin or heparin will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of PT-INR / PTT will be required until stability is achieved (as defined by local standard of care and based on prestudy PT-INR / PTT values)
    h. Serum albumin > 30 g/L
    i. Serum potassium ≥ 3.5 mmol/L

	12. Able to swallow abiraterone and prednisone / prednisolone as whole tablets 13. Subjects who have partners of childbearing potential must be willing to use a method of effective birth control during treatment and for 6 months following completion of treatment with radium-223 dichloride / placebo or 13 weeks of the last administration of abiraterone, whichever occurs later. The contraception measures must be discussed with the subject. Suitable contraception could be, for example, an oral contraceptive combined with the use of condoms.
Study design	International, phase III, double-blind, randomized, placebo-controlled, parallel group study. Randomization will be stratified by: • Geographical regions (Western Europe / North America / Australia versus Asia versus rest of world) • Concurrent use of denosumab or bisphosphonates or none • Total ALP < 90 U/L versus total ALP ≥ 90 U/L
Methodology	The study will comprise 4 periods: **Screening period:** All trial-related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the ICF. The screening period will consist of multiple evaluations that will take place within 2 weeks (+ 7 days) prior to randomization to ensure that all eligibility criteria are met. **Randomization:** Once eligibility is confirmed, eligible subjects will be randomized 1:1 to treatment with radium-223 dichloride plus abiraterone and prednisone / prednisolone (Arm A) or placebo (normal saline) plus abiraterone and prednisone / prednisolone (Arm B). **Treatment period:** Treatment consists of up to 6 cycles of radium-223 dichloride (Arm A) or placebo (Arm B) in combination with abiraterone plus prednisone / prednisolone followed by ongoing treatment for all subjects with abiraterone plus prednisone / prednisolone. • Up to 6 cycles of treatment in Arm A or Arm B: Treatment consists of 6 IV administrations of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) body weight (Arm A) or placebo (Arm B) each separated by an interval of 4 weeks plus abiraterone acetate 1000 mg every day plus prednisone / prednisolone 5 mg twice daily.

- Ongoing treatment with abiraterone plus prednisone / prednisolone: After the completion of treatment with radium-223 dichloride (Arm A) or placebo (Arm B), all randomized subjects will continue to receive abiraterone acetate 1000 mg every day plus prednisone / prednisolone 5 mg twice daily until disease progression (or other withdrawal criteria are met).

After the final OS analysis (Amendment 7):

In order to reduce the burden to study subjects, evaluation of efficacy and exploratory endpoints will be discontinued, except for SSE and OS. Discontinuation of abiraterone acetate plus prednisone/prednisolone will follow standard clinical practice; therefore, subjects who present disease progression defined as radiological progression (either by RECIST or bone progression by PCWG2), SSE, clinical progression (clinical deterioration or lack of clinical benefit, assessed by investigator) or initiation of a new anti-cancer therapy, should be discontinued from study treatment. After disease progression, abiraterone acetate will be considered standard of care (i.e., non-investigational medicinal product [non-IMP]) and will not be supplied as study medication.

Subject management, unless defined otherwise in this protocol, will be in accordance with routine clinical practice, at the discretion of the investigator. Subjects will be assessed every 4 weeks (± 7 days) for, safety and clinical progression, at each treatment visit and will be evaluated every 12 weeks (± 7 days) for radiological progression until disease progression occurs or subject is discontinued from study treatment, whichever occurs sooner. After discontinuation from study treatment, no additional radiological assessments will be required by protocol.

The treatment period extends from the initiation of treatment until 4 weeks after the last administration of abiraterone as IMP and prednisone / prednisolone. Until then, subjects will be followed by a visit every 4 weeks ± 7 days. Subjects with a platelet count or white blood cell count less than the lower limit of normal at 6 months will be followed additionally until resolution at a frequency based on local clinical practice.

Active follow-up period *with* clinic visits and active follow-up period *without* clinic visits:

After the final OS analysis (Amendment 7), subjects who are discontinued from study treatment will initiate the long-term follow-up period; therefore, the active follow-up period will no longer be applicable. Subjects who are in active follow-up at the time Amendment 7 is implemented should have the end of active follow-up completed (protocol driven decision) and should be directly transitioned into the extended safety follow-up study.

	Long-term follow-up: After the final OS analysis (Amendment 7), subjects who are discontinued from study treatment will initiate the long-term follow-up period in order to collect safety and OS information. The long-term follow-up period will end when the subject has completed 7 years of follow-up, dies, is lost to follow-up, withdraws informed consent, actively objects to collection of further data, or is transitioned to the extended safety follow-up study. During this period, subjects will be monitored via telephone call every 6 months for survival, treatment-related AEs and SAEs; and all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia; and primary bone cancer or any other new primary malignancy. All bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. In addition, subjects who receive cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice. Once a separate extended safety follow-up protocol for the inclusion of subjects who received radium-223 dichloride / placebo in the course of Bayer sponsored clinical trials has been implemented, the study subjects who are in active follow-up or in long-term follow-up will be transitioned to a separate extended safety follow-up study in order to complete 7 years of safety follow-up. All efforts will be made to transition all subjects to the extended safety follow-up study. **End of study (after implementation of Amendment 8):** The end of the study (EOS) is defined as the date of the last subject last visit in the study. The EOS will occur at the time the last subject on study completes 7 years of follow-up unless the subject dies, withdraws consent or is lost to follow-up.
Number of subjects	800 in total (with 1:1 randomization)
Primary variable	SSE-FS
Plan for statistical analysis	The analysis of efficacy will be performed using the intent-to-treat population, defined as all subjects who are randomized. The overall 2-sided type I error rate for the analysis of primary efficacy endpoint, SSE-FS, is 0.05. Symptomatic skeletal event-free survival will be analyzed using a stratified log-rank test with the same stratification factors as for randomization. The hazard ratio (HR; radium-223 dichloride / placebo) will be computed together with the 2-sided 95% confidence interval (CI) using a stratified Cox regression model, with

	the same stratification factors as strata in the model. Kaplan-Meier estimates and plots for both treatment groups will be produced to accompany these analyses. Each of the secondary variables will be tested using an overall 2-sided alpha of 0.025. The secondary efficacy time-to-event endpoints will be analyzed using a stratified log-rank test, with the factors from the randomization used for stratification. An HR with a 95% CI from a stratified Cox proportional hazards model will also be provided. Kaplan-Meier plots will be produced to accompany these analyses. Data collected following the final OS analysis will be analyzed descriptively only. Analysis may be done through listings.
Independent Data Monitoring Committee (IDMC)	An IDMC will be established for this study to review accumulating efficacy and 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. Independent Data Monitoring Committee meetings will be held every 6 months throughout the blinded trial phase. Ad hoc meetings will take place if needed. Note: No longer applicable after primary analysis.

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List of abbreviations

AAWD	Anti-androgen withdrawal
abi+pred	Abiraterone plus prednisone / prednisolone
ACTH	Adrenocorticotropic hormone
ADT	Androgen deprivation therapy
AE	Adverse event
ALP	Alkaline phosphatase
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
AST	Aspartate aminotransferase
BHA	Bone health agent
bid	Twice daily (bis in die)
BPI-SF	Brief Pain Inventory-Short Form
BUN	Blood urea nitrogen
CI	Confidence interval
Cl_2	Dichloride
CRO	Contract research organization
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events; version 4.03
CV	Coefficient of variation
CYP	Cytochrome P450
DES	Diethylstilbestrol
DK	Decay correction factor
DNA	Deoxyribonucleic acid
EBRT	External beam radiotherapy
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
ePRO	Electronic patient-reported outcome
EQ-5D	European Quality of Life-5 Dimensions
EQ-VAS	European Quality–Visual Analogue Scale
ERA 223	Evaluation of Radium-223 dichloride in combination with Abiraterone in CRPC
EU	European Union
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FPSI-DRS-P	NCCN-FACT FPSI-17 disease related symptoms - physical
FU	Follow-up

G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GM-CSF	Granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's brochure
ICF	Informed consent form
ICSR	Individual case safety report
ID	Identification number
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
IXRS	Interactive voice / web response system
K+	Potassium
LDH	Lactate dehydrogenase
LET	Linear energy transfer
LHRH	Luteinizing hormone-releasing hormone; also known as gonadotropin-releasing hormone (GnRH)
LLOQ	Lower limit of quantification
LSLV	Last subject last visit
LT FU	Long-term follow-up
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCCN-FACT FPSI-17	Functional assessment of cancer therapy / National Comprehensive Cancer Network prostate cancer symptom index 17 item questionnaire
NCI	National Cancer Institute
NF-κB	Nuclear factor kappa-B
NIST	National Institute of Standards and Technology
NYHA	New York Heart Association
OS	Overall survival
PCWG2	Prostate Cancer Working Group 2
PD	Progressive disease
PK	Pharmacokinetics
PLC	Placebo
PLT	Platelet count
po	Oral (per os)
PRD	Patient ready dose
PS	Performance status

PSA	Prostate specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
q	Every
qd	Every day (quaque die)
Ra-223	Radium-223
RANKL	Receptor activator of NF-κB ligand
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiological progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SD	Standard deviation
SPECT	Single photon emission tomography
SRE	Skeletal-related event
SSE	Symptomatic skeletal event
SSE-FS	Symptomatic skeletal event-free survival
SUSAR	Suspected unexpected serious adverse reaction
tx	Treatment
ULN	Upper limit of normal
US	United States
WBC	White blood cell
W/O	Without
WPS	Worst pain score

Definitions of terms

Radium-223 dichloride	The investigational product, a targeted alpha particle emitting radiopharmaceutical, is a ready-to-use solution for intravenous injection containing the drug substance radium-223 dichloride. The active moiety is the alpha particle emitting nuclide radium-223, present as a divalent cation ($^{223}Ra^{2+}$).
Dose	Doses are given as kiloBecquerel (kBq) per kilogram body weight, with the corresponding dose given in millicurie (mCi) per kilogram in parenthesis. The term “dose” is used to describe the quantity of radioactivity from radium-223 administered.
Bone scan	Whole body technetium-99m bone scan

1. Introduction

1.1 Castrate resistant prostate cancer: Disease and treatment

Prostate cancer has become an increasingly important health issue globally. Prostate cancer is the fifth most common tumor type worldwide, with 679,060 men diagnosed each year,(1) and is one of the leading causes of cancer-related morbidity and death.(2)

Prostate cancer is hormone sensitive at the time of initial diagnosis. Although most patients with advanced metastatic disease initially respond to conventional androgen deprivation therapy (ADT) with medical (3) or surgical (4) castration, the median duration of disease control has been 13 to 22 months and overall survival (OS) 28 to 36 months.(5) After progression to castration-resistant disease, close to 90% of those men already have bone metastases, and all their related undesirable effects, such as pain and deterioration of health-related quality of life (HRQoL). Patients with metastatic castration-resistant prostate cancer (CRPC) have a very limited life expectancy and most often die of their prostate cancer.

1.1.1 Chemotherapies

Several agents have been approved as palliative therapy for prostate cancer. Estramustine was approved in the 1970s; however, in a randomized study where OS was compared, diethylstilbestrol (DES), a hormonal agent, was found to be superior to estramustine.(6) In 1996, mitoxantrone and prednisone were approved in the United States (US) for palliation of pain and improvement in HRQoL in a randomized study with prednisone as control.(7)

Docetaxel was the first agent that has demonstrated a survival benefit in CRPC. In the TAX-327 study, a 3-weekly docetaxel regimen had a median OS of 18.9 months (95% confidence interval [CI] 17.0 to 21.2) compared with the mitoxantrone control arm of 16.5 months (95% CI, 14.4 to 18.6 months). The hazard ratio (HR) for death was 0.76 (95% CI, 0.62 to 0.94, p = 0.009) in the docetaxel regimen as compared with control.(8) Results from the Southwest Oncology Group Study 99-16 in 770 men (3-weekly docetaxel + estramustine + dexamethasone versus mitoxantrone + prednisone) demonstrated a median OS of 17.5 months versus 15.6 months, respectively, p = 0.02 and were consistent with the TAX-327 data.(8,9) The results of these 2 studies established docetaxel as the new standard agent for first-line treatment of CRPC, and the toxicity of this agent was considered acceptable.

Cabazitaxel, a novel member of the taxane class of anti-microtubule agents, demonstrated effectiveness in preclinical models that were resistant to paclitaxel and docetaxel.(10,11) Furthermore, cabazitaxel is able to cross the blood-brain barrier, a potential advantage in the treatment of some malignancies.(12) In a phase III clinical trial that was launched with the aim of comparing cabazitaxel to mitoxantrone in docetaxel-refractory CRPC,(13) 755 patients were treated with prednisone (10 mg daily) and randomized to receive either cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m^2) every 3 weeks, with OS as the primary endpoint. The median OS was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group (HR = 0.70; p < 0.0001). Cabazitaxel was associated with a higher incidence of adverse events (AEs) than mitoxantrone. The most common toxicities associated with cabazitaxel were neutropenia, anemia, and diarrhea. Of note, peripheral neuropathy was uncommon and typically mild or moderate in severity. The results of this

phase III clinical trial led to the approval of cabazitaxel for the second-line treatment of CRPC in many countries.

1.1.2 Secondary hormonal therapies

Secondary hormonal therapies in prostate cancer include anti-androgens, ketoconazole or abiraterone acetate, steroids, DES, or other estrogens based on the National Comprehensive Cancer Network (NCCN) guideline, version 3.(14)

Ketoconazole inhibits several adrenal enzymes required for steroid biosynthesis. Its efficacy in prostate cancer in terms of prostate specific antigen (PSA) response is comparable to that of aminoglutethimide. Pilot studies in patients after failure of combined androgen blockade where ketoconazole was given simultaneously with anti-androgen withdrawal (AAWD) showed that 55% of patients achieved a 50% PSA decline.(15) When administered after AAWD, 36% to 62.5% of patients had a 50% PSA decline.(16,17) In a phase III study conducted by the Cancer and Leukemia Group B, the PSA response rate was 27% with a median duration of response of 9 months in the group of patients randomized to the combination arm of AAWD and ketoconazole plus hydrocortisone versus the AAWD alone arm. Objective responses were observed in 2% of patients treated with AAWD alone compared to 20% in patients treated with AAWD / ketoconazole ($p = 0.02$). The median time to PSA progression was 8.6 months in patients treated with simultaneous AAWD and ketoconazole while it was only 5.9 months with AAWD alone. There was no difference in survival.(18) However, ketoconazole inhibits cytochrome P450 (CYP) 3A4 with substantial risk of drug-drug interactions, such as warfarin and statins,(19) and it is often poorly tolerated by patients, with commonly occurring side effects including diarrhea, nausea, vomiting, and depression.(16-18) Ketoconazole is not approved for the treatment of CRPC.

Glucocorticoids appear to possess both hormonal and direct anti-tumor effects in prostate cancer. Patients with CRPC may still have hormone-sensitive disease that is stimulated by weak androgens of adrenal origin, and these androgens are suppressed by prednisone through its negative feedback on secretion of adrenocorticotropic hormone (ACTH). Tannock et al. have demonstrated that low-dose prednisone treatment (7.5 to 10 mg daily) led to a decrease in the concentration of serum testosterone in 7 of 9 patients where it was not initially suppressed below 2.0 nmol/mL, and caused a decrease in serum levels of androstenedione and dehydroepiandrosterone sulfate in more than 50% of patients.(20) These changes were associated with symptomatic and clinical improvement. Glucocorticoids may also have direct inhibitory effects on prostate cancer cells through enhanced growth inhibitory transforming growth factor beta-1 signaling and suppression of the transcriptional activities of nuclear factor kappa-B (NF-κB).(21,22).

Prednisone, dexamethasone, and hydrocortisone have been frequently administered as standard of care in advanced prostate cancer because of their modest anti-tumor activity and palliative effects on disease. Two prospective phase III studies have documented the safety profile and palliative benefit of prednisone. Prednisone 7.5 to 10 mg daily was examined among 81 patients in one arm of a phase III trial, with 22% of patients achieving a 50% PSA decline and a median time to progression of 4.0 months.(23) Likewise, in a randomized study control arm where 201 patients were treated with prednisone 5 mg twice daily, a PSA decline of ≥ 50% was observed in 21% of patients.(24) Significant improvements in pain, HRQoL, and fatigue were also reported. Other glucocorticoids have similar activity in advanced prostate cancer.

Prostate cancer normally expresses estrogen receptors, and estrogenic compounds have been used for the treatment of CRPC. The most commonly used estrogen is DES.(25-27) Although estrogens remain an option for the secondary hormonal treatment of CRPC, their use is limited by concerns regarding cardiovascular toxicity.(28)

1.1.3 Bone metastasis in castration-resistant prostate cancer

The most common site of cancer spread in men with CRPC is bone. Development of bone metastases is a major problem in prostate cancer and is a serious threat to a patient's survival and HRQoL. Untreated patients face severe morbidity, including bone pain, bone fracture, compression of the spinal cord, and hematological consequences of bone marrow involvement.

Skeletal homeostasis is carried out by continuous destruction and rebuilding of skeletal tissue. There are several potential explanations for the marked predisposition of prostate cancer to metastasize preferentially to bones.(29) Both osteoblasts and osteoclasts appear to play a critical role in the interactions between prostate cancer cells and bone, and the receptor activator of NF-κB ligand (RANKL) is a key element in osteoclastogenesis, bone resorption, and chemo-attraction of tumor cells.(30) The prominent role of bone metastases in the natural history of metastatic prostate cancer has prompted investigators to target this site of metastasis in hopes of palliating symptoms and prolonging survival through the use of androgen ablation, bisphosphonates, radiopharmaceuticals, focal radiation, chemotherapy, and targeted agents.(29)

Unfortunately, therapeutic options at this stage of illness are still limited.

Zoledronic acid, a bisphosphonate, has been shown to delay and reduce skeletal-related events (SREs) in patients with CRPC (31) by inhibiting osteoclast mediated bone resorption in this population; however, these results may not apply to other bisphosphonates (e.g., pamidronate results were not positive in the same setting). None of these agents improved the overall or prostate cancer-specific survival of patients with CRPC.

More recently, denosumab, a monoclonal antibody that binds RANKL, has been found to be more effective than zoledronic acid as measured by the time to first and subsequent on-study SREs in patients with CRPC. The median time to the first on-study SRE was 20.7 months for the denosumab group compared with 17.1 months for the zoledronic acid group (HR = 0.82; 95% CI, 0.71 to 0.95; p = 0.008 for superiority).(32) Denosumab was approved for the treatment of patients with metastatic solid tumors in bone by the US Food and Drug Administration (FDA) and the European Commission in 2010.

Bone-seeking radionuclides have been developed for palliation of bone pain from metastases.(33) Metastron (strontium-89) and Quadramet (samarium-153 EDTMP) (34) have been approved in several countries. The bone-seeking nature of these agents results in direct delivery of beta radiation to the sites of disease. Due to the long range of the beta particles from these radioisotopes, the major dose-limiting factor with this treatment modality is toxicity to the bone marrow cells, limiting the use of these agents to pain palliation only as they have not demonstrated an OS benefit. This toxicity has seriously limited their clinical use.

1.1.4 Asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer

Approximately 50% of patients with metastatic prostate cancer will have no noticeable symptoms related to the tumor.(35) Cytotoxic chemotherapy (docetaxel or mitoxantrone) is ordinarily reserved for patients with symptomatic or rapidly progressive cancer.(36) The American Society of Clinical Oncology / Cancer Care of Ontario and European Association of Urology guidelines for the cytotoxic treatment of CRPC (28,37) emphasize the need to individualize the timing of non-hormonal therapy for prostate cancer and consider routine docetaxel questionable in men who have metastatic disease but lack symptoms. Similarly, the current European Society of Medical Oncology guidelines (38) for metastatic prostate cancer recommend that patients with castrate-resistant disease should receive second and possibly third-line hormonal therapies, while chemotherapy with docetaxel given every 3 weeks should be considered for patients with CRPC who are symptomatic.(38)

Patients with metastatic CRPC who are not good candidates for immediate chemotherapy may still benefit from alternate therapies since they develop symptomatic disease progression in a short period of time.

Abiraterone acetate, a pro-drug of abiraterone and a selective inhibitor of androgen biosynthesis that potently blocks CYP17, has been approved for the treatment of metastatic CRPC in patients who have failed treatment with docetaxel. Recently, this agent in combination with prednisone / prednisolone was shown to significantly delay disease progression, when compared to placebo in combination with prednisone / prednisolone (HR = 0.43; p-value = 0.0001).(39) As a result, abiraterone plus prednisone / prednisolone was approved by the US FDA and the European Commission as treatment for patients with chemotherapy-naïve metastatic CRPC. Despite this advance in treatment, skeletal events remain a therapeutic challenge; therefore, the combination of abiraterone and prednisone / prednisolone with bone-targeted therapies may further improve clinical benefit.

1.2 Study medications

1.2.1 Radium-223 dichloride

1.2.1.1 Drug development

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

Biodistribution studies have shown that radium-223 is selectively concentrated in bone compared to soft tissues, and that radium-223 is retained in the bone matrix.(40,41) Due to increased bone metabolism in skeletal metastases, preferential uptake in these lesions

compared to normal bone is observed. A significant radium-223 anti-tumor effect has been demonstrated in an experimental skeletal metastases model in nude rats.(41)

The clinical development of radium-223 dichloride was initiated in August 2001. A phase I clinical study in patients with skeletal metastases from breast and prostate cancer was performed in order to evaluate whether the product could be administered safely at therapeutically relevant doses. A total of 31 patients were enrolled. Twenty-five patients received a single intravenous (IV) injection in the dose escalating part of the study, with 5 patients at each dose level of 46, 93, 163, 213, and 250 kBq/kg body weight radium-223 dichloride. The results of this phase I study were encouraging (low toxicity, significant pain relief, and decreased serum alkaline phosphatase [ALP]); thus, a phase II trial (BC1-02 study) for CRPC was conducted,(40) where patients received multiple doses of either 50 kBq/kg body weight radium-223 dichloride or saline 4 times at 4-week intervals. In both studies, the results showed modest dose-dependent reversible hematological toxicity. No significant deleterious changes in chemistry parameters were seen, and the most frequent AE was transient diarrhea, which responded well to medication. In terms of efficacy, the BC1-02 phase II results showed a significant improvement in serum bone markers, i.e., bone ALP (a primary efficacy endpoint), and perhaps more importantly, a delayed time to PSA progression. Median OS at 2 years was 65.3 weeks for radium-223 dichloride and 46.3 weeks for placebo (HR = 2.1; p = 0.017 based on an intent-to-treat [ITT] population and adjusting for baseline covariates).

Following the positive results of the phase II trial, the phase III, double-blind, randomized, BC1-06, ALSYMPCA (**Alp**haradin in **Sym**ptomatic **P**rostate **Ca**ncer) trial was started in 2008. A total of 922 patients with CRPC and symptomatic bone metastases were randomized to receive 6 injections of radium-223 dichloride (50 kBq/kg IV) or matching placebo every 4 weeks. Based on data of an interim analysis (n = 809), the study was unblinded in June 2011, since radium-223 dichloride significantly improved OS, compared to placebo (the median OS was 14.0 versus 11.2 months, respectively; HR = 0.695; p = 0.00185). Symptomatic skeletal events (SSEs) were lower in the radium-223 dichloride arm, and time to first SSE was significantly delayed (the median time to SSE was 13.6 months versus 8.4 months, respectively; HR = 0.610; p = 0.00046). A low incidence of myelosuppression was observed, with Grade 3/4 events of neutropenia (1.8%) and thrombocytopenia (6.2%). Adverse events of any grade were described in 88% of the subjects who received radium-223 dichloride versus 94% in the placebo arm (Grade 3/4 AEs were described for 51% and 59%, respectively). The updated analysis (performed in June 2012) also showed that radium-223 dichloride significantly improved OS compared to placebo (median OS 14.9 versus 11.3 months, respectively; p = 0.00007; HR = 0.695).(42)

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

1.2.1.2 Benefits and risks

Anticipated benefits of treatment with radium-223 dichloride include prolongation of OS, delay of SSEs, and anti-tumor efficacy measured by PSA response, palliation of bone pain, and improvement in quality of life.

The risk profile attributed to radium-223 dichloride is favorable compared with available products for the treatment of CRPC. The anticipated risks attributed to radium-223 dichloride include the following AEs: gastrointestinal (constipation, transient but treatable

diarrhea, nausea, and vomiting); hematological (transient reduction in neutrophil count, mild to moderate myelosuppression, low grade thrombocytopenia); and, because of its radioactive nature, it cannot be excluded that radium-223 dichloride may, in the longer term, induce other primary cancers and bone marrow changes.

1.2.1.3 Dosing rationale

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

Currently, no data are available to assess if similar effects could be achieved with a dose lower than 50 kBq/kg body weight. However, patients diagnosed with CRPC have a poor prognosis with a median survival of approximately 3 years and, as no curative treatment is available, it is important that the dose administered is effective and well tolerated.

1.2.2 Abiraterone acetate

1.2.2.1 Drug development

Abiraterone (JNJ-589485, formerly CB7598) is 17-(3-pyridyl) androsta-5,16-dien-3β-ol and is a selective irreversible steroidal inhibitor of CYP17 (17α hydroxylase/C17,20-lyase). This enzyme is found in the testes, adrenals, and in prostate tumors and blocks 2 important enzymatic activities in the synthesis of testosterone (Figure 1–1). Abiraterone is a potent inhibitor with an apparent inhibition constant of 0.5 nM. Pharmacodynamic studies demonstrated that its effects on adrenal steroid synthesis were consistent with its mechanism of action. Anti-tumor effects were evident with PSA response and durable objective responses using Response Evaluation Criteria in Solid Tumors (RECIST) (43) in phase I and phase II studies conducted to date.

Abiraterone acetate (JNJ-2120482, formerly CB7630, Zytiga®) is the 3-acetylated analog of abiraterone and, thus, a pro-drug of abiraterone. The chemical nomenclature of abiraterone acetate is 3β-acetoxy-17-(3-pyridyl) androsta-5, 16-diene; its empirical formula is $C_{26}H_{33}NO_2$; and molecular weight is 391.55. Once absorbed after oral administration,

abiraterone acetate is rapidly converted to the active form, abiraterone (Figure 1–2). Administration as an acetate reduces the variability in absorption seen with abiraterone.

Figure 1–1: The enzyme complexes inhibited by abiraterone

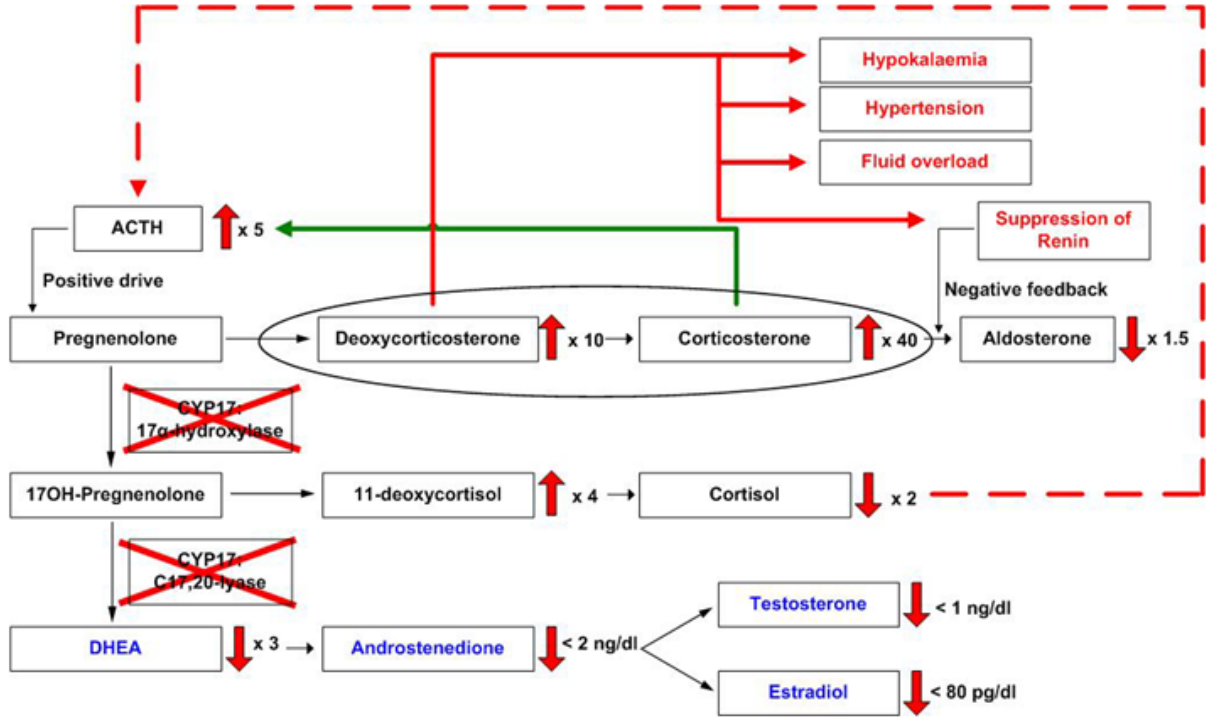
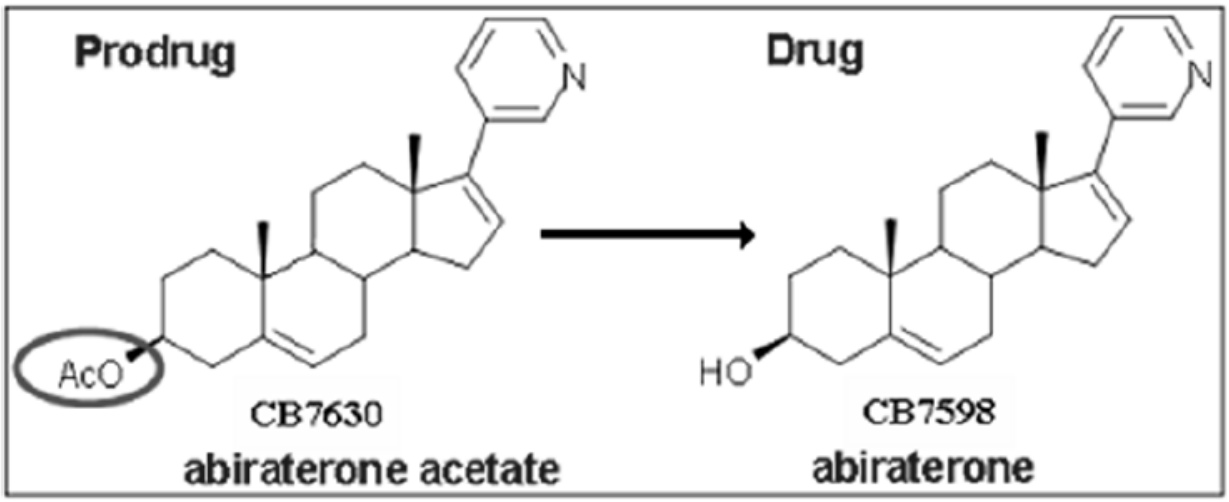


Figure 1–2: Pro-drug abiraterone acetate is converted to abiraterone after absorption



1.2.2.2 Abiraterone in chemotherapy-naïve castration-resistant prostate cancer

Following selection of the 1000-mg dosing regimen, chemotherapy-naïve men (n = 54) with CRPC resistant to multiple hormonal therapies were treated in the second part of the 2-stage phase I/II study, COU-AA-001. Declines in PSA ≥ 30%, ≥ 50%, and ≥ 90% were observed in 43 (80%), 38 (70%), and 14 (24%) of patients, respectively. Radiological evaluation reported objective response by RECIST (complete response or progressive response) in 52%

of patients. Declines in circulating tumor cell counts,(44) normalization of lactate dehydrogenase (LDH), and improving symptoms with a reduction in analgesic use were commonly documented. Twenty-three patients received abiraterone acetate capsules for more than 12 months as part of an extension protocol.(45) Similar response rates were observed in COU-AA-002, a parallel phase I/II study investigating tablet formulation.(46)

In the double-blind phase III study (COU-AA-302), 1088 chemo-naïve patients with asymptomatic or mildly symptomatic metastatic CRPC were randomized and received abiraterone acetate (1000 mg) plus prednisone (5 mg twice daily) or placebo plus prednisone.(47) The co-primary endpoints were radiological progression-free survival (rPFS) and OS. The study was unblinded after the Independent Data Monitoring Committee (IDMC) unanimously recommended unblinding treatment and allowing subjects in the placebo group to receive abiraterone acetate. This was after a planned interim analysis that was performed after 43% of the expected deaths had occurred. The median rPFS was 16.5 months with abiraterone–prednisone and 8.3 months with prednisone alone (HR = 0.53; 95% CI, 0.45 to 0.62; $p < 0.001$). Over a median follow-up period of 22.2 months, OS was improved with abiraterone–prednisone (median not reached, versus 27.2 months for prednisone alone; HR = 0.75; 95% CI, 0.61 to 0.93; $p = 0.01$) but did not cross the efficacy boundary. Abiraterone–prednisone showed superiority over prednisone alone with respect to time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, PSA progression, and decline in performance status. Grade 3 or 4 mineralocorticoid-related AEs and abnormalities on liver-function tests were more common with abiraterone–prednisone.

The results of this phase III clinical trial led to the recent approval of abiraterone–prednisone for the treatment of patients with asymptomatic or mildly symptomatic metastatic CRPC before chemotherapy by the US FDA and European Commission.

1.2.2.3 Dosing rationale

The dose of abiraterone acetate in this study is 1000 mg daily based on results of 2 Phase I dose-finding studies (48) and the pivotal phase III trial COU-AA-302.(49)

In the first phase I study with capsule formulation (COU-AA-001), abiraterone acetate was evaluated for safety, PK, and its effects on adrenal steroid synthesis at dose levels ranging from 250 to 2000 mg. Preliminary analysis showed that abiraterone acetate had an acceptable safety profile at all dose levels. Patients received abiraterone acetate during the study and in an extension protocol, with some patients on treatment for more than 48 months. In the second phase I study (COU-AA-002) (45,48) that evaluated the safety and tolerability of abiraterone acetate tablet formulation at doses ranging from 250 to 1000 mg, a daily dose of 1000 mg was also found to have an acceptable safety profile for further development.

Consistent with abiraterone acetate's mechanism of action, hypertension, hypokalemia, and lower extremity edema were the most commonly observed drug-related AEs, which were all manageable with medication. Pharmacokinetic studies showed increased systemic drug exposure at higher doses. Adrenal metabolite analysis showed inhibition of CYP17 even at low doses of abiraterone acetate and a compensatory increase of corticosterone and deoxycorticosterone. Data from the dose-finding studies indicated that when PK, adrenal CYP17 inhibition, and efficacy signals were taken into consideration, the 1000-mg dose offered consistent pharmacological effects without additional side effects. Based upon these findings, the 1000-mg dose was chosen for further efficacy and safety evaluation in the pivotal phase III studies which led to the approval of this dose in CRPC.

1.2.3 Concurrent prednisone / prednisolone

Data from early studies have contributed to the current understanding of the mechanism of abiraterone action. These suggest that a state of mineralocorticoid excess can occur after pharmacologic inhibition of CYP17, with the resulting reduced cortisol levels leading to a compensatory ACTH surge and accompanying hypertension, hypokalemia, and fluid retention.(50) These side effects were readily managed with potassium supplementation, eplerenone (selective mineralocorticoid antagonist), antihypertensive agents, and low dose corticosteroids. Grade 1 to 2 fatigue was observed in some patients and was associated with discontinuation of corticosteroids as required per phase II protocol entry criteria and extended duration of treatment with abiraterone acetate. Although there was no evidence of an abiraterone dose-response relationship, administration of low dose corticosteroids as specified in the study improved symptoms of fatigue and tolerability of abiraterone acetate, including symptoms of mineralocorticosteroid excess. The improved tolerability of abiraterone acetate after concomitant administration of low-dose corticosteroids was associated with suppression of ACTH and upstream adrenal steroids, suggesting that this combination may be a better tolerated and safer regimen in this older and frail patient population. Prednisone was selected over other corticosteroids because it is commonly used as standard of care (28) in combination with approved chemotherapy agents or as a monotherapy for palliation of symptoms.

The safety and efficacy of abiraterone acetate with concurrently administered prednisone has been evaluated in phase II and III studies. In patients with CRPC without previous chemotherapy, fatigue, arthralgia, and peripheral edema were among the AEs reported more frequently in the abiraterone–prednisone group than in the prednisone-alone group. Grade 3 or 4 AEs classified as hepatotoxicity, consisting primarily of a reversible elevation in aminotransferase levels, were reported in 8% of patients in the abiraterone–prednisone group and 3% of patients in the prednisone-alone group. Mineralocorticoid-related toxic effects were more common in the abiraterone–prednisone group than in the prednisone-alone group, including hypertension (22% versus 13%), hypokalemia (17% versus 13%), and fluid retention or edema (28% versus 24%), and were mostly Grade 1 or 2 AEs.(39) The regimen of abiraterone acetate 1000 mg daily and low-dose prednisone 5 mg twice daily has been chosen in this study.

1.3 Study rationale

The treatment options for asymptomatic or mildly symptomatic patients with bone predominant metastasis CRPC are still limited.

Radium-223 dichloride has shown significant anti-tumor activity in phase II and III studies in subjects with bone predominant metastatic CRPC. Anticipated benefits of the treatment, according to previous studies, include prolongation of OS, delay of SSEs, anti-tumor efficacy measured by PSA response, palliation of cancer pain, and improvement in HRQoL. The safety profile and tolerability for radium-223 dichloride appear to be acceptable in this study population.

Although this study is blinded, randomized, and placebo controlled for radium-223 dichloride, the subjects on the control arm will receive active treatment in the form of abiraterone acetate and prednisone. Abiraterone acetate plus prednisone constitutes the standard of care in patients with CRPC who are asymptomatic or mildly symptomatic and, therefore, not eligible for cytotoxic chemotherapy with docetaxel.

As the side effect profiles for radium-223 dichloride and abiraterone acetate are not overlapping, a dose-finding study or a run-in dose escalation evaluation is not considered necessary for an analysis of combination treatment. The mode of action differs for both compounds, as abiraterone targets androgen synthesis in testes, adrenal glands, and prostate cancer cells; whereas, radium-223 dichloride delivers alpha radiation to bone lesions of prostate cancer. Based upon these individual effects, it is expected that the combination of both agents will prolong symptomatic skeletal event-free survival (SSE-FS) compared to treatment with abiraterone acetate alone.

The study described herein has been designed to investigate the effects of radium-223 dichloride added to abiraterone acetate and prednisone / prednisolone in subjects with chemotherapy-naïve CRPC who are asymptomatic or mildly symptomatic and who have bone predominant metastasis, which has progressed during ADT. The study will be a randomized, double-blind, placebo-controlled phase III trial comparing radium-223 dichloride (50 kBq/kg [55 kBq/kg after implementation of NIST update] body weight, every 4 weeks for 6 single doses) administered with abiraterone acetate and prednisone / prednisolone versus placebo administered with abiraterone acetate and prednisone / prednisolone.

1.4 Primary efficacy endpoints

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

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

a. the use of external beam radiotherapy (EBRT) to relieve skeletal symptoms

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

c. the occurrence of spinal cord compression

d. a tumor-related orthopedic surgical intervention.

(2) Death from any cause

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

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

In 2007, Saad and colleagues were able to demonstrate that pathologic fractures correlate with reduced survival in patients with malignant bone disease. After adjustment for baseline characteristics, including performance status and prior skeletal complications, patients with prostate cancer had a > 20% increased risk of death.(51) As this correlation is not universally accepted, in the trial herein, the time to first SSE and OS will be combined as SSE-FS. Thus, either a SSE or death will count as an event.

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

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

2. Study objectives

The **primary objective** is to compare, in subjects with asymptomatic or mildly symptomatic chemotherapy-naïve bone predominant metastatic CRPC, the clinical benefit of radium-223 dichloride versus placebo in combination with abiraterone and prednisone / prednisolone, with the primary efficacy endpoint being:

- SSE-FS

The **secondary objectives** are to compare the radium-223 dichloride and placebo treatments to establish additional clinically relevant improvements in subjects with CRPC bone predominant metastasis using the variables below:

- OS
- Time to opiate use for cancer pain
- Time to pain progression
- Time to cytotoxic chemotherapy
- rPFS
- Safety, acute and long term, including new primary malignancies and hematopoietic reserve for tolerability of subsequent chemotherapy

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

- Time to first on-study SSE
- Percentage change in total ALP from baseline
- Time to ALP progression
- Time to PSA progression
- ALP response
- PSA response
- Bone scan-specific rPFS
- Time to increase in physical symptoms of disease based on the functional assessment of cancer therapy / NCCN prostate cancer symptom index 17 item questionnaire (NCCN-FACT FPSI-17) disease related symptoms - physical (FPSI-DRS-P) subscale score measured during the treatment period

- Time to increase in physical symptoms of disease based on the FPSI-DRS-P subscale score measured during the period between start of treatment and end of active follow-up with clinic visits
- Assessment of PK of abiraterone (see Section 7.4)
- Resource utilization
- Biomarker assessments

An explorative objective is to evaluate the impact of baseline total body weight and ideal body weight on SSE-FS and AEs.

Note: Evaluation of efficacy and exploratory endpoints, except for SSE and OS, will be discontinued following the final OS analysis.

3. Investigators and other study personnel

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the 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 study center, or an appropriately qualified, trained, and delegated individual of the investigational study center.

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

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

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

3.1 Independent Data Monitoring Committee

An IDMC will be established for this study to review accumulating efficacy and 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. Independent Data Monitoring Committee meetings will be held as per separate IDMC Charter, approximately every 6 months throughout the blinded trial phase. 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.

Note: No longer applicable after primary analysis.

3.2 Independent radiological review

Radiological progression of subjects will be determined by an independent assessment of imaging examinations. The process for the independent radiological review of radiological progression is described in a separate charter.

All the available scans that confirmed the fracture diagnosis will be sent from clinical sites to an independent central review center and will be reviewed by the independent central reviewers. The process for the independent radiological review of fracture diagnosis is described in a separate charter.

Note: No longer applicable after primary analysis.

4. Study design

4.1 Design overview

This study is a phase III, multinational, multicenter, randomized, double-blind, placebo-controlled study with a randomization allocation ratio of 1:1 (radium-223 dichloride plus abiraterone acetate plus prednisone / prednisolone:placebo plus abiraterone acetate plus prednisone / prednisolone). Randomization will be stratified by:

- Geographical regions (Western Europe / North America / Australia versus Asia versus rest of world)
- Concurrent use of denosumab or bisphosphonates or none
- Total ALP < 90 U/L versus total ALP ≥ 90 U/L

This study will be conducted at approximately 170 investigative study centers and approximately 800 subjects will be enrolled.

4.1.1 Study periods and duration

Until the final OS analysis, the study period consisted of screening / randomization, treatment, active follow-up with clinic visits, active follow-up without clinic visits, and long-term follow-up phases. Up until this point, subjects received study treatment (radium-223 dichloride or placebo in addition to abiraterone acetate plus prednisone / prednisolone for the first 6 cycles followed by abiraterone acetate plus prednisone / prednisolone thereafter) until an on-study SSE occurred (or other withdrawal criteria were met).

After the final OS analysis (Amendment 7), in order to reduce the burden to study subjects, evaluation of efficacy and exploratory endpoints will be discontinued, except for SSE and OS. Subjects who are discontinued from study treatment will initiate the long-term follow-up period; therefore, active follow-up periods will no longer be applicable. Subjects who are in active follow-up at the time of Amendment 7 is implemented should have the end of active follow-up completed (protocol driven decision) and should be directly transitioned into the extended safety follow-up study.

Long term follow-up period will end when the subject has completed 7 years of follow-up, dies, is lost to follow-up, withdraws informed consent, actively objects to collection of further data, or is transitioned to the extended safety follow-up study. Subjects will be followed for safety for up to 7 years, which eventually will be completed in this study or in the extended safety follow-up 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 2 weeks (+ 7 days) prior to randomization to ensure that all eligibility criteria are met (Section 5.1).

Randomization:

Once eligibility is confirmed, eligible subjects will be randomized 1:1 to treatment with radium-223 dichloride plus abiraterone and prednisone / prednisolone (Arm A) or placebo (normal saline) plus abiraterone and prednisone / prednisolone (Arm B).

Treatment period:

Treatment consists of up to 6 cycles of radium-223 dichloride (Arm A) or placebo (Arm B) in combination with abiraterone plus prednisone / prednisolone followed by ongoing treatment for all subjects with abiraterone plus prednisone / prednisolone.

- Up to 6 cycles of treatment in Arm A or Arm B: Treatment consists of 6 IV administrations of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) body weight (Arm A) or placebo (Arm B) each separated by an interval of 4 weeks plus abiraterone acetate 1000 mg every day plus prednisone / prednisolone 5 mg twice daily.
- Ongoing treatment with abiraterone plus prednisone / prednisolone: After the completion of treatment with radium-223 dichloride (Arm A) or placebo (Arm B), all randomized subjects will continue to receive abiraterone acetate 1000 mg every day plus prednisone / prednisolone 5 mg twice daily until disease progression occurs (or other withdrawal criteria are met).

After final OS analysis (Amendment 7):

In order to reduce the burden to study subjects, evaluation of efficacy and exploratory endpoints will be discontinued, except for SSE and OS. Discontinuation of abiraterone acetate plus prednisone/prednisolone will follow standard clinical practice; therefore, subjects who present disease progression defined as radiological progression (either by RECIST or bone progression by PCWG2), SSE, clinical progression (clinical deterioration or lack of clinical benefit, assessed by investigator), or initiation of a new anti-cancer therapy, should be discontinued from study treatment. After disease progression, abiraterone acetate will be

considered standard of care (i.e., non-investigational medicinal product [non IMP]) and will not be supplied as study medication.

Subject management, unless defined otherwise in this protocol, will be in accordance with routine clinical practice, at the discretion of the investigator. Subjects will be assessed every 4 weeks (± 7 days) for safety and clinical progression, at each treatment visit and will be evaluated every 12 weeks (± 7 days) for radiological progression until disease progression occurs or subject is discontinued from study treatment, whichever occurs sooner. After discontinuation from study treatment, no additional radiological assessments will be required by protocol.

The treatment period extends from the initiation of treatment until 4 weeks after the last administration of abiraterone as IMP and prednisone / prednisolone. If the subject receives abiraterone/prednisone as the standard of care (non-IMP) after disease progression, as defined above, this will not be considered part of the treatment period and it will not be considered as new anti-cancer therapy. During the treatment period, subjects will be followed by a visit every 4 weeks ± 7 days. Subjects with a platelet count (PLT) or white blood cell (WBC) count less than the lower limit of normal at 6 months will be followed additionally until resolution at a frequency based on local clinical practice.

Active follow-up period *with* clinic visits and active follow-up period *without* clinic visits:

After the final OS analysis (Amendment 7), subjects who are discontinued from study treatment will initiate the long term follow-up period; therefore, the active follow-up periods will no longer be applicable. Subjects who are in active follow-up at the time Amendment 7 is implemented should have the end of active follow-up completed (protocol driven decision) and should be directly transitioned into the extended safety follow-up study. For additional information, please refer to Section 13.6.

Long-term follow-up:

After the final OS analysis (Amendment 7), subjects who are discontinued from study treatment will initiate the long-term follow-up period in order to collect safety and OS information. The long-term follow-up period will end when the subject has completed 7 years of follow-up, dies, is lost to follow-up, withdraws informed consent, actively objects to collection of further data, or is transitioned to the extended safety follow-up study.

During this period, subjects will be monitored via telephone call every 6 months for survival; treatment-related AEs and SAEs, and all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia; and primary bone cancer or any other new primary malignancy. All bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. In addition, subjects who receive cytotoxic chemotherapy will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months at a frequency based on local clinical practice.

Once a separate extended safety follow-up protocol for the inclusion of subjects who received radium-223 dichloride / placebo in the course of Bayer sponsored clinical trials has been implemented, the surviving study subjects who are in active follow-up or the long-term follow-up will be transitioned to a separate extended safety follow-up study in order to complete 7 years of safety follow-up. All efforts will be made to transition all subjects to the extended safety follow-up study. The end of the study (EOS) is defined as the date of the last subject last

visit (LSLV) in the study. The EOS will occur at the time the last subject on study completes 7 years of follow-up unless the subject dies, withdraws consent or is lost to follow-up (FU).

4.1.2 Study endpoints

Primary endpoint: The primary endpoint is SSE-FS.

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

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

a. the use of EBRT to relieve skeletal symptoms

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

c. the occurrence of spinal cord compression

d. a tumor-related orthopedic surgical intervention.

(2) Death from any cause

Secondary endpoints

- OS
- Time to opiate use for cancer pain*
- Time to pain progression*
- Time to cytotoxic chemotherapy*
- rPFS*
- Safety, acute and long term, including new primary malignancies and hematopoietic reserve for tolerability of subsequent chemotherapy

Exploratory endpoints*:

- Time to first on-study SSE*
- Percentage change in total ALP from baseline*
- Time to ALP progression*
- Time to PSA progression*
- ALP response*
- PSA response*
- Bone scan-specific rPFS*
- Time to increase in physical symptoms based on the FPSI-DRS-P subscale score measured during the treatment period*
- Time to increase in physical symptoms of disease based on the FPSI-DRS-P subscale score measured during period between start of treatment and end of active follow-up with clinic visits*

- Assessment of PK of abiraterone (see Section 7.4)*
- Resource utilization*
- Biomarker assessments*

Evaluation of endpoints indicated with an asterisk (*) including all exploratory endpoints will be discontinued following the final OS analysis.

4.2 Primary variables

The primary variable is SSE-FS. The definition for this variable is provided in Section 4.1.2.

4.3 End of study

All efforts will be made to transition all subjects to the extended safety follow-up study. The EOS is defined as the date of the LSLV in the study. The EOS will occur at the time the last subject on study completes 7 years of follow-up unless the subject dies, withdraws consent or is lost to FU.

In case a subject is still on oral study treatment and still benefits based on the investigator's opinion after 7 years of follow-up, options for treatment continuation (e.g., switch to commercial drug supply, a continued access program, or any other means of continued drug supply) will be discussed and agreed between the investigator, sponsor, and the subject in compliance with local regulations.

For each participating European Union (EU) country, the EOS according to the EU Clinical Trial Directive will be reached when the LSLV in any center has occurred.

5. Study population

Approximately 800 medically or surgically castrated male subjects with bone predominant metastatic CRPC who have shown tumor progression and are non- or mildly symptomatic by prospectively defined criteria (Section 5.1) will be enrolled and treated.

5.1 Eligibility

Eligibility should be confirmed within 2 weeks (+ 7 days) of randomization. At Visit 2, the hematology values need to be confirmed to be within the treatment ranges prior to first dose.

Rescreening

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

- Subjects who underwent screening procedures (i.e., scans and laboratory work) that expired (are outside of the 14-day window) may need the screening procedures to be repeated in order to be within the window required prior to randomization. However, rescreening is not permitted in cases in which the initial laboratory test results do not support eligibility.
- Rescreening is also permitted where the screening procedures for subject's eligibility expired due to completion of washout periods as per protocol (e.g., 4 weeks from

treatment with an investigational drug), in case of expiry of investigational product that requires replacement, or for extraordinary logistical issues.

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

5.1.1 Inclusion criteria

The following criteria are to be met for inclusion into the study:

1. Have provided written informed consent. Subjects must be able to understand and be willing to sign the written ICF. A signed, written ICF must be appropriately obtained prior to the conduct of the any trial-specific procedure.
2. Histologically confirmed adenocarcinoma of the prostate
3. Male subjects of age ≥ 18 years. The lower limit may be higher if legally required in the participating country.
4. Prostate cancer progression documented by PSA according to the Prostate Cancer Working Group 2 (PCWG2) criteria (Section 14.2) or radiological progression according to RECIST, version 1.1 (52)
5. Two or more bone metastases on bone scan within 4 weeks prior to randomization with no lung, liver, other visceral, and / or brain metastasis
6. Asymptomatic or mildly symptomatic prostate cancer. A worst pain score (WPS) of 0 on the Brief Pain Inventory-Short Form (BPI-SF) (Section 14.9) Question #3 (worst pain in last 24 hours) will be considered asymptomatic, and a WPS of 1 to 3 will be considered mildly symptomatic. This is to be assessed once during the screening period.
7. Subjects who received combined androgen blockade with an anti-androgen must have shown PSA progression after discontinuing the anti-androgen prior to enrollment (≥ 4 weeks since last flutamide, ≥ 6 weeks since last bicalutamide or nilutamide).
8. Maintenance of medical castration or surgical castration with testosterone less than 50 ng/dL (1.7 nmol/L). If the subject is being treated with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists (subject who has not undergone orchiectomy), this therapy must have been initiated at least 4 weeks prior to randomization and must be continued throughout the study.
9. Eastern Cooperative Oncology Group performance status (ECOG PS) score 0 or 1
10. Life expectancy ≥ 6 months
11. Laboratory requirements:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    b. PLT ≥ 100 x 10^9/L
    c. Hemoglobin (Hb) ≥ 9.0 g/dL (90 g/L; 5.6 mmol/L)
    d. Total bilirubin level ≤ 1.5 x institutional upper limit of normal (ULN) (except for subjects with documented Gilbert's disease)

e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN

f. Estimated glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 (Section 14.4)

g. International normalized ratio (INR) of prothrombin time (PT; PT-INR) and partial thromboplastin time (PTT) ≤ 1.5 times the ULN. Subjects treated with warfarin or heparin will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of PT-INR / PTT will be required until stability is achieved (as defined by local standard of care and based on pre-study PT-INR / PTT values)

h. Serum albumin > 30 g/L

i. Serum potassium ≥ 3.5 mmol/L

12. Able to swallow abiraterone and prednisone / prednisolone as whole tablets
13. Subjects who have partners of childbearing potential must be willing to use a method of effective birth control during treatment and for 6 months following completion of treatment with radium-223 dichloride / placebo or 13 weeks of the last administration of abiraterone, whichever occurs later. The contraception measures must be discussed with the subject. Suitable contraception could be, for example, an oral contraceptive combined with the use of condoms.

5.1.2 Exclusion criteria

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

1. Prior cytotoxic chemotherapy for the treatment of CRPC, including taxanes, mitoxantrone, and estramustine
2. Administration of immunotherapies (e.g., sipuleucel-T) within 4 weeks before randomization
3. Prior treatment with abiraterone acetate
4. Administration of an investigational therapeutic within 4 weeks of randomization
5. Active infection or other medical condition that would make prednisone / prednisolone (corticosteroid) use contraindicated
6. Any chronic medical condition requiring a higher dose of corticosteroid than 5 mg prednisone / prednisolone twice daily
7. Pathological finding consistent with small cell carcinoma of the prostate
8. History of visceral metastasis, or presence of visceral metastasis detected by screening imaging examinations
9. History of or known brain metastasis
10. Malignant lymphadenopathy exceeding 3 cm in short-axis diameter

11. Prior hemibody external radiotherapy is excluded. Subjects who received other types of prior external radiotherapy are allowed provided that the bone marrow function is assessed and meets the protocol requirements for Hb, ANC, and PLT.
12. Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186, rhenium-188, or radium-223
13. Blood transfusion or erythropoietin stimulating agents prior 4 weeks of screening and during the whole screening period before randomization
14. Other malignancy treated within the last 5 years (except non-melanoma skin cancer or low-grade superficial bladder cancer)
15. Imminent spinal cord compression based on clinical findings and / or magnetic resonance imaging (MRI). Subjects with history of spinal cord compression should have completely recovered.
16. Use of opiate analgesics for cancer-related pain, including codeine and dextropropoxyphene, currently or anytime during the 4- week period prior to randomization
17. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg). Subjects with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment.
18. Active or symptomatic viral hepatitis or chronic liver disease
19. History of pituitary or adrenal dysfunction
20. Any other serious illness or medical condition such as, but not limited to:
    a. Any infection ≥ National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 Grade 2
    b. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II to IV (Section 14.5) heart disease or cardiac ejection fraction measurement of ≤ 50% at baseline
    c. Atrial fibrillation, or other cardiac arrhythmia requiring therapy
    d. Crohn's disease or ulcerative colitis
    e. Bone marrow dysplasia
    f. Moderate and severe hepatic impairment (Child-Pugh Classes B and C)
    g. Unmanageable fecal incontinence
21. Hypersensitivity to radium-223 dichloride or abiraterone acetate
22. Previous assignment to treatment during this study
23. Any condition which, in the opinion of the investigator, would preclude participation in this trial

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

All subjects who enter the trial should complete all phases of the protocol:

1. Screening
2. Randomization
3. Treatment period
4. Long-term follow up

Note: Study drug discontinuation (i.e., discontinuation during the treatment period) does not constitute withdrawal from the study. Every effort should be made to transition subjects who discontinue the treatment period for any reason to the extended safety follow-up study .

Subjects are expected to participate in the follow-up unless they explicitly object. Withdrawal of consent should be documented in the subject's medical file. If the subject does not wish to be followed up further, he should sign the '*Declaration of objection to collection of study data after withdrawal of consent form.'*

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

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

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

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

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

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

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

- If, in the investigator's opinion, continuation of the study treatment would be harmful to the subject's well-being.
- If the subject experiences unacceptable toxicities to any study drugs.
- Delay in all study treatment of > 4 weeks (maximum of 8 weeks between 2 injections of radium-223 dichloride / placebo).
- If the subject starts treatment with a prohibited prostate cancer therapy (Section 6.9.1).
- At his own request or at the request of his legally acceptable representative.
- At the specific request of the sponsor and in liaison with the investigator (e.g., obvious non-compliance, safety concerns).

- For disease progression characterized by radiological progression (either by RECIST or bone progression by PCWG2), SSE, clinical progression (clinical deterioration or lack of clinical benefit, assessed by investigator), or initiation of a new anti-cancer therapy.

After the final OS analysis (Amendment 7):

In order to reduce the burden to study subjects, evaluation of efficacy and exploratory endpoints will be discontinued, except for SSE and OS. Discontinuation of abiraterone acetate plus prednisone/prednisolone will follow standard clinical practice, therefore, subjects who present disease progression, as defined above, or that start a new anti-cancer therapy should be discontinued from study treatment. After disease progression, abiraterone acetate will be considered standard of care (i.e., non-investigational medicinal product [non-IMP]) and will not be supplied as study medication.

5.2.1.2 Withdrawal from treatment period and all follow-up

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

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

5.2.2 Replacement

Withdrawn subjects will not be replaced.

5.3 Subject identification

A subject number (a unique identification number) will be assigned via an interactive voice / web response system (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 center will send an order (using the IXRS) to the manufacturer for drug shipment based on the planned visit date of the subject. See Section 6.3.

6. Treatments

6.1 Treatments to be administered

Investigational product: Radium-223 dichloride, 50 kBq/kg (55 kBq/kg after implementation of NIST update) body weight will be administered IV as a slow bolus injection (approximately 1 minute) 6 times at intervals of 4 weeks.

Reference therapy: A solution of isotonic saline (0.9% sodium chloride solution for injection) will be administered IV as a slow bolus injection (approximately 1 minute) 6 times, at intervals of 4 weeks (see Section 6.2.1.2 for supply information).

Co-administered therapy: Abiraterone (abiraterone acetate; Zytiga®, Janssen, a division of Johnson and Johnson) will be administered orally, 1000 mg every day as a dose of four

250-mg tablets. Prednisone / prednisolone will be administered orally, 5 mg twice daily. If a subject has been receiving glucocorticoids other than prednisone or prednisolone prior to randomization, it will be necessary to switch the glucocorticoid to prednisone or prednisolone 5 mg twice daily prior to Cycle 1, Day 1.

6.2 Identity of study treatment

The alpha particle emitting radiopharmaceutical BAY 88-8223 is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of radium-223 dichloride for IV administration. Radium-223 dichloride is an alpha particle emitter with a physical half-life of 11.4 days. The product is isotonic and has a pH of 6.0 to 8.0. The radioactive concentration at the reference date is 1000 kBq/mL (1100 kBq/mL after implementation of NIST update). The product has a pre-calibration of 14 days. When administered on a day other than the reference day, the volume should be corrected according to the physical decay table supplied with each shipment.

For study sites in the US, sites will receive patient ready doses (PRDs) of radium-223 dichloride prepared by a radiopharmacy (Cardinal Health 414, LLC, Nuclear Pharmacy Services). Dose will be delivered to the sites in pre-filled syringes.

Abiraterone (abiraterone acetate) is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Abiraterone is a lipophilic compound and is practically insoluble in water. The product is supplied in 250-mg tablet form with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, and colloidal silicon dioxide.

Open label prednisone or prednisolone will be provided in 5-mg tablet form. Where prednisone is not commercially available, prednisolone will be substituted.

6.2.1 Study medication supply and packaging

All study drugs will be labeled according to the requirements of local law and legislation. Label text for all sponsor-supplied study drugs will be approved according to the sponsor's agreed procedures. For all sponsor-supplied study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor for sponsor-supplied study drugs. A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor study file.

Saline will be supplied locally by the study center's commercial supply. The unblinded staff will record the assignment, batch numbers, and expiry dates, which will be retained at the study center with a copy provided for the sponsor unblinded study file.

6.2.1.1 Radium-223 dichloride

The sponsor will provide radium-223 dichloride, which is manufactured by Bayer HealthCare. Radium-223 dichloride is produced according to GMP and will be delivered in a glass vial, ready-to-use with a certified activity. This alpha particle emitting radiopharmaceutical is shipped in a lead container and a Type A radioactive package according to international transportation guidelines for radioactive materials.

The volume per vial is 6 mL, corresponding to 6 MBq (6.6 MBq after implementation of NIST update), at the calibration reference day. Radium-223 dichloride has a shelf life of 28 days from production day, when stored at ambient temperature. The shelf life is valid for all climate zones I to IV. In addition, it has been shown that the product quality is not jeopardized upon freezing.

If administration must be postponed for more than 3 days compared to the original schedule, replacement of the drug order may be required (in case the available amount of radium-223 at site is insufficient or expired for the re-scheduled administration date).

6.2.1.2 Saline

Isotonic saline (0.9% sodium chloride solution for injection) 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.

The same process must be followed, regardless of treatment arm assignment, to maintain the study blind.

6.2.1.3 Abiraterone acetate

Abiraterone acetate will be provided with appropriate labeling to each study center by the sponsor.

As of Amendment 7, after disease progression, abiraterone will be considered standard of care (i.e., non-IMP) and will not be supplied as study medication; instead, abiraterone should be prescribed locally and recorded on the systemic anti-cancer therapy CRF.

Abiraterone should be stored at the investigator site. Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F).

6.2.1.4 Prednisone / prednisolone

Prednisone / prednisolone (5-mg tablets) will be provided. Where prednisone is not commercially available, prednisolone will be provided instead.

Prednisone should be stored at the investigator site. Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F).

6.3 Treatment assignment

To accomplish random assignment of treatment, a computer-generated randomization list will be prepared by the sponsor and provided to the IXRS. The IXRS will assign each eligible subject a randomization number and the respective treatment in a ratio of 1:1 to radium-223 dichloride or placebo. In addition, randomization will be stratified by geographical regions (Western Europe / North America / Australia versus Asia versus rest of world), concurrent use of denosumab or bisphosphonates or none, and by total ALP < 90 U/L versus total ALP ≥ 90 U/L.

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 center will be responsible for providing saline corresponding to the IXRS treatment day. This should not be made available before to avoid unblinding the subject and blinded study personnel.

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

6.4 Dosage and administration

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

In general, the administration of radioactive drugs involves a potential risk for third parties, due to radiation from the subject and due to possible contamination by spilling urine or feces. When radium-223 dichloride has been injected intravenously into a subject, the risk for external radiation exposure to third parties is extremely low, due to the short range of the alpha particles (< 100 µm) and the low portion of beta and gamma radiation. For these reasons the product can be administered on an out-patient basis. To minimize the risk of contamination, the subject and his caregivers will receive oral and written instructions regarding hygiene precautions to abide by after receiving the radioactive drug according to the investigational study center radiation protection guidelines. These instructions will be given to all subjects, as neither the principal investigator nor subject will know the assignment to radium-223 dichloride or placebo injections.

Aseptic technique should be used in the administration of radium-223 dichloride. The syringe should be handed to the blinded individual who will perform the injection. The study medication will be administered as a slow bolus IV injection. The actual radioactivity administered must be within the tolerance limits of ± 10% of the calculated radioactivity.

Abiraterone acetate (ZYTIGA®) 1000 mg (four 250-mg tablets) will be administered orally once daily in combination with prednisone / prednisolone 5 mg administered orally twice daily. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone acetate is taken and for at least 1 hour after the dose of abiraterone acetate is taken. The tablets should be swallowed whole with water and should not be crushed or chewed. If an abiraterone acetate dose is missed, it should be omitted and will not be made up.

It is not required for the prednisone to be taken at the same time as abiraterone acetate. The dose of prednisone will remain unchanged in the event that the study drug dose is changed. If a prednisone dose is missed, it should be omitted and will not be made up.

Based on its mechanism of action, abiraterone acetate may harm a developing fetus; therefore, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection, e.g., gloves. 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 center have been received by the sponsor, a vial of radium-223 dichloride for technical use will be sent to the study center.

Different clinical study centers possess dose calibrators from various suppliers; thus, the isotope calibration factor may differ from center to center. Consequently, each center must perform the radium-223 dial setting on their relevant dose calibrator(s), if no isotope calibration factor for radium-223 is being provided by the vendor of the dose calibrator. For dial setting, the clinical study center will receive a sealed vial or 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.

6.4.1 Radium-223 dichloride dose calibration

As of Amendment 2, NIST has established an updated standardization for radium-223 dichloride, which indicates that an approximately 10% difference existed between activity values obtained using the current standard and the updated standardization.

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

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

6.4.2 Radium-223 dichloride dose ordering and handling

At least 2 unblinded personnel should be nominated at each study center (Section 6.5). 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 dose should be ordered through IXRS as soon as possible (i.e., the day of the previous dose or at a minimum the country lead time) prior to the planned date of administration. The subject’s weight will be submitted with the dose request. The site is not required to assess safety labs prior to placing the order.

Assessments other than weight will be repeated (as needed to be within the window prior to the dose day / time). The site must obtain safety labs and review the hematology results within 3 days prior to the dose. If a laboratory result does not meet the criterion for dosing, the radium-223 dichloride dose should not be given; the sponsor is aware this may require the site to waste / destroy the dose.

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 the PRD. Patient ready doses prepared by Cardinal Health for US sites have an extended expiry (see Section 6.4.4). These doses should be administered within the specified shelf-life of the individual PRD.

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

6.4.3 Radium-223 dose calculation

The dosage of radium-223 dichloride is 50 kBq/kg (55 kBq/kg after implementation of NIST update) 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 injection for non-US sites or 3 to 5 days prior to the injection for US sites, the 50 kBq/kg (55 kBq/kg after implementation of NIST update) dosage level, and the decay correction factor (DK) to correct for physical decay of radium-223. A table with DKs according to physical decay of the study medication will be provided with each vial / syringe of radium-223 dichloride. The total amount (volume to be drawn into the syringe) to be administered to a subject should be calculated as follows:

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

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

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

[c] The volume to be injected will remain the same before and after implementation of the NIST update

Data regarding activity, calculations, and volume to be injected must be recorded in the subject's medical record by the unblinded person.

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

- The subject's weight measured at the dosing visit will be obtained at the site 3 to 5 days prior to the planned dosing date.
- This weight will be communicated to the country PRD depot for preparation of the current dose 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 non-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 syringe-ready doses

based on the subject weight provided to Cardinal Health within 3 to 5 days prior to the day of administration. Therefore, no other weight measurement is needed.

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

6.4.4 Study drug dose preparation

In order to keep the treating physician blinded to the assignment of study medication, the unblinded person (e.g., from the hospital pharmacy or nuclear medicine department) will be responsible for blinding the syringe and responsible for calculating the required dosage. Data regarding activity and volume to be injected should be recorded in the IMP preparation log and in the appropriate eCRF, both of which will not be available to the blinded treating physician or other blinded staff. 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 the US, a third-party vendor (Cardinal Health) will be used to prepare the injections to be used by the study center.

Patient ready doses prepared by Cardinal Health for US sites have an expiry. The measured activity of the PRD will be within 10% of the ordered amount (planned dose). The dose should be ordered through IXRS at least 3 days prior to the planned date of administration, and should be administered within the specified shelf-life of the individual PRD. The subject's weight will be submitted with the dose request. The site is not required to assess safety labs prior to placing the order. Assessments other than weight are repeated (as needed to be within the window prior to the dose day / time). The site must obtain safety labs and review the hematology results within 3 days prior to the dose. If a laboratory result does not meet the criterion for dosing, the radium-223 dichloride or placebo dose should not be given.

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

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

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

The study medication will be administered as a slow bolus IV injection. After administration, the equipment used in connection with the preparation and administration of drug are to be treated as radioactive waste and should be disposed in accordance with hospital procedure for the handling of radioactive material and according to local laws. Written information about radium-223 dichloride and instructions for the handling and injection of radioactive material will be provided to study personnel.

6.4.5 Dose adjustments for study drug-related adverse events

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

The investigator should delay cytotoxic chemotherapy, other systemic radioisotope, hemibody external radiotherapy, or other investigational drug until the subject experiences a SSE. If such treatments must be given during the treatment period, further study drug administrations must be discontinued. These treatments should not be given before a 4-week wash-out period after last administration of study drug, provided the subject's bone marrow is not compromised.

Recommendations

Every effort will be made to administer the full dosing regimen. Single dose level adjustment of radium-223 dichloride is not permitted. Treatment delays or discontinuations of radium-223 dichloride / placebo may be instituted for the AEs described in Section 6.4.6.1 and dose adjustments, treatment delays, or discontinuations of abiraterone may be instituted for AEs described in Section 6.4.6.2.

6.4.6 Dose adjustments, delays, and treatment discontinuations

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

Treatment with abiraterone may be delayed by no more than 4 weeks for recovery of AEs. If treatment is delayed for > 4 weeks, treatment should be discontinued. Some AEs as described in Section 6.4.6.2 will lead to a reduction in dose. No more than 2 reductions in dose are permitted. If further dose reductions are considered, treatment should be discontinued.

6.4.6.1 Radium-223 dichloride / placebo

Myelosuppression

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

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

In case of thrombocytopenia CTCAE Grade 3 to 4, the study drug administration should be delayed until recovery to CTCAE Grade 2 (minimum PLT 50 x 10^9/L) or better.

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

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

Blood transfusion is acceptable between study drug administrations. Use of biologic response modifiers, such as granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF), is allowed in the management of acute toxicity.

Gastrointestinal events

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

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

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

Non-pathological fractures

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

Treatment *must* be discontinued in the following cases:

- If a subject experiences any non-hematological CTCAE Grade 4 toxicity lasting > 1 week despite adequate treatment
- If the period between injections is greater than 8 weeks

6.4.6.2 Abiraterone

Based upon experience from a number of clinical studies, abiraterone acetate is generally well tolerated.

The most common adverse reactions (≥ 10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection, and contusion.

The most common laboratory abnormalities (> 20%) are anemia, elevated ALP, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT, and hypokalemia. It has been documented that following prolonged therapy with corticosteroids, subjects may develop Cushing's syndrome characterized by central adiposity, thin skin, easy bruising, and proximal myopathy. Withdrawal of the corticosteroid may result in symptoms that include fever, myalgia, fatigue, arthralgia, and malaise. This may occur even without evidence of adrenal insufficiency.

If dose-reduction is used for AE management, 2 dose reductions are allowed for abiraterone. At each dose reduction, one tablet of abiraterone will be removed, e.g., 4→3 tablets and

3→2 tablets. Any return to protocol dose level after dose reduction may only be instituted after documentation of resolution of the AE.

Hypokalemia

At the initial observation of Grade 1 hypokalemia (serum potassium < 3.5 mM or below lower limit of normal range, but ≥ 3.0 mM), oral potassium supplement will be initiated. The dose of potassium supplement must be carefully titrated to maintain serum potassium at ≥ 3.5 mM but ≤ 5.0 mM. Any subject with low potassium while on study or a history of hypokalemia from a pre-existing or concurrent medical condition will undergo weekly or more frequent laboratory electrolyte evaluation. The investigator should consider maintaining the subject's potassium level at ≥ 4.0 mM in these subjects.

If any subject experiences Grade 3 hypokalemia (serum potassium levels < 3.0 to 2.5 mM, NCI-CTCAE v4.03) or life-threatening hypokalemia with potassium levels < 2.5 mM (NCI-CTCAE v4.03 Grade 4 hypokalemia), abiraterone will be withheld and prednisone / prednisolone tapered. The subject will hospitalized for IV potassium replacement and cardiac monitoring. Prednisone / prednisolone should then be tapered.

Table 6–1: Management of hypokalemia

Serum potassium	Grade	Action	Further action or maintenance
Low K+ and / or history of hypokalemia		Weekly or more frequent laboratory evaluations	Titrate subjects to maintain a serum K+ ≥ 3.5 mM ≤ 5.0 mM (maintenance at ≥ 4.0 mM is recommended)
< 3.5 mM to 3.0 mM	1, 2	Initiate oral K+ supplementation	Titrate subjects to maintain a serum K+ ≥ 3.5 mM ≤ 5.0 mM (maintenance at ≥ 4.0 mM is recommended)
< 3.0 mM to 2.5 mM	3	Withhold abi+pred treatment and initiate IV K+ and cardiac monitoring	Discuss with Medical Monitor prior to re-initiating study treatment
< 2.5 mM	4	Withhold abi+pred treatment and initiate IV K+ and cardiac monitoring	Discuss with Medical Monitor prior to re-initiating study treatment

Abbreviations: abi+pred = abiraterone plus prednisone / prednisolone; IV = intravenous; K+ = potassium.

Hypertension

- Grade 1 to 2: Management per investigator. No abiraterone dose reduction.
- Grade 3: Hold abiraterone and taper prednisone / prednisolone treatment. Adjust or add medications to mitigate the toxicity and / or consider the specific mineralocorticoid receptor blocker, eplerenone (Inspra). When hypertension resolves to ≤ Grade 1 or baseline, resume abiraterone and prednisone / prednisolone at full dose.
- Grade 4: Hold abiraterone and taper prednisone / prednisolone treatment. Adjust or add medications to mitigate the toxicity and / or consider the specific mineralocorticoid receptor blocker, eplerenone (Inspra). When hypertension resolves to ≤ Grade 1 or baseline, resume abiraterone and prednisone / prednisolone with the first dose level reduction (3 tablets, 750 mg of abiraterone).

- If toxicity recurs, hold abiraterone and taper prednisone / prednisolone, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1 or baseline, resume abiraterone and prednisone / prednisolone with one dose level reduction (2 tablets, 500 mg abiraterone or 3 tablets, 750 mg of abiraterone).
- If toxicity recurs despite optimal medical management and 2 dose level reductions, treatment with abiraterone is to be discontinued and prednisone / prednisolone is to be tapered.

Edema or Fluid Retention

- Pedal edema: Supportive management per investigator. No abiraterone dose reduction.
- Anasarca and / or pulmonary edema requiring supplemental oxygen: Hold treatment with abiraterone and taper prednisone / prednisolone. Adjust or add medications to mitigate the toxicity and / or consider the specific mineralocorticoid receptor blocker, eplerenone (Inspra). When toxicity resolves to ≤ Grade 1, resume abiraterone and prednisone / prednisolone at full dose. If toxicity recurs, hold abiraterone and taper prednisone / prednisolone, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume abiraterone and prednisone / prednisolone with the first dose level reduction (3 tablets, 750 mg of abiraterone).
- If toxicity recurs, hold abiraterone and taper prednisone / prednisolone, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume abiraterone and prednisone / prednisolone with the second dose level reduction (2 tablets, 500 mg of abiraterone).
- If toxicity recurs despite optimal medical management and 2 dose level reductions, treatment with abiraterone is to be discontinued and prednisone / prednisolone is to be tapered.

Abnormal liver function

- If Grade 1 increases in AST, ALT, or bilirubin occur (e.g., increase in AST or ALT from ULN to 3.0 x ULN; increase in total bilirubin from ULN to 1.5 x ULN), the frequency of liver function test monitoring should be increased, if the investigator judges that the laboratory abnormalities are potentially related to study medication. No reduction of abiraterone dose is required.
- If Grade 2 increases in AST, ALT, or bilirubin occur (e.g., increase in AST or ALT to > 3.0 to 5 x ULN; increase in total bilirubin from > 1.5 to 3 x ULN), the frequency of liver function test monitoring should be increased to ≥ once a week, if the investigator judges that the laboratory abnormalities are potentially related to study medication. No reduction of abiraterone dose is required.
- If Grade 3 increases in AST, ALT, or bilirubin occur (e.g., increase in AST or ALT to > 5 x ULN; increase in total bilirubin to > 3 x ULN), hold abiraterone and taper prednisone / prednisolone and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once weekly) should be conducted until the liver function tests return to baseline value or Grade 1. Liver

enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.

- If abiraterone and prednisone / prednisolone resumption is considered for subjects who have experienced Grade 3 increases in AST, ALT, or bilirubin, and the medical monitor agrees, resume abiraterone and prednisone / prednisolone with the first dose level reduction (3 tablets, 750 mg of abiraterone) when Grade 3 toxicities resolve to Grade 1 or baseline.
- If Grade 3 increases in AST, ALT, or bilirubin recur after the first dose reduction, hold abiraterone and taper prednisone / prednisolone and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at least once weekly) until the liver function tests return to baseline value or Grade 1. Liver enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.
- If abiraterone and prednisone / prednisolone resumption is considered for subjects who have experienced Grade 3 increases in AST, ALT, or bilirubin with the first dose reduction, and the medical monitor agrees, resume abiraterone and prednisone / prednisolone with the second dose level reduction (2 tablets, 500 mg of abiraterone) when AST, ALT, or bilirubin returns to baseline value or Grade 1.

- If Grade 4 increases in AST, ALT, or bilirubin occur (e.g., increase in AST or ALT to > 20 x ULN; increase in total bilirubin to > 10 x ULN), subjects must discontinue abiraterone and taper prednisone / prednisolone immediately and will not be re-challenged. They should be followed until resolution of abnormal liver function tests.

Non-mineralocorticoid-based side effects

- If Grade 1 to 2 toxicities occur, give supportive care per institutional guidelines. No reduction of abiraterone dose is required.
- If Grade 3 or higher toxicities, including headache, nausea, vomiting, or any other toxicity judged to be related to study treatment, is observed where the subject's safety is jeopardized, hold abiraterone and taper prednisone / prednisolone. When toxicity resolves to ≤ Grade 1, resume abiraterone and prednisone / prednisolone at full dose.
  - If toxicity recurs, hold abiraterone, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume abiraterone and prednisone / prednisolone with the first dose level reduction (3 tablets, 750 mg of abiraterone).
  - If toxicity recurs, hold abiraterone and taper prednisone / prednisolone, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume abiraterone and prednisone / prednisolone with the second dose level reduction (2 tablets, 500 mg of abiraterone).

- If toxicity recurs despite aggressive medical management and 2 dose level reductions, discontinue treatment with abiraterone and taper prednisone / prednisolone.

6.4.7 Supportive care guidelines

Ancillary Treatment (guidelines)

- Persistent neutropenia (neutrophils / granulocytes CTCAE Grade 4 (< 0.5 x 10^9/L) without fever: These subjects may be started on G-CSF 5 µg/kg/d subcutaneously until the neutrophil count has reached the local hospital's reference range.
- Neutropenia with fever (neutrophils / granulocytes CTCAE Grade 3 to 4 (< 1 x 10^9/L); fever > 38.5°C): Blood cultures will be obtained and the subject started on empiric antibiotics for as long as clinically indicated. It is highly recommended that the subject receive G-CSF 5 µg/kg/d subcutaneously until the neutrophil count has reached the local hospital's reference range with 2 separate measurements, at least 12 hours apart.
- Severe thrombocytopenia (CTCAE Grade 4 [< 25.0 x 10^9/L] or bleeding with CTCAE Grade 3 to 4 (< 50.0 x 10^9/L): Platelets will be transfused to maintain PLT >50 x 10^9/L or higher if clinically indicated to control bleeding. Epsilon aminocaproic acid may be given to subjects with mucosal bleeding and PLT CTCAE Grade 3 to 4.
- Severe anemia (Hb CTCAE Grade 3 [< 80 x 10^9 g/L; 8.0 g/dL; 4.9 mmol/L]): Subjects will be transfused with packed red cells to maintain Hb value > 80 g/L; 8.0 g/dL; 4.9 mmol/L.

6.5 Blinding

Every effort will be made to keep the study blinded. Subjects will be randomized to receive radium-223 dichloride or placebo in a double-blind fashion; however, treatment with abiraterone and prednisone / prednisolone will be the same in both treatment arms and will be provided in an open-label format.

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

Unblinding

In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reaction (SUSAR) (see Section 7.5.1.5), the subject's treatment code will usually be unblinded before reporting to the health authorities, ethic committees (see Section 7.5.1.4) if the SUSAR was related to the blinded treatment. Investigators may only unblind subjects under emergency unblinding rules. If a subject is unblinded by the investigator, they must discontinue study drug(s).

Investigators should note that the occurrence of a SAE or progressive disease (PD) should not routinely precipitate the immediate unblinding of the label. If emergency unblinding is necessary for the treatment of a subject for a SAE, the study treatment can be unblinded via the IXRS (refer to the IXRS manual for instructions).

The participating site has unrestricted and immediate access to break the treatment code in IXRS. Should the blind code be broken for a subject, the medical monitor or designee should be contacted by the Principal Investigator within one working day of unblinding to discuss the rationale for the premature unblinding.

Individual subjects may be unblinded per investigator's request after they have a SSE, allowing the investigator to determine if the subject would be a candidate to receive treatment with radium-223 dichloride. This would be an option if the subject had been randomized to the control arm of the trial and radium-223 dichloride was approved in the country where the subject was under treatment.

The study will be unblinded for analysis purposes at the time of the final analysis of SSE-FS. However, no subject-level unblinding information will be communicated to the sites until the final OS analysis has been completed.

Following the IDMC's recommendation, the study was prematurely unblinded in NOV 2017 and subject level unblinding information has been communicated to the sites.

6.6 Drug logistics and accountability

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

In some countries / study centers it will be required to use a third party vendor to prepare the injections to be used by the study center. A log of study medication (received, administered to subjects, and destroyed) must be maintained and signed by the dedicated person responsible for drug handling at each center. Any labels or mandatory logs provided by the sponsor are to be utilized according to instructions. A copy of study drug documentation will be collected for the sponsor file.

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

For radium-223 dichloride:

Radium-223 dichloride will be shipped to study center upon IXRS shipment request. Lead times differ per country but the shipment will arrive at the study center one day before the

planned treatment at the latest. The responsible unblinded study center personnel will confirm receipt of sponsor-supplied study drug via IXRS.

The unblinded person at the study center 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 center 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 center.

For abiraterone and prednisone / prednisolone:

Abiraterone and prednisone / prednisolone will be shipped to the study center upon IXRS shipment request. The responsible site personnel will confirm receipt of sponsor-supplied study drug in writing and / or via IXRS. A log of this study medication (assigned, dispensed, administered to subjects, returned to site by subject, and destroyed) must be maintained and signed by the dedicated person responsible for drug handling at each center in addition to the completion of the appropriate pages of the eCRF. All study drug packages assigned (opened, unopened, or empty) must be stored until the drug accountability has been completed by the monitor. Based on its mechanism of action, abiraterone acetate may harm a developing fetus; therefore, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection, e.g., gloves.

For isotonic saline (placebo):

Isotonic saline (placebo) will be provided by the study center pharmacy. Drug accountability for saline will also be performed. At a minimum, storage conditions, dispensing, batch numbers, and expiry dates will be retained in the study center files. All study drug packages assigned (opened, unopened, or empty) must be stored until the drug accountability has been completed by the monitor or unblinded monitor (for saline accountability). Thereafter, the packages should be disposed in accordance with the local regulations and the hospital procedure, respectively. A log of locally provided study medication (assigned, dispensed, administered to subjects, returned to study center by subject, and destroyed) must be maintained and signed by the dedicated person responsible for drug handling at each center.

6.7 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 blinded treating physician or blinded site personnel. Only the unblinded monitor will review overall drug accountability and destruction per the site documentation.

Daily intake of abiraterone and prednisone / prednisolone will be the responsibility of the subject or his at-home caregiver, or clinic staff if the subject is hospitalized. Compliance will be monitored by pill counts performed on returned used medication bottles at each study

visit. Pill counts will be recorded on the non-investigational product study dispensing log and on the appropriate eCRF page.

6.8 Post-study treatment therapy

Treatment with radium-223 dichloride / placebo will be halted following completion of the full assigned treatment (6 injections every 4 weeks) or at early termination. Further treatment with abiraterone and prednisone / prednisolone should be continued until the time of disease progression or other withdrawal criteria occur.

At the end of an individual subject's participation in the trial or the EOS, subjects will be treated and followed as per the institutional standard of care and / or according to the physician's clinical judgment. Details of post-study anti-cancer treatment will be recorded on the appropriate eCRF page.

During follow-up, radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone.

In case a subject is still on oral study treatment at the EOS and still benefits based on the investigator's opinion after 7 years of follow-up, options for treatment continuation (e.g., switch to commercial drug supply, a continued access program, or any other means of continued drug supply) will be discussed and agreed between the investigator, sponsor, and the subject in compliance with local regulations.

6.9 Prior and concomitant therapy

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

All concomitant medications taken by the subject from signing of the ICF to 4 weeks after last study drug administration must be recorded in the eCRF. Thereafter, until the end of the active follow-up period, **only** medications given to treat **any grade** AEs **related to the study drug** 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 code all therapy and medication according to well-recognized dictionaries of medical codes.

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

6.9.1 Prohibited concomitant therapy

Abiraterone is administered as part of the study therapy. No other anti-androgen therapies (except LHRH agonists and antagonists, see Section 6.9.2) are permitted.

Subjects receiving bisphosphonates or denosumab prior to randomization may be maintained on such therapy throughout all or part of the study. The bisphosphonate or denosumab treatment may be stopped at the discretion of the investigator. Based on the available data on radium-223 dichloride, the option of starting a bone health agent (BHA) including

bisphosphonates or denosumab should be considered, taking into consideration applicable guidelines.

Other cancer treatment with established efficacy in prostate cancer, including but not limited to cytotoxic chemotherapy, estrogens (e.g., stilbestrol), ketoconazole, other systemic radioisotope or hemibody external radiotherapy, or other investigational drugs, 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 study drug administrations must be discontinued and the subject should enter the active follow-up period.

All medication for the clinical benefit or supportive care for the subject may be provided at the discretion of the investigator.

Note that all treatments for prostate cancer, including other investigational drugs taken after withdrawal from treatment with radium-223 dichloride or placebo, will be recorded in the eCRFs until the end of the active follow-up period without clinic visits.

The following concomitant therapies are **prohibited** during screening, between randomization and the start of treatment, and during the treatment phase of the study:

- Systemic glucocorticoids, unless clinically indicated to treat a life-threatening acute medical condition
- 5 α-reductase inhibitor
- Chemotherapy
- Immunotherapy, e.g., sipuleucel-T
- Bicalutamide, nilutamide, flutamide, enzalutamide
- Systemic ketoconazole (or other azole drugs such as fluconazole and itraconazole)
- Diethylstilbestrol, PC-SPES, and other preparations such as saw palmetto thought to have endocrine effects on prostate cancer
- Radiopharmaceuticals such as strontium-89 or samarium-153
- Aldactone, Spironol (spironolactone)
- Digoxin, digitoxin, and other digitalis drugs
- Cyproterone acetate
- Fludrocortisone acetate (Florinef)

Please note the following **cautions**:

- Caution is advised when abiraterone acetate is administered with drugs activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic index drugs metabolized by CYP2D6 should be considered.
- Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital) during treatment with abiraterone acetate are to be avoided.

- Abiraterone inhibits CYP2C8 in vitro. Subjects should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

During follow-up, radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone.

6.9.2 Permitted concomitant therapy

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

- LHRH agonists or antagonists to maintain testosterone < 50 ng/dL (< 1.7 nmol/L)
- Conventional multivitamins, selenium, and soy supplements
- Additional systemic glucocorticoid administration such as "stress dose" glucocorticoid is permitted if clinically indicated for a life threatening medical condition, and in such cases, the use of steroids will be documented as concomitant drug.
- Bisphosphonates or denosumab usage is allowed. Based on the available data on radium-223 dichloride, the option of starting a BHA including bisphosphonates or denosumab should be considered, taking into consideration applicable guidelines.
- Blood transfusions and treatment with erythropoietin stimulating agents are allowed after randomization (if required to ensure that the treatment range for Hb ≥ 8.0 g/dL is met at Day 1 of each cycle) but not within 4 weeks prior to screening and during the screening period.
- Use of biologic response modifiers, such as G-CSF or GM-CSF, is allowed in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the discretion of the investigator.
- Analgesic use will be captured via electronic patient-reported outcome (ePRO) device and the eCRF (analgesic consumption diary and recorded analgesics, respectively, see schedule of assessments, Table 7–1). Subjects will be asked to track their analgesic use on an ePRO / analgesic consumption diary for 1 week prior to their clinic visit (6 days prior to the visit plus the day of the visit). Each day the pain question is asked of the subject, 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 at each visit. Note that analgesic medication should be recorded in the eCRF until the end of the treatment period while EBRT treatment should be recorded in the eCRFs until end of the active follow-up period without clinic visits.

7. Procedures and variables

7.1 Schedule of procedures

All laboratory values will be conducted by local laboratories.

7.1.1 Tabulated overview

Efficacy and safety measurements obtained during the course of the study are summarized in the schedule of assessments (Table 7–1).

Table 7–1: Schedule of assessments

Study Period	Screening[a]	Treatment[b,c]														End of Active Follow-up		Long-term Follow-up	
		Radium-223 dichloride / Placebo + Abiraterone acetate + Prednisone									Abiraterone acetate + Prednisone		EOT visit					LT FU	End of LT FU
Visit:	**0-1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12+**	**-**					**-**	**-**
Cycle:	**-**	**1**		**2**		**3**		**4**	**5**	**6**	**7**	**8+**	**-**					**-**	**-**
Timing:	**Day -14 to Day 0**	**Day 1**	**Day 15[d]**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 1**	**28 days post-last dose of Ra-223 / PLC**	**q4 wk until disease progression[d,e]**	**4 wk/ 6 mo[f]**					**q6 mo until death[i]**	
Window (days):	**+7**		**±3**	**+7**	**±3**	**+7**	**±3**	**+7**	**+7**	**+7**	**± 7**	**± 7**	**± 7**					**± 14**	
Informed consent[j]	X																		
Subject ID assignment	X																		
Review of eligibility	X																		
Demographic data	X																		
Medical history	X																		
Disease history	X																		
Randomization[a]	X																		
HRQoL NCCN-FACT FPSI-17 form		X		X		X		X	X	X	X								
HRQoL EQ-5D form		X		X		X		X	X	X	X								
BPI-SF[k]	X	X		X		X		X	X	X	X								
Resource utilization questionnaire		X		X		X		X	X	X	X								
AEs, SAEs, new 1° malignancies	X	X	X	X	X	X	X	X	X	X	X	X	X			$X^{m,n}$		$X^{m,n}$	$X^{m,n}$
Bone fracture[o]	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X
Prior and con meds[p]	X	X	X	X	X	X	X	X	X	X	X	X	X			X			

Table 7-1: Schedule of assessments (continued)

Study Period	**Screening[a]**	**Treatment[b,c]**														**End of Active Follow-up**		**Long-term Follow-up**	
		Radium-223 dichloride / Placebo + Abiraterone acetate + Prednisone									**Abiraterone acetate + Prednisone**		**EOT visit**					**LT FU**	**End of LT FU**
Visit:	**0-1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12+**	**-**					**-**	**-**
Cycle:	**-**	**1**		**2**		**3**		**4**	**5**	**6**	**7**	**8+**	**-**					**-**	**-**
Timing:	**Day -14 to Day 0**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 1**	**28 days post-last dose of Ra-223 / PLC**	**q4 wk until disease progression [d,e]**	**4 wk[f]**					**q6 mo until death[i]**	
Window (days):	**+7**		**±3**	**+7**	**±3**	**+7**	**±3**	**+7**	**+7**	**+7**	**± 7**	**± 7**	**± 7**					**± 14**	
Cancer-related tx[q]	X	X	X	X	X	X	X	X	X	X	X	X	X			X[n]		X	X
Analgesic consumption diary (ePRO)[r]		X		X		X		X	X	X	X								
Record 24h analgesic use[r]	X	X		X		X		X	X	X	X								
Vital signs[s]	X	X	X	X	X	X	X	X	X	X	X	X	X			X			
12-lead ECG (at the discretion of the investigator)	X					X			X		X	X	X						
Weight (kg)	X	X[t]	X	X[t]	X	X[t]	X	X[t]	X[t]	X[t]	X	X	X						
Height (cm)	X																		
Physical examination	X	X		X		X		X	X	X	X	X	X			X			
ECOG-PS	X	X		X		X		X	X	X	X	X	X			X			
Hematology[u]	X[v]	X[w]		X[w]		X[w]		X[w]	X[w]	X[w]	X	X	X			X			
Clinical chemistry[x]	X	X[y]	X	X[y]	X	X[y]	X	X[y]	X[y]	X[y]	X	X	X			X			
Coagulation panel[z]	X																		
Serum testosterone (at the discretion of the investigator)	X	X									X								
PSA	X	X		X		X		X	X	X	X	X	X			X			

Table 7-1: Schedule of assessments (continued)

Study Period	**Screening[a]**	**Treatment[b,c]**															**End of Active Follow-up**		**Long-term Follow-up**	
		Radium-223 dichloride / Placebo + Abiraterone acetate + Prednisone										**Abiraterone acetate + Prednisone**		**EOT visit**					**LT FU**	**End of LT FU**
Visit:	**0-1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12+**		**-**			**-**	**-**	**-**	**-**
Cycle:	**-**	**1**		**2**		**3**		**4**	**5**	**6**	**7**	**8+**		**-**			**-**	**-**	**-**	**-**
Timing:	**Day -14 to Day 0**	**Day 1**	**Day 15[d]**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 1**	**28 days post-last dose of Ra-223 / PLC**	**q4 wk until disease progression[d,e]**		**4 wk[f]**					**q6 mo until death[i]**	
Window (days):	**+7**		**±3**	**+7**	**±3**	**+7**	**±3**	**+7**	**+7**	**+7**	**± 7**	**± 7**		**± 7**					**± 14**	
Serum and urine for bone biomarkers[aa]		X							X			X								
Serum and plasma for tumor-related biomarkers[bb]		X																		
Archival prostate cancer tissue sample	←											once								→
ECHO or MUGA scan	X[cc]																			
Technetium-99m bone scan[dd]	X[ee]					X[ff]			X[ff]		X	q12 wk[ff]					X			
Chest, abdominal and pelvic CT scan[ff,gg,hh]	X[ii]					X[ff]			X[ff]		X	q12 wk[ff]					X			
Progression		X	X	X	X	X	X	X	X	X	X	X	X				X			
SSEs	X	X	X	X	X	X	X	X	X	X	X	X	X				X[n]			

Table 7-1: Schedule of assessments (continued)

Study Period	Screening[a]	Treatment[b,c]														End of Active Follow-up		Long-term Follow-up	
		Radium-223 dichloride / Placebo + Abiraterone acetate + Prednisone									Abiraterone acetate + Prednisone		EOT visit					LT FU	End of LT FU
Visit:	**0-1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12+**	**-**					**-**	**-**
Cycle:	**-**	**1**		**2**		**3**		**4**	**5**	**6**	**7**	**8+**	**-**					**-**	**-**
Timing:	**Day -14 to Day 0**	**Day 1**	**Day 15[d]**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 1**	**28 days post-last dose of Ra-223 / PLC**	**q4 wk until disease progression[d,e]**	**4 wk[f]**					**q6 mo until death[i]**	
Window (days):	**+7**		**±3**	**+7**	**±3**	**+7**	**±3**	**+7**	**+7**	**+7**	**± 7**	**± 7**	**± 7**					**± 14**	
Ra-223 order (if applicable)[ii]	X	X		X		X		X	X										
Abi+pred order[ii]	X	X		X		X		X	X	X	X	X							
Survival status	X	X	X	X	X	X	X	X	X	X	X	X	X			X^n		X^n	X^n
Radium-223 Cl_2 or placebo injection[kk]		X		X		X		X	X	X									
Abi+pred		X		X		X		X	X	X	X	X							
PK sampling[ll]			X	X	X														
Drug accountability[mm]		X	X	X	X	X	X	X	X	X	X	X	X						

Abbreviations: abi+pred = abiraterone plus prednisone / prednisolone; AE = adverse event; BPI-SF = brief pain index-short form; Cl_2 = dichloride; con med = concomitant medication; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EOT = end of treatment; ePRO = electronic patient reported outcome; EQ-5D = European quality of life-5 dimensions; HRQoL = health-related quality of life; ID = identification number; IMP = investigational medicinal product; IXRS = interactive voice / web response system; LT FU = long-term follow-up; mo = month; MUGA = multi-gated acquisition; NCCN-FACT FPSI-17 = functional assessment of cancer therapy / National Comprehensive Cancer Network prostate cancer symptom index 17 item questionnaire; PK= pharmacokinetic; PLC = placebo; PRD = patient ready dose; PSA = prostate specific antigen; PT-INR = prothrombin time-international normalized ratio; PTT = partial thromboplastin time; Ra-223 = radium-223 dichloride; q = every; SAE = serious adverse event; SSE = symptomatic skeletal event; tx = treatment; US = United States; wk = week; W/O = without.

a. All screening evaluations must be complete and reviewed prior to randomization. Screening evaluations must be complete within 2 weeks (+ 7 days) prior to randomization. If all screening data are available and the subject is eligible for the study, randomization may occur at the end of the screening visit. In the US, Cycle 1, Day 1 should occur at least 7 days after randomization, whenever possible.
b. All assessments at treatment visits should be performed before study drug administration.
c. Footnote removed in Amendment 7; not applicable after the final OS analysis. .
d. Any unscheduled visits are to be conducted in the same manner as visits described for Visits 12+.
e. Every 4 weeks until the discontinuation of abiraterone as IMP plus prednisone / prednisolone
f. EOT follow-up visit will be conducted 4 weeks after last dose of abiraterone as IMP and prednisone / prednisolone
g. Footnote removed in Amendment 7; not applicable after the final OS analysis.
h. Footnote removed in Amendment 7; not applicable after the final OS analysis.
i. Telephone follow-up every 6 months (± 14 days) for a maximum of 7 years post the last study treatment, until death, or the subject is transitioned to a separate extended safety follow-up study for radium-223 dichloride.
j. Informed consent is to be collected before the initiation of any study-related procedures.
k. Footnote removed in Amendment 7; not applicable after the final OS analysis.
l. All (S)AEs, regardless of grade or relatedness, that occur during the treatment period and up to 4 weeks after the last administration of abiraterone as IMP and prednisone / prednisolone must be reported.
m. All treatment-related AEs and SAEs occurring during the long-term follow-up period are to be documented.
n. It is the clinical site's responsibility to obtain and make available the source documentation for the information collected from the telephone call and to document it in the eCRF.
o. All fractures and bone associated events (e.g., osteoporosis) occurring during the treatment periodand long-term follow up period need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment. Since the definition for measuring skeletal events will not use pre-specified imaging assessments, the use of imaging to identify a fracture or spinal cord compression will be triggered by symptoms. As such, only symptomatic events will be captured. Scans will be read locally.
p. At baseline screening, all prior concomitant medications are to be recorded. Thereafter, collect all concomitant medications up to 4 weeks post last study drug administration. Analgesic use has to be recorded via the analgesic concomitant medication eCRF.
q. Record any cancer-related treatments or medications (including androgen synthesis inhibitors / androgen receptor antagonists; excluding analgesics).
r. Footnote removed in Amendment 7; not applicable after the final OS analysis.
s. The measurement of vital signs will include: blood pressure, heart rate, respiratory rate, and temperature.
t. Subject's weight should be re-checked prior to each injection to calculate appropriate drug dosing. Weight is to be measured within 3 days prior to dosing for non-US sites and 3 to 5 days prior to dosing for US sites. For US sites using the central PRD depot only, the subject weight for the dose day must be reported in a timely manner to the country PRD depot to allow adequate time for the PRD preparation and delivery. 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. Subjects at non-US sites only 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 at US sites will not be measured on the day of dosing.
u. Hematocrit, hemoglobin, platelet counts, red blood cell counts, white blood cell counts, and white blood cell differential. Subjects with abnormal platelet count or white blood cell counts at EOT should be followed until resolution.
v. The screening hematology values are recommended to be measured within 1 week prior to randomization if feasible (a 2-week maximum is permitted) and the first injection should be done as soon as possible after randomization.
w. Blood sample for hematology must be taken, analyzed, and evaluated within 3 days prior to each study drug administration.
x. Sodium, potassium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total alkaline phosphatase, serum creatinine, blood urea nitrogen, bilirubin (total), and albumin.
y. Blood sample for clinical chemistry must be taken within 3 days prior to each study drug administration, but may be evaluated after the administration, if results are not available.

z. Subjects treated with warfarin or heparin will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of PT-INR / PTT will be required until stability is achieved (as defined by local standard of care and based on pre-study PT-INR / PTT values).

aa. Footnote removed in Amendment 7; not applicable after the final OS analysis.

bb. Footnote removed in Amendment 7; not applicable after the final OS analysis.

cc. A MUGA scan or a cardiac ECHO should be obtained. A MUGA scan or cardiac ECHO taken within 4 weeks prior to randomization is acceptable.

dd. Scans to be scheduled for Cycle 3, Day 1, Cycle 5, Day 1, and Cycle 7, Day 1 and then every 12 weeks. Scans will be read locally . The time window for the scans is ± 7 days. If a subject experiences radiological progression, whole body technetium-99m bone scan can be discontinued.

ee. A historic bone scan is acceptable if taken within 4 weeks of randomization. If one is not available, it will be required as part of the protocol procedures within the screening period.

ff. Scans to be scheduled for Cycle 3, Day 1, Cycle 5, Day 1, and Cycle 7, Day 1 and then every 12 weeks until discontinuation of study treatment (except in cases where local regulations apply). The time window for the scans is ± 7 days. If a subject experiences radiological progression, MRI / CT scan of chest, abdomen, and pelvis can be discontinued.

gg. Chest / abdominal / pelvic magnetic resonance imaging will be accepted instead of chest / abdominal / pelvic CT.

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

ii. A historic chest / abdominal / pelvic CT is acceptable if taken within 4 weeks of randomization. If not available, a scan is required as part of the protocol within the screening period.

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

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

ll. For those study sites that participate in abiraterone PK sampling, serial blood samples will be collected for subjects in Subgroup 1 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours post-administration of abiraterone on Cycle 1, Day 8 or Cycle 2, Day 8 only. These samples will undergo non-compartmental analysis. Blood samples for subjects in Subgroup 2 will be collected prior to abiraterone administration on Cycle 1, Days 8 and 15 (Visit 3) and Cycle 2, Days 1 (Visit 4), 8, and 15 (Visit 5). In addition, a second blood sample will be collected for subjects in Subgroup 2 at each of these visits, 0.5 to 3 hours post administration of abiraterone. These samples will undergo population PK analysis.

mm. Based on its mechanism of action, abiraterone acetate may harm a developing fetus; therefore, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection, e.g., gloves.

7.1.2 Timing of assessments

At any time during the study an archival prostate cancer tissue sample should be collected and stored. This sample is only to be collected once.

7.1.2.1 Screening period (Visit 1)

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. Imaging may be done before obtaining informed consent if done routinely. Subjects will not be required to undergo additional scanning if suitable images taken within 4 weeks of randomization are available. Pre-treatment evaluations will be performed according to the eligibility criteria. If the subject is eligible for the study, the parameters at the screening visit showing subject health status, including blood values, will be recorded in the eCRF.

The following procedure and evaluations will be performed within **2 weeks (+ 7 days)** prior to randomization:

- 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 AEs
- Record concomitant medications / therapy
- Record prostate cancer-related treatment (prior and current, including androgen synthesis inhibitors / androgen receptor antagonists; excluding analgesics)
- BPI-SF questionnaire (to be completed using paper)
- Record analgesics
- Perform full physical examination
- 12-lead electrocardiogram (ECG). Potassium levels should be considered when obtaining the ECG. Hypokalemia should be corrected before ECG collection.
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Record height (cm) and weight (kg). The subject's weight should be rechecked prior to each injection to calculate appropriate drug dosing. Weight is to be measured within 3 days prior to dosing for non-US sites and 3 to 5 days prior to dosing for US sites.
- ECOG-PS

- A multi-gated acquisition (MUGA) scan or a cardiac echocardiogram (ECHO) should be obtained. A MUGA scan or cardiac ECHO taken within 4 weeks prior to randomization is acceptable.
- A chest / abdominal / pelvic CT if no suitable images taken within 4 weeks prior to randomization are available. (Chest / abdominal / pelvic MRI will be accepted in place of chest / abdominal / pelvic CT)
- Bone technetium-99m scan with careful identification of all disease-related hotspots, if no scan taken within 4 weeks prior to randomization is available. Any confirmatory scan such as single photon emission tomography (SPECT) or MRI (with and without contrast media) should be obtained or collected if performed within 4 weeks of randomization.
- Blood draw for clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, serum creatinine, blood urea nitrogen (BUN), bilirubin (total), and albumin
- Serum testosterone
- PSA level
- The subjects should be given a handheld electronic device to be used for subject questionnaires and the analgesic consumption diary and should receive training in its use.
- 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
- Record survival status

The following procedures and evaluations should be performed within 1 week prior to randomization unless infeasible (a 2-week maximum timeframe is permitted). Results must be available, reviewed, and signed and dated by the investigator prior to randomization.

- Blood draw for hematology: hematocrit, Hb, PLT, red blood cell (RBC) counts, WBC counts, and WBC differential. If any values are low, transfusions or bone marrow growth factors support are permitted as described in Section 6.9.2.
- A coagulation panel: PT, PTT, and INR. Subjects treated with warfarin or heparin will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of PT-INR / PTT will be required until stability is achieved (as defined by local standard of care and based on pre-study PT-INR / PTT values)

The following should occur 3 to 5 days prior to dosing:

- For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported in a timely manner to the country PRD depot to allow adequate time for PRD preparation and delivery. 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.

Important Note: If rescreening is indicated, it must be completed with approval from the medical monitor of the sponsor. No more than one rescreening attempt will be allowed for each subject. Please refer to Section 5.1 for further guidance on cases in which rescreening is allowed and the time window for rescreening.

7.1.2.2 Randomization

Randomization in the IXRS may occur only after the completion of the screening evaluations and re-confirmation of subject eligibility. Randomization may coincide with the end of a screening visit if all evaluations are complete; otherwise, randomization may be performed in a separate clinic visit. Once the subject is registered in IXRS, the initial drug shipment will be triggered. In the US, Cycle 1, Day 1 should occur at least 7 days after randomization, whenever possible.

7.1.2.3 Treatment period

The treatment period extends from the day of first treatment with radium-223 dichloride / placebo to 4 weeks post the final abiraterone as IMP and prednisone / prednisolone treatment.

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

During the treatment period, the subject will visit the study center at regular intervals. Radium-223 dichloride / placebo will be injected at 4-week intervals for 6 cycles on an out-patient basis (Section 7.1). Abiraterone and prednisone / prednisolone will be taken orally on a daily basis.

It is the responsibility of the unblinded person to calculate the required volume of radioactivity (i.e., dose of radium-223 dichloride or saline placebo) for the subject based on the subject's body weight within 3 days prior to administration for non-US sites and 3 to 5 days prior to administration for US sites and the reference date of the received study medication (Section 6.4.3).

For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported to the country PRD depot in a timely manner to allow adequate time for the PRD preparation and delivery. All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments in order to avoid 2 pre-dose clinic visits.

Before administration of radium-223 dichloride / placebo, the subject must be well hydrated; thus, the subject should be instructed to drink *ad libitum*. The blood samples for clinical chemistry and hematology should be taken within 3 days before each study drug administration, and the hematology parameters must be evaluated before each study drug administration (within 3 days). The Hb level should not be lower than 8.0 g/dL within 3 days before any injection.

If, prior to first injection, the subject has a Hb level of less than 8.0 g/dL, he should not receive study drug and should go directly into the active follow-up period without clinic visits, and may then be transfused if needed.

Between study drug administrations, if Hb levels are below 8 g/dL, the Hb needs to recover to 8.0 g/dL or higher before next study drug administration. If there is more than a 4-week delay in the next injection (i.e., more than 8 weeks between injections), the study drug should be permanently discontinued and the subject should enter the active follow-up period without clinic visits. Treatment of low Hb is acceptable between study drug administrations.

7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)

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

- Review handheld device and ensure subjects complete the following:
    - NCCN-FACT FPSI-17 questionnaire
    - European Quality of Life-5 Dimensions (EQ-5D) questionnaire
    - BPI-SF questionnaire for one week (6 days prior to the dosing visit plus the day of the dosing visit)
- Resource utilization questionnaire (to be completed by the site in the eCRF)
- Recording of analgesic use will be performed by:
    - Analgesic use recorded via the analgesic concomitant medication eCRF
    - Analgesic consumption diary recorded directly on ePRO (handheld device completion to be checked by site) to be filled in by the subjects for one week (6 days prior to the dosing visit plus the day of the dosing visit)
    - Analgesic use during the last 24 hours recorded in eCRF, by site, assessing subject pain medication. Subjects should bring all pain medication to each visit.
- Record AEs and SAEs; all occurrences of bone fractures and bone associated events (e.g., osteoporosis); all occurrences of leukemia, myelodysplastic syndrome, and aplastic anemia; and primary bone cancer or any other new primary malignancy.
    - All the imaging scans that confirmed the diagnosis of fractures should be sent to the independent review center for central review.
- Record concomitant medications / therapy
- Record prostate cancer-related treatment (including androgen synthesis inhibitors / androgen receptor antagonists; excluding analgesics)
- Record weight (kg) (subjects at non-US sites only need to be reweighed on the day of dosing)

- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- 12-lead ECG (Cycle 3, Day 1 and Cycle 5, Day 1). Potassium levels should be considered when obtaining the ECG. Hypokalemia should be corrected before ECG collection.
- Perform full physical examination
- ECOG-PS
- Blood draw for hematology evaluation (within 3 days before radium-223 dichloride or placebo administration): hematocrit, Hb, PLT, RBC count, WBC count, and WBC differential. Results to be assessed and documented prior to study drug treatment. The Hb values need to be confirmed to be at least 8 g/dL prior to each dose.
- Blood draw for clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, creatinine, BUN, bilirubin (total), and albumin (blood sample for clinical chemistry must be taken and evaluated within 3 days prior to each study drug administration). Results should be assessed and documented prior to study drug treatment, if the clinical chemistry results are available.
- Serum testosterone (Cycle 1, Day 1 only) (as of Amendment 7, laboratory confirmation of testosterone level is only done at the discretion of the investigator)
- PSA level
- Blood draws and urine samples for exploratory bone biomarker analysis: serum and urine samples will be collected at Cycle 1, Day 1 and Cycle 4, Day 1.
- Blood draw for exploratory tumor-related biomarker analysis: serum and plasma samples will be collected at Cycle 1, Day 1.
- At Visit 6 (Cycle 3, Day 1) and Visit 9 (Cycle 5, Day 1) only:
    - A chest / abdominal / pelvic CT. The same imaging modalities are to be used as were used at baseline. A chest / abdominal / pelvic MRI will be accepted instead of chest / abdominal / pelvic CT only if MRI chest / abdomen / pelvis was performed at baseline.
    - Bone technetium-99m scan with careful identification of all disease-related hotspots and any confirmatory SPECT or MRI scan (with and without contrast media)
    - Bone scans and CT / MRI scans will be read both locally and by independent assessment.
- Record progression
- 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

- Administer radium-223 dichloride or placebo
- Dispense abiraterone plus prednisone / prednisolone
- Perform drug accountability
- Record survival status

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

- IXRS must be called 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.
- For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported to the country PRD depot in a timely manner to allow adequate time for the PRD preparation and delivery. 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.

For those study sites that participate in abiraterone PK sampling:

- Subjects in Subgroup 1 will return to the site on Cycle 1, Day 8 or Cycle 2, Day 8. Serial blood samples will be collected prior to abiraterone administration and 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours post administration of abiraterone.
- Subjects in Subgroup 2 will return to the site on Cycle 1 Day 8, Cycle 2, Day 1 (Visit 4), and Cycle 2, Day 8 (see also Section 7.1.2.3.2). Blood samples will be collected twice at each of these visits: prior to abiraterone administration and 0.5 to 3 hours post administration of abiraterone.

7.1.2.3.2 Visits 3, 5, and 7 (Cycles 1, 2, and 3, Day 15 ± 3 days)

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

- Record AEs and SAEs, all occurrences of bone fractures and bone associated events (e.g., osteoporosis); all occurrences of leukemia, myelodysplastic syndrome, and aplastic anemia; and primary bone cancer or any other new primary malignancy.
    - All the imaging scans that confirmed the diagnosis of fractures should be sent to the independent review center for central review.
- Record concomitant medications / therapy
- Record prostate cancer-related treatment (including androgen synthesis inhibitors / androgen receptor antagonists; excluding analgesics)
- Recording of analgesic use will be performed by:

- Analgesic use recorded via the analgesic concomitant medication eCRF

- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Record weight
- Blood draw for clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, creatinine, BUN, bilirubin (total), and albumin
- Record progression
- Record SSEs
- Perform drug accountability

For those study sites that participate in abiraterone PK sampling:

- Subjects in Subgroup 2 return to the site on Cycle 1, Day 15 (Visit 3) and Cycle 2, Day 15 (Visit 5) (see also Section 7.1.2.3.1). Blood samples will be collected twice at each of these visits: prior to abiraterone administration and 0.5 to 3 hours post administration of abiraterone.
- Record survival status

7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) and unscheduled visits up until discontinuation of abiraterone as IMP and prednisone / prednisolone

During these visits, subjects will no longer receive treatment with radium-223 dichloride or placebo, but should continue to receive therapy with abiraterone plus prednisone / prednisolone. The following assessments are to be performed on Cycle 7, Day 1 and every 4 weeks thereafter until discontinuation of abiraterone as IMP and prednisone / prednisolone.

- Record AEs and SAEs; all occurrences of bone fractures and bone associated events (e.g., osteoporosis); all occurrences of leukemia, myelodysplastic syndrome, and aplastic anemia; and primary bone cancer or any other new primary malignancy.
- Record concomitant medications / therapy
- Record prostate cancer-related treatment (including androgen synthesis inhibitors / androgen receptor antagonists; excluding analgesics)
- Full physical examination
- At the discretion of the investigator, a 12-lead ECG can be ordered, if deemed necessary. Potassium levels should be considered when obtaining the ECG. Hypokalemia should be corrected before ECG collection.
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Record weight
- ECOG-PS

- Blood draw for hematology: hematocrit, Hb, PLT, RBC count, WBC count, and WBC differential
- Blood draw for clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, creatinine, BUN, bilirubin (total), and albumin
- Serum testosterone (Cycle 7, Day 1 only) (at the discretion of the investigator)
- PSA level
- Starting at Visit 11 (Cycle 7, Day 1):
    - A chest / abdominal / pelvic CT scan every 12 weeks (± 7 days). The same imaging modalities are to be used as were used at baseline. An abdominal / pelvic MRI will be accepted instead of abdominal / pelvic CT scan only if MRI abdomen / pelvis was performed at baseline.*
    - Bone technetium-99m scan every 12 weeks (± 7 days) with careful identification of all disease related hotspots*

      **except in cases where local regulations apply*
    - Note: Bone scans and CT / MRI scans will be read locally
- Record progression
- Record SSEs
- Dispense abiraterone plus prednisone / prednisolone until termination of treatment as IMP
- Perform drug accountability
- Record survival status

7.1.2.3.4 End of treatment visit

An EOT visit will be performed within 4 weeks (± 7 days) post discontinuation of abiraterone as IMP and prednisone / prednisolone and the subject will proceed to the long-term follow-up

After the final OS analysis, the following procedures / evaluations should be performed at this visit:

- Record AEs and SAEs
- 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 all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy
- Record concomitant medications / therapy for 4 weeks after the last study drug administration

- Record prostate cancer-related treatment (including androgen synthesis inhibitors / androgen receptor antagonists; excluding analgesics)
- Perform full physical examination
- At the discretion of the investigator, a 12-lead ECG can be ordered, if deemed necessary. Potassium levels should be considered when obtaining the ECG. Hypokalemia should be corrected before ECG collection.
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Record weight
- ECOG-PS
- Blood draws for hematology: hematocrit, Hb, PLT, RBC counts, WBC counts, and WBC differential
- Blood draws for clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, creatinine, BUN, bilirubin (total), and albumin
- Serum testosterone (at the discretion of the investigator)
- PSA level
- Record progression
- Record SSEs
- Perform drug accountability
- Site staff should record the answer to the following question: What treatment arm do you believe this subject was on?
- Record survival status

If subjects cannot travel to the clinical site due to deterioration of disease, the EOT visit will be replaced by a follow-up telephone call from the clinical site. Adverse events; all occurrences of bone fractures and bone associated events (e.g., osteoporosis); information on all occurrences of leukemia, myelodysplastic syndrome, and aplastic anemia; and primary bone cancer or any other new primary malignancy, as well as any anti-cancer therapies, will be discussed and captured in the eCRFs. Since this information will be collected over the telephone from the subject, it is the clinical site's responsibility to obtain and make available the source documentation for the information collected from the subject and document it in the eCRF.

7.1.2.4 Active follow-up

After the final OS analysis (Amendment 7), subjects who are discontinued from study treatment will initiate the long term follow-up period; therefore, active follow-up periods will no longer be applicable. Subjects who are in active follow-up at the time Amendment 7 is implemented should have the end of active follow-up completed (protocol driven decision)

and should be directly transitioned into the extended safety follow-up study. For additional information, please refer to Section 13.5.

7.1.2.4.1 Active follow-up with clinic visits assessments (Every 12 weeks ± 7 days at each visit)

Section removed in Amendment 7

7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)

Section removed in Amendment 7

7.1.2.4.3 End of active follow-up

After the final OS analysis (Amendment 7), the procedures for subjects who complete the active follow-up will include:

- All AEs and SAEs must be documented and reported if considered to be related to study medication or study-related procedures.
- All bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs regardless of the investigator's causality assessment. The anti-cancer therapies associated with these events will be collected. If a subject is unable to provide required details for events of interest, this information may need to be obtained from the primary provider.
- Record concomitant medications / therapy only if used to treat adverse drug reaction (any grade)
- Record prostate cancer-related treatment (including androgen synthesis inhibitors / androgen receptor antagonists; excluding analgesics)
- Perform full physical examination
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- ECOG-PS
- Blood draws for hematology: hematocrit, Hb, PLT, RBC counts, WBC counts, and WBC differential
- Blood draws for clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, creatinine, BUN, bilirubin (total), and albumin
- PSA level
- Record progression

- Record SSEs
- Record survival status
- A chest / abdominal / pelvic CT. The same imaging modalities are to be used as were used at baseline. An abdominal / pelvic MRI will be accepted instead of abdominal / pelvic CT only if MRI abdomen / pelvis was performed at baseline.
- Bone technetium-99m scan with careful identification of all disease-related hotspots and any confirmatory SPECT or MRI scan (with and without contrast media)

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

Subjects who are in active follow-up at the time of Amendment 7 should have the end of active follow-up completed (protocol driven decision) and should be directly transitioned into the extended safety follow-up study. For additional information, please refer to Section 13.5.

7.1.2.5 Long-term follow-up

After the final OS analysis (Amendment 7), this period will start when subjects have discontinued study treatment, and will end when the subject has completed 7 years of follow-up, dies, is lost to follow-up, withdraws informed consent, actively objects to collection of further data, or is transitioned to the extended safety follow-up study.

Once a separate extended safety follow-up protocol for the inclusion of subjects who received radium 223 dichloride / placebo in the course of Bayer sponsored clinical trials, has been implemented, the study subjects who are in active or long-term follow-up will be transitioned to a separate extended safety follow-up study in order to complete 7 years of safety follow-up. All efforts will be made to transition all subjects to the extended safety follow-up study.

The EOS is defined as the date of the LSLV in the study. The EOS will occur at the time the last subject on study completes 7 years of follow-up unless the subject dies, withdraws consent or is lost to FU.

In case a subject is still on oral study treatment and still benefits based on the investigator's opinion after 7 years of follow-up, options for treatment continuation (e.g., switch to commercial drug supply, a continued access program, or any other means of continued drug supply) will be discussed and agreed between the investigator, sponsor, and the subject in compliance with local regulations. For each participating European Union (EU) country, the EOS according to the EU Clinical Trial Directive will be reached when the LSLV in any center has occurred.

7.1.2.5.1 Long-term follow-up (telephone follow-up)

Subjects will be contacted by telephone every 6 months (± 14 days) to determine the following:

- Record survival status

- All AEs and SAEs must be documented and reported if considered to be related to study medication or study-related procedures
- All bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs regardless of the investigator's causality assessment. The anti-cancer therapies associated with these events will be collected. If a subject is unable to provide required details for events of interest, this information may need to be obtained from the primary provider.
- Record prostate cancer-related treatment (including androgen synthesis inhibitors / androgen receptor antagonists; excluding analgesics)

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

7.1.2.5.2 End of long-term follow-up

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

- Record survival status
- All AEs and SAEs must be documented and reported if considered to be related to study medication or study-related procedures.
- All bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs regardless of the investigator's causality assessment. The anti-cancer therapies associated with these events will be collected. If a subject is unable to provide required details for events of interest, this information may need to be obtained from the primary provider.
- Record prostate cancer-related treatment (including androgen synthesis inhibitors / androgen receptor antagonists; excluding analgesics)

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

7.1.2.6 End of study

The EOS is defined as the date of the LSLV in the study. The EOS will occur at the time the last subject on study completes 7 years of follow-up unless the subject dies, withdraws consent or is lost to FU.

In case a subject is still on oral study treatment and still benefits based on the investigator's opinion after 7 years of follow-up, options for treatment continuation (e.g., switch to commercial drug supply, a continued access program, or any other means of continued drug supply) will be discussed and agreed between the investigator, sponsor, and the subject in compliance with local regulations.

Note:

- If the study is terminated by the sponsor and the latest follow-up visit has taken place within the previous 3 months, the end of follow-up will be the date of the latest follow-up.
- If subjects are receiving subsequent treatments with radium-223 dichloride as part of non-Bayer studies such as investigator-sponsored studies or through commercially available drugs, follow-up and data collection should continue in the 15396 study until the subject's death or termination of the program by the sponsor.

7.2 Population characteristics

7.2.1 Demographic

The following demographic characteristics will be collected:

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

7.2.2 Medical history

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

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study

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

7.2.3 Other baseline characteristics

The following other baseline characteristics will be collected:

- Date of prostate cancer diagnosis

- Date of diagnosis of metastatic prostate cancer
- Stage of prostate cancer at diagnosis
- Treatment of prostate cancer before enrollment (e.g., surgery, radiation)
- Gleason score at diagnosis of prostate cancer
- PSA and total ALP at diagnosis of prostate cancer
- Weight (kg)
- Vital signs: blood pressure (mmHg), heart rate, respiratory rate, and temperature (°C)
- ECOG-PS
- Cancer pain assessment
- Laboratory assessments
    - Hematology: hematocrit, Hb, PLT, RBC count, WBC count, and WBC differential
    - Clinical chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, total ALP, creatinine, BUN, total bilirubin, and albumin
    - PSA
    - Testosterone

7.3 Efficacy

7.3.1 Efficacy variables

The primary efficacy variable is:

- SSE-FS

The secondary efficacy variables are specified below:

- OS
- Time to opiate use for cancer pain*
- Time to pain progression*
- Time to cytotoxic chemotherapy*
- rPFS*

Exploratory efficacy variables are:*

- Time to first on-study SSE*
- Percentage change in total ALP from baseline*
- Time to ALP progression*
- Time to PSA progression*

- ALP response*
- PSA response*
- Bone scan-specific rPFS*
- Time to increase in physical symptoms of disease based on the FPSI-DRS-P subscale score measured during the treatment period*
- Time to increase in physical symptoms of disease based on the FPSI-DRS-P subscale score measured during the period between start of treatment and end of active follow-up with clinic visit.*

Note: Variables indicated with an asterisk (*) including all exploratory variables will not be assessed following final OS analysis.

7.3.2 Definition of efficacy variables

7.3.2.1 Primary endpoint

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

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

- the use of EBRT to relieve skeletal symptoms
- the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)
- the occurrence of spinal cord compression
- a tumor-related orthopedic surgical intervention.

(2) Death from any cause

7.3.2.2 Secondary efficacy endpoints

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

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

Time to opiate use will be determined by analgesic use captured via ePRO device and / or the eCRF (analgesic consumption diary and recorded analgesics, respectively, see schedule of assessments).

Time to pain progression is defined as the interval from randomization to the first date a subject experiences pain progression based on WPS:

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

OR

initiation of short- or long-acting opioid use for pain.

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

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

OR

initiation of short- or long-acting opioid use for pain.

Assessments will occur daily for one week (including the visit date). An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 daily questions. Subjects who have not experienced pain progression at the time of analysis will be censored on the last date the subject was known to have not progressed. Subjects with no on-study assessment or no baseline assessment will be censored at the date of randomization. The BPI-SF (Section 14.9) is a short, self-administered questionnaire with 11 items, which was designed to evaluate the intensity of, and the impairment caused by pain. All BPI-SF items are scored using rating scales. Four items measure pain intensity (pain now, average pain, worst pain, and least pain) using 0 ("no pain") to 10 ("pain as bad as you can imagine") numeric rating scales, and 7 items measure the level of interference with function caused by pain (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) using 0 (no interference) to 10 (complete interference) rating scales.

The items are aggregated into 2 dimensions: (1) Pain severity index, using the mean of the 4 items on the pain intensity, and (2) Function interference index, using the mean of the 7 pain interference items. All 4 severity items must be completed for aggregating the pain severity index. The function interference index is scored as the mean of the item scores multiplied by 7, given that more than 50% or 4 of 7, of the items have been completed.

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

Radiological progression-free survival is defined as the time (days) from the date of randomization to the date of confirmed radiological progression or death (if death occurs before progression). Subjects without confirmed radiological progression or death at the time

of analysis will be censored at their last date of radiological tumor assessment (see statistical analysis plan [SAP] for detailed censoring rules). Bone scans (i.e., whole body technetium-99m bone scan) and CT / MRIs will be read both locally and by blinded independent central assessment. If there is an inconsistency between local assessment and central review, then the assessment will be based on central review. If progression is detected by bone scan, a confirmatory scan is required at least 6 weeks later. A single SPECT or MRI (with and without contrast media) should be obtained to confirm any suspicious bone scan findings. The date of confirmed radiological progression will be the date of first observation of radiological progression. Radiological progression is determined if at least one of the following criteria is met:

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

If bone scans are repeated the best scan should be submitted to the core imaging lab as per judgment of the site.

A mask should be placed over the bladder during interpretation to facilitate detection of lesions in the pelvis. If the bladder obscures the pelvis, oblique images of the pelvis should be obtained. If there is concern over underlying bone lesions, a SPECT scan may be performed. Subjects should void before bone scan or, alternatively, may need a urinary catheter placed for bladder drainage.

Progression in soft tissue and occurrence of visceral disease will be assessed by CT or MRI every 8 weeks (± 7 days) then every 12 weeks (± 7 days) based on RECIST 1.1. CT or MRI scans will be read both locally and by blinded independent central assessment. The RECIST will be used to assess soft tissue and visceral disease only. Bone lesions detected by CT or MRI cannot be selected as target or non-target lesions. Bone lesions will be evaluated by bone scans.

Note: Following the final OS analysis, images will only be read locally and confirmatory scans will no longer be necessary to document progression. The date of radiological progression will be the date of first observation of radiological progression.

7.3.2.3 Exploratory efficacy endpoints

Note: Exploratory efficacy endpoints will not be assessed following the final OS analysis.

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

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

Time to ALP progression is defined as the time (days) from the date of randomization to the date of first ALP progression. Alkaline phosphatase progression is defined as a ≥ 25% increase from the baseline value, at least 12 weeks from baseline in subjects with no ALP decline from baseline; or a ≥ 25% increase above the nadir value, which is confirmed by a second value obtained 3 or more weeks later in subjects with an initial ALP decline from baseline.

Time to PSA progression is defined as the time (days) from the date of randomization to the date of first PSA progression. Prostate specific antigen progression is defined as ≥ 25% increase from the baseline value and an increase in absolute value of ≥ 2 ng/mL, at least 12 weeks from baseline in subjects with no PSA decline from baseline; or ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir value, which is confirmed by a second value obtained 3 or more weeks later in subjects with an initial PSA decline from baseline.

Alkaline phosphatase response is defined as ≥ 30% reduction of the blood level, compared to the baseline value. Confirmed ALP response is defined as a ≥ 30% reduction of the blood level, compared to the baseline value, confirmed by a second ALP value 4 or more weeks later. ALP responses will be evaluated at Weeks 12 and 24 after treatment is started.

Prostate specific antigen response is defined as ≥ 30% reduction of the blood level, compared to the baseline value. A confirmed PSA response is defined as ≥ 30% reduction of the blood level, compared to the baseline value, confirmed by a second PSA value 4 or more weeks later. PSA responses will be evaluated at Weeks 12 and 24 after treatment is started.

Radiological progression free survival based on bone scans (bone rPFS) is defined as the time (days) from the date of randomization to the date of confirmed radiological progression detected by bone scans or death (if death occurs before progression). Subjects without confirmed radiological progression or death at the time of analysis will be censored at their last date of radiological tumor assessment (see the SAP for detailed censoring rules). Bone scans will be read both locally and by blinded independent central assessment. If there is an inconsistency between local assessment and central review, then the assessment will be based on central review. If progression is detected by bone scan, a confirmatory scan is required at least 6 weeks later. The date of confirmed radiological progression will be the date of first observation of central assessment of radiological progression. Radiological progression is determined if at least one of the following criteria is met:

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

If bone scans are repeated the best scan should be submitted to the core imaging lab as per judgment of the site.

A mask should be placed over the bladder during interpretation to facilitate detection of lesions in the pelvis. If the bladder obscures the pelvis, oblique images of the pelvis should be obtained. If there is concern over underlying bone lesions, a SPECT scan may be performed. Subjects should void before bone scan or, alternatively, may need a urinary catheter placed for bladder drainage.

Time to increase in physical symptoms of disease based on the FPSI-DRS-P subscale score measured during the treatment period will be assessed using the NCCN-FACT FPSI-17 questionnaire (Section 14.7**).**

The NCCN-FACT FPSI-17 is a validated instrument that was developed to assess symptoms prostate cancer, symptoms of treatment of prostate cancer, and HRQoL of prostate cancer patients.(52) The instrument was developed in accordance with recent FDA guidance for development of instruments for ePRO. The instrument contains 17 items, each of which utilize a Likert scale with 5 possible responses. The 10 items reflect disease-related physical symptoms of disease and the responses on the items are to be summed to calculate a disease-related physical symptom subscale score. One item represents emotion symptom of disease and the response to that item is used to calculate a disease-related emotional symptom subscale score. Four items represent treatment-related symptoms and the responses to these items are summed to calculate a treatment side effect subscale score. Finally, 2 items represent functional well-being and responses to those items are summed to calculate a functions / well-being subscale score.

The NCCN-FACT FPSI-17 will be self-administered by the subject via ePRO device. Some subjects may skip an item altogether if they feel that it is not applicable to them.

Time to increase in physical symptoms of disease based on the FPSI-DRS-P subscale score measured during the period from start of treatment to end of active follow-up with clinic visits will be assessed using the NCCN-FACT FPSI-17 questionnaire (Section 14.7).

The NCCN-FACT FPSI-17 is a validated instrument that was developed to assess symptoms of prostate cancer, symptoms of treatment of prostate cancer, and HRQoL of prostate cancer patients.(52) The instrument was developed in accordance with recent FDA guidance for development of instruments for ePRO. The instrument contains 17 items, each of which utilize a Likert scale with 5 possible responses. The 10 items reflect disease-related physical symptoms of disease and the responses on the items are to be summed to calculate a disease-related physical symptom subscale score. One item represents emotional symptoms of disease and the response to that item is used to calculate a disease-related emotional symptom subscale score. Four items represent treatment-related symptoms and the responses to these items are summed to calculate a treatment side effect subscale score. Finally, 2 items represent functional well-being and responses to those items are summed to calculate a functions / well-being subscale score.

The NCCN-FACT FPSI-17 will be self-administered by the subject via ePRO device. Some subjects may skip an item altogether if they feel that it is not applicable to them.

7.4 Pharmacokinetics (selected sites only)

Note: Pharmacokinetic data will not be assessed following final OS analysis.

7.4.1 Drug measurement

Pharmacokinetics of radium-223 dichloride will not be evaluated in this study; however, the PK of abiraterone will be investigated in 2 subgroups. In each subgroup, 40 subjects (approximately 20 per treatment arm) will be enrolled. Blood samples will be collected at pre-defined times as specified below.

The following time ranges are provided:

- for planned time points ≤ 6 hours, PK samples should be collected within ± 15 minutes of the planned time
- for planned time points > 6 hours, PK samples should be collected within ± 30 minutes

Subgroup 1 (Non-compartmental analysis):

Serial blood samples will be collected at the following time points: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours post-abiraterone administration, 1 week after the first or second administration of radium-223 dichloride / placebo (collection on Cycle 1, Day 8 or Cycle 2, Day 8).

Sampling times outside these suggested intervals will not be considered to be protocol deviations. It is of importance that the actual date and time of blood sampling are documented in the eCRF because PK calculations will be based on the actual sampling times relative to dosing times.

Subgroup 2 (Population PK analysis):

Blood samples will be collected prior to the abiraterone administration at Cycle 1, Days 8 and 15 (Visit 3) and Cycle 2, Days 1 (Visit 4), 8, and 15 (Visit 5). In addition, a second blood sample will be collected at each of these visits within the time window of 0.5 to 3 hours post abiraterone administration.

Plasma will be prepared from the collected blood samples and analyzed using a validated analytical method for abiraterone.

Special Meal Instruction:

For the 3 nights preceding each PK visit, subjects must have an overnight fast (approximately 10 hours) before taking abiraterone. Subjects should not eat until 1 hour after abiraterone dosing. Food intake prior to the PK fasting periods should be recorded in the eCRF.

Detailed instructions for sample collection and handling will be provided in a Laboratory Manual.

7.4.2 Pharmacokinetic evaluation

Subgroup 1:

Pharmacokinetic parameters will be calculated using a non-compartment approach. Based on the plasma concentration time data, the following PK parameters will be calculated for

abiraterone 1 week after the first or second administration of radium-223 dichloride / placebo:

- Maximum concentration at a steady state
- Time to maximum concentration at a steady-state
- Area under the curve from zero to 24 hours

Subgroup 2:

A population PK analysis of plasma concentration-time data of abiraterone will be performed to assess the similarity or difference in PK of abiraterone between subjects treated with radium-223 dichloride plus abiraterone and prednisone / prednisolone and placebo plus abiraterone and prednisone / prednisolone using nonlinear mixed-effects modeling. The population PK modeling will include all subjects with sufficient and interpretable PK assessments. The data from Subgroup 2 will be combined together with the data from Subgroup 1 for the analysis. The effect of diarrhea on the PK of abiraterone may be explored. The population PK analysis results will be presented in a separate report.

7.5 Safety

Safety variables

Safety variables will include the analysis of acute and long-term effects and the appearance of new primary malignancies. The complete list of variables to be analyzed for this study will be provided in the SAP.

All subjects who receive at least one dose of study drug will be valid for safety analysis. All AEs will be reported and graded according to NCI-CTCAE v4.0. Laboratory evaluations, vital signs, and changes in physical examination findings will also be assessed.

7.5.1 Adverse events

7.5.1.1 Definitions

Adverse event

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

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

The clinical manifestation of any failure of expected pharmacological action is not recorded as an AE if it is already reflected as a data point captured in the eCRF. If, however, the event fulfills any of the criteria for a SAE (see below) then it must be recorded and reported as such. If PD leads to signs and symptoms that meet the serious criteria (i.e., hospitalization,

disability, death, or important medical event), the signs and symptoms must be reported as a SAE and not the underlying disease (i.e., PD).

Adverse event versus medical history

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

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are considered as **medical history** (e.g., seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are considered as **medical history** (e.g., allergic pollinosis).
- Symptoms that were present prior to signing of informed consent but for which the diagnosis was confirmed after signing of informed consent should be documented as **medical history**.
- Conditions that started or deteriorated after signing of informed consent will be documented as **adverse events**.

Serious adverse event

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

a. Results in death

b. Is life-threatening

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

c. Requires in-subject hospitalization or prolongation of existing hospitalization

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

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
  (i.e., elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE
  (e.g., social hospitalization for purposes of respite care).

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

d. Results in persistent or significant disability / incapacity

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

e. Is a congenital anomaly / birth defect

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

7.5.1.2 Classifications for adverse event assessment

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

7.5.1.2.1 Seriousness

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

7.5.1.2.2 Intensity

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

7.5.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no"

An assessment of "no" would include:

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

Or

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

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

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

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Subject's response after de-challenge or subject's response after

re-challenge should be considered in the view of the usual clinical course of the event in question.

- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and PK of the study treatment: The PK properties (absorption, distribution, metabolism, and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s). Possible answers are "yes" or "no"

7.5.1.2.4 Action taken with study treatment

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

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

7.5.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

7.5.1.2.6 Outcome

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

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

- Fatal
- Unknown

7.5.1.3 Assessments and documentation of adverse events

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the trial), requiring treatment, causing apparent clinical manifestations, or judged as relevant by the investigator should be reported as an AE. Each event should be described in detail along with start and stop dates (onset and resolution of event), intensity, temporal and causal relationship to investigational product and / or protocol-related procedures, possible alternative factors (co-morbidities, co-medications), therapeutic action taken, result of therapeutic action, and ultimate outcome of the AE.

All (S)AEs, regardless of grade or relatedness, that occur during the treatment period and up to 4 weeks after the last administration of abiraterone as IMP and prednisone / prednisolone or 6 months after the last administration of radium-223 dichloride / placebo, whichever occurs later, unless a new anti-cancer therapy is initiated, must be reported in the appropriate eCRF (SAEs must be reported within 24 hrs of the investigator's awareness). If more than one AE occurs, each event should be recorded separately. All AEs and SAEs are to be followed until resolved or as clinically required.

All AEs and SAEs occurring after the EOT visit until the EOS must be documented and reported if considered to be related to study medication. *However, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs at any time, and regardless of the investigator's causality assessment*.

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. All the imaging scans that confirmed the diagnosis of fractures should be sent to the independent review center for central review.

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

Note: After Amendment 7, scans will only be read locally.

7.5.1.4 Reporting of serious adverse events

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

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

Investigator's notification of the sponsor

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

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

Additionally, all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy must be reported as SAEs at any time, and regardless of the investigator's causality assessment (Section 7.5.1.3). 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. All the imaging scans that confirmed the diagnosis of fractures should be sent to the independent review center for central review. Grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as a SAE, specifically when they are allowed or not excluded by the protocol inclusion / exclusion criteria. If an investigator is in doubt about the applicable reporting obligations, he / she should consult with the medical monitor.

For subjects who die after the treatment period defined in Section 7.5.1.3, submission of the AE page of the eCRF is not required. However, the SAE Complementary Form should be submitted to the applicable Bayer HealthCare Pharmacovigilance department if the death is considered related to study treatment. In addition, this death information will also be collected in the end of active follow-up page of the eCRF.

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

Note: After Amendment 7, scans will only be read locally.

Notification of the independent ethics committees/ institutional review boards

Notification of the independent ethics committees / institutional review boards (IECs / IRBs) about all relevant events (e.g., SAEs, SUSARs) will be performed by the sponsor and / or by the investigator according to all applicable regulations.

Notification of the authorities

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

Sponsor's notification of the investigational study center

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

7.5.1.5 Expected adverse events and suspected unexpected adverse reactions

For this study, the most current version of the IB for radium-223 dichloride will be the reference document for the determination of whether an AE is expected or unexpected. Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating study centers. The applicable reference document for abiraterone and prednisone / prednisolone is the most current summary of product characteristics.

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

7.5.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a study subject's partner, during the subject's participation in this study. The report should be submitted within the same timelines as a SAE, although a pregnancy per se is not considered a SAE.

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

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

7.5.3 Symptomatic skeletal events

A SSE is defined as:

- The use of EBRT to relieve skeletal symptoms
- The occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)
- The occurrence of spinal cord compression
- A tumor-related orthopedic surgical intervention

7.6 Other procedures and variables

Other exploratory variables including self-reported health status scores, and biomarkers will not be assessed following final OS analysis.

Other exploratory variables that will be explored in this study are utility scores and self-reported health status scores based on EQ-5D, NCCN-FACT FPSI-17 disease-related symptoms - emotional subscale score, resource utilization, and assessment of biomarkers.

7.6.1 Self-reported health status

Patient reported outcomes will also be assessed with the EQ-5D questionnaire at each study visit during each visit when treatment is administered and at each in-clinic follow-up visit.

The EQ-5D questionnaire (Section 14.8) developed by the HRQoL group is a generic, standardized instrument that provides a simple, descriptive profile and a single index value

for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. The EQ-5D comprises 5 health dimensions of health: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension consists of 3 levels of response to reflect the degree of problems subjects have experienced: no problem (level 1), some problems (level 2), and extreme problems (level 3), generating a total of 243 theoretically possible health states.

These 5 health dimensions are summarized into a single score, the EQ-5D index score. The EQ-5D index score ranges between 0 and 1, with 0 representing the worst imaginable health state or death and 1 representing perfect health. This questionnaire also contains a European Quality-Visual Analogue Scale (EQ-VAS), which records the respondents self-rated health status on a vertical graduated visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). On average, it requires 5 minutes to complete the questionnaire.

The NCCN-FACT FPSI-17 (Section 14.7) is a validated instrument that was developed to assess symptoms of prostate cancer, symptoms of treatment of prostate cancer, and HRQoL of prostate cancer patients.(54) The instrument was developed in accordance with recent FDA guidance for development of instruments for ePRO. The instrument contains 17 items, each of which utilize a Likert scale with 5 possible responses. The 10 items reflect disease-related physical symptoms of disease and the responses on the items are to be summed to calculate a disease-related physical symptom subscale score. One item represents emotional symptoms of disease and the response to that item is used to calculate a disease-related emotional symptom subscale score. Four items represent treatment-related symptoms and the responses to these items are summed to calculate a treatment side effect subscale score. Finally, 2 items represent functional well-being and responses to those items are summed to calculate a functions / well-being subscale score.

The NCCN-FACT FPSI-17 will be self-administered by the subject via ePRO device. Some subjects may skip an item altogether if they feel that it is not applicable to them.

7.6.2 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 14.10).

7.6.3 Biomarker assessments

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

7.6.3.1 Urine, serum, and plasma based biomarker analysis

Blood samples will be obtained from all subjects at the following time points: Cycle 1, Day 1 (Visit 2), Cycle 4, Day 1 (Visit 8), Cycle 7, Day 1 (i.e., 28 days post-last dose of radium-223 dichloride / placebo), Cycle 13, Day 1, and at EOT or disease progression, whichever occurs first. Urine samples will be collected on Cycle 1, Day 1 (Visit 2), Cycle 4, Day 1 (Visit 8), Cycle 7, Day 1, and at EOT or disease progression, whichever occurs first.

Urine and serum from blood samples (Cycle 1, Day 1, Cycle 4, Day 1, Cycle 7, Day 1 [i.e., 28 days post-last dose of radium-223 dichloride / placebo], and EOT / disease progression) may be evaluated for expression levels of bone-related biomarkers. Elevated levels of bone biomarkers are indicative for e.g., more aggressive disease and are prognostic of worse long-term clinical outcome. In this study, levels of bone biomarkers (measured before, during, and after treatment) that are indicative of bone remodeling (e.g., ALP and bone ALP) and bone resorption (e.g., n-telopeptide, c-telopeptide, carboxyterminal telopeptide of type I collagen, procollagen I N-terminal propeptide, and osteocalcin) may be evaluated and correlated with clinical outcomes (including SSEs, survival, and levels of other biomarkers).

In addition, serum and plasma samples (Cycle 1, Day 1, Cycle 13, Day 1, and EOT / disease progression) may be used to analyze levels of circulating messenger ribonucleic acid (mRNA) / micro-ribonucleic acid (miRNA) and anomalies of tumor-related genes. Analyses will not include germline genetic mutations. The genes of interest will include genes in androgen / androgen receptor (AR) signaling axis (AR and its splice variants, AR-regulated genes, cell cycle genes, steroidogenic genes, etc.) and other genes relevant to abiraterone resistance or prostate cancer.

7.6.3.2 Tumor based biomarker analysis

Archival formalin-fixed, paraffin-embedded (FFPE) tumor samples will be requested from all subjects. If a tissue block cannot be sent, unstained slides containing FFPE tumor tissue will be accepted.

Requests to return any unused tumor tissue material at study completion will be honored.

Tumor tissue may be used for global or targeted mRNA and miRNA expression profiling. The genes of interest will include genes in androgen / AR signaling axis or other genes relevant to abiraterone resistance or prostate cancer. Data from expression profiling of mRNA and miRNA may be compared to data obtained from prior studies, e.g., in chemotherapy-naïve CRPC, newly-diagnosed metastatic prostate cancer (M1), or primary prostate cancer to identify RNA profiles that correlate with clinical outcome. Data may also be combined from similar data collected in other studies to further characterize the diverse biology of prostate cancer with the anticipation that the disease may be segmented into major subtypes.

In addition, tumor-related DNA analysis, such as targeted or whole exome sequencing of tumor DNA, may be performed to characterize somatic anomalies that are associated with clinical outcome to abiraterone or to prognosis of prostate cancer.

Detailed instructions for sample collection and handling will be provided in a Laboratory Manual.

7.7 Appropriateness of procedures / measurements

The procedures chosen for the evaluation of safety in this study population are consistent with the appropriate and ethical standards used in phase III trials of oncology drugs.

Procedures and variables following OS analysis are appropriate for safety follow-up and limited efficacy.

8. Statistical methods and determination of sample size

8.1 General considerations

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

- Geographical regions (Western Europe / North America / Australia versus Asia versus rest of world)
- Concurrent use of denosumab or bisphosphonates or none
- Total ALP < 90 U/L versus total ALP ≥ 90 U/L

To prevent sparse data, strata for current use of denosumab and current use of bisphosphonates will be combined in all stratified analysis for this study.

Exploratory analysis of the primary variable will be performed for each subgroup for individual stratification factors.

Statistical analysis will be performed using Statistical Analysis System (SAS); the version used will be specified in the SAP. Analysis details for all efficacy and safety endpoints will be specified in the SAP.

8.2 Analysis sets

The following 3 populations will be analyzed:

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

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

PK set: All subjects in Subgroup 1 with a valid PK profile for abiraterone will be included in the PK set.

8.3 Efficacy variables

Definition for each variable is given in Section 7.3.

The primary efficacy variable is SSE-FS.

The secondary efficacy variables following final OS analysis are specified below:

- OS

No other secondary and exploratory efficacy variables will be assessed following final OS analysis.

8.4 Statistical and analytical plans

8.4.1 Primary efficacy analysis

The overall 2-sided type I error rate for the analysis of primary efficacy endpoint SSE-FS is 0.05.

The hypotheses to be tested are:

H_0: S Radium-223 dichloride = S Placebo

H_a: S Radium-223 dichloride ≠ S Placebo,

where S is the survival distribution.

The SSE-FS will be analyzed using a stratified log-rank test with the same stratification factors as for randomization. The HR (radium-223 dichloride / placebo) will be computed together with the 2-sided 95% CI using a Cox regression model stratified by the same factors. Kaplan-Meier estimates and plots for both treatment groups will be produced to accompany these analyses.

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

8.4.2 Secondary efficacy analysis

Secondary efficacy endpoints are specified in Section 7.3.

Each secondary variable will be tested using an overall 2-sided alpha of 0.025.

The secondary efficacy time-to-event endpoints will be analyzed using a stratified log-rank test, with the factors from the randomization used for stratification. An HR with a 95% CI from a stratified Cox proportional hazards model will also be provided. Kaplan-Meier plots will be produced to accompany these analyses.

8.4.3 Safety analysis

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

8.4.4 Pharmacokinetic data

No pharmacokinetic data will be assessed following final OS analysis.

Statistical analysis will be done only for Subgroup 1; Subgroup 2 PK analysis results will be presented in a separate report.

The concentration-time courses of abiraterone will be tabulated separated by treatment. The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation (SD), and coefficient of variation (CV); geometric mean, geometric SD

(re-transformed SD of the logarithms), and CV; minimum, median, maximum value, and the number of measurements.

Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value, a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual and geometric mean concentration versus time curves of abiraterone (using the actual sampling times for individual plots and the planned sampling times for mean plots) will be plotted by treatment using both a linear and semilogarithmic scale.

Pharmacokinetic characteristics (t_{max} excluded) will be summarized by the statistics mentioned above. The t_{max} will be described utilizing minimum, maximum, and median as well as frequency counts.

8.5 Planned interim analyses

There is no formal interim analysis for efficacy planned for the primary endpoint SSE-FS.

For the secondary efficacy endpoint of OS, one interim analysis (to be performed at the same time as the final SSE-FS analysis) and one final analysis are planned. At the interim OS analysis, it is expected that 275 deaths will have occurred (assuming 35.3 months median survival in the control arm). If the analysis of OS after 275 deaths following treatment with radium-223 dichloride plus abiraterone plus prednisone / prednisolone is statistically significantly better compared to control ($p \leq 0.0015$, based on O'Brien-Fleming alpha spending function), then OS will be declared positive for the interim analysis, assuming the final event number for OS is 500. The actual nominal alpha levels will be calculated based on the actual number of events accrued at the OS interim analysis. If the interim OS analysis is not statistically significant, the final analysis for OS will be performed when approximately 500 deaths have occurred, corresponding to an approximately 60% power to detect a 25% improvement (in OS with radium-223 dichloride compared with placebo) with a 2-sided alpha of 0.025.

Planned updated analysis

A descriptive updated analysis will be performed after last subject last visit has occurred. Data may be reported through listings.

8.6 Determination of sample size

Sample size is calculated based on the primary endpoint, SSE-FS. Using a test with a 2-sided alpha of 0.05, power of 90%, and a randomization ratio of 1:1 between the experimental (radium-223 dichloride) and control (placebo) arms, 389 events are required to detect a 39% increase in SSE-FS (i.e., an overall 0.05 level 2-sided log-rank test has approximately 90% power to detect a difference between the 2 SSE-FS curves if the alternative hypothesis HR is 0.72 [assuming the median SSE-FS is 29.2 months for radium-223 dichloride versus 21.0 for control]). The expected study duration for SSE-FS is 37 months, assuming subjects enroll at

a rate of 50 subjects per month, an enrollment ramp-up time of 9 months, a dropout rate of 10%, exponentially distributed event time, 21 months in SSE-FS median time for the control group, and a total of 800 subjects in the 2 treatment groups combined.

This study is also powered (~60%) for the analysis of OS. For the concluding analysis of OS, 500 deaths are projected to occur by approximately 71.4 months after the first subject is randomized, assuming the median OS for the control arm is 35.3 months and a 25% improvement for the radium-223 dichloride arm. If the final analysis of OS after 500 deaths reveals that the experimental treatment is statistically significantly better than treatment with control ($p \leq 0.0245$), then the OS endpoint will be declared positive for the final analysis.

9. Data handling and quality assurance

9.1 Data recording

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

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

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

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

- All information about the SAE
- All information related to the SAE such as:
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page

9.2 Monitoring

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

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

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

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

9.3 Data processing

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

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

9.4 Audit and inspection

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

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

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

9.5 Archiving

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

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

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

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

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

10. Premature termination of the study

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

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g., SAEs), upon the recommendation of the IDMC
  - Results of any interim analysis which might be necessary after the study begins
  - Results of parallel clinical studies
  - Results of parallel animal studies (e.g., toxicity, teratogenicity, carcinogenicity, or reproduction toxicity).
- If the study conduct (e.g., recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

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

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g., IEC[s] / IRB[s]; competent authority[ies]; study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at study center) must be returned to the sponsor or (for radium-223 dichloride samples) be destroyed at the study center in accordance with the local radioprotection regulations. The Investigator will retain all other documents until notification given by the sponsor for destruction.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 5.2.1.

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

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

Documented approval from appropriate 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 10.

11.2 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and ICF provided by the sponsor or the study center. A sample subject information and ICF is provided as a document separate to this protocol.

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

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

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

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

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

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 his own will. His refusal or the withdrawal of his consent may not be disregarded.

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

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

11.3 Publication policy

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

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator / institution. Authorship will be determined according to the International Committee of Medical Journal Editors uniform requirements for manuscripts submitted to biomedical journals.

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

11.4 Compensation for health damage of subjects / insurance

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

11.5 Confidentiality

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

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the 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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13. Protocol amendments

13.1 Amendment 1

Amendment 1 (dated 26 AUG 2014) is an amendment to the original protocol dated 05 Nov 2013. Changes to the protocol include:

- Changed the short title of the study and added the study acronym
- Added the exploratory objective to the synopsis
- Clarified that subjects must provide “written” informed consent
- Modified the inclusion criterion to clarify the permitted age range
- Corrected inconsistencies between the synopsis and body of the protocol
- Modified the inclusion criterion to expand the permitted estimated GFR
- Clarified the birth control requirements
- Added a 7-day window to the screening period
- Clarified study treatment is either radium-223 dichloride (Arm A) or placebo (Arm B)
- Clarified the maximum radium-223 dichloride treatment duration
- Clarified that abiraterone is not considered study medication after an on-study SSE
- Corrected inconsistencies in the text versus the schedule of assessments table
- Clarified the long-term follow-up period would end after a maximum of 7 years
- Clarified that the EOS may occur when the last subject is transferred to a separate follow-up study
- Specified the analysis of PK data
- Clarified the eCRF will be used for recording data
- Clarified the term bone scan
- Updated the number of study centers to 170
- Clarified the administration of study drug
- Updated information regarding PRDs
- Clarified that abiraterone acetate and prednisone / prednisolone will be centrally sourced and saline will be sourced locally
- Clarified the process for maintaining the blind
- Updated the manufacturer of radium-223 dichloride
- Clarified the storage conditions and expiry for radium-223 dichloride
- Clarified the radium-223 dichloride ordering process
- Clarified body weight must be measured within 3 days prior to dosing and on the day of dosing for non-US sites or 3 to 5 days prior to dosing for US sites

- Corrected the Hb level that must be met for dosing
- Clarified when the analgesic consumption diary and BPI-SF would be assessed with respect to the visit
- Corrected the window for the dosing visits
- Corrected the window for the active follow-up without clinic visits
- Clarified that the HRQoL forms will not be administered at the screening visit
- Added completion of the resource utilization questionnaire to the active follow-up without clinic visits
- Added completion of the analgesic consumption diary and recording 24 hour analgesic use to the end of active follow-up without clinic visits
- Clarified bone and tumor-related biomarker assessment in serum, plasma, and / or urine
- Added collection of SSEs during the screening period
- Clarified when radium-223 dichloride versus abiraterone and prednisone / prednisolone will be ordered
- Clarified that survival status will be collected throughout the study
- Clarified that in the US, dosing should occur at least 7 days after randomization, whenever possible
- Corrected the study days to be in relation to the cycle number (i.e., Cycle 1, Day 8) and added corresponding visits
- Clarified that collection of cancer-related treatments includes androgen synthesis inhibitors / AR antagonists and excludes analgesics
- Corrected when the handheld device will be provided to subjects
- Specified that biochemistry results should be evaluated before study drug administration if the results are available
- Clarified the resource utilization questionnaire will be completed by the sites
- Clarified that both subjects and sites should record to which treatment they believe the subjects were randomized
- Clarified when the active follow-up period begins
- Corrected how the BPI-SF items are calculated
- Specified the time points for ALP response and PSA response
- Clarified the fasting requirements prior to each PK visit
- Corrected the expected study durations used for the sample size calculations
- Clarified that race and ethnicity will only be collected if allowed by local regulation
- Added the modified RECIST 1.1 criteria
- Added the correction factor for Black subjects to the Modification of Diet in Renal Disease formula

- Corrected typographical errors

13.1.1 Overview of changes

Modification 1

Changed the short title of the study to reflect the study acronym.

Sections affected include:

- Title page
- Synopsis: Short title
- List of abbreviations

Modification 2

Added the exploratory objective (to evaluate the impact of baseline total body weight and ideal body weight on SSE-FS and AEs) to the synopsis to be consistent with the body of the protocol.

Sections affected include:

- Synopsis: Study objectives

Modification 3

Clarified that subjects must provide “written” informed consent for this study.

Sections affected include:

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

Modification 4

Modified the inclusion criterion to clarify subjects must be at least 18 years old, or older if legally required in their participating country.

Sections affected include:

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

Modification 5

Corrected inconsistencies between the synopsis and the body of the protocol.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion
- Synopsis: Methodology
- 3.1 Independent Data Monitoring Committee
- 4.1.1 Study periods and duration
- Figure 4-1 Study design schematic
- 5.1.1 Inclusion criteria
- 7.1.2.5 Long-term follow-up for up to 7 years following last dose

Modification 6

Changed the minimum estimated GFR from 60 to 30 mL/min/1.73 m^2 to increase subject eligibility. This change will not compromise subject safety based on available data on the investigational drugs.

Sections affected include:

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

Modification 7

Clarified the birth control requirements to be consistent with the requirements in Spain.

Sections affected include:

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

Modification 8

Added a window of + 7 days to the screening period to increase flexibility for the sites and for consistency among the radium-223 dichloride program.

Sections affected include:

- Synopsis: Methodology
- 4.1.1 Study periods and duration
- 5.1 Eligibility
- Table 7-1 Schedule of assessments
- 7.1.2.1 Screening period (Visit 1)

Modification 9

Clarified that study treatment is either radium-223 dichloride (Arm A) or placebo (Arm B).

Sections affected include:

- Synopsis: Methodology
- 4.1.1 Study periods and duration
- Figure 4-1 Study design schematic
- 4.3 End of study
- 5.2.1.1 Withdrawal from treatment period (collection of follow-up data)
- 6.4.4 Dose adjustments for study drug-related adverse events
- 6.4.5 Dose adjustments, delays, and treatment discontinuations
- 6.4.5.1 Radium-223 dichloride / placebo
- 6.7 Treatment compliance
- 6.8 Post-study treatment therapy
- Table 7-1 Schedule of assessments
- 7.1.2.3 Treatment period
- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.1.2.3.4 End of treatment visit
- 7.1.2.4.3.1 End of active follow-up with clinic visits
- 7.1.2.5 Long-term follow-up for up to 7 years following last dose
- 7.1.2.6 End of study
- 7.4.1 Drug measurement
- 7.4.2 Pharmacokinetic evaluation

Modification 10

Clarified that a maximum of 6 doses of radium-223 dichloride treatment will be administered every 4 weeks.

Sections affected include:

- Synopsis: Methodology
- 4.1.1 Study periods and duration
- 5.2.1.1 Withdrawal from treatment period (collection of follow-up data)
- 6.8 Post-study treatment therapy

- Table 7-1 Schedule of assessments

Modification 11

Clarified that abiraterone is not considered study medication when administered after an on-study SSE.

Sections affected include:

- Synopsis: Methodology
- 4.1.1 Study periods and duration
- 5.2.1.1 Withdrawal from treatment period (collection of follow-up data)
- 6.2.1.3 Abiraterone acetate
- Table 7-1 Schedule of assessments
- 7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone as IMP and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.1.2.3.4 End of treatment visit
- 7.5.1.3 Assessments and documentation of adverse events

Modification 12

Corrected inconsistencies in the text versus the schedule of assessments. These include clarifying the timing of the visits; the timing of the collection of vital signs, weight, progression, SSEs, AEs, cancer related treatments, 24-hour analgesic use, drug accountability, and PK sampling; when the ePRO device is dispensed; the timing of the bone scans and CT / MRI during Cycles 12+; concomitant medication recording; and the assessments performed during the Active Follow-up period without clinic visits.

Sections affected include:

- Synopsis: Methodology
- 4.1.1 Study periods and duration
- Figure 4-1 Study design schematic
- Table 7-1 Schedule of assessments
- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.2 Visits 3, 5, and 7 (Cycles 1, 2, and 3, Day 15 ± 3 days) and unscheduled visits
- 7.1.2.3.4 End of treatment visit
- 7.1.2.4.1 Active follow-up with clinic visits assessments (Every 12 weeks ± 7 days at each visit)

- 7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.3.1 End of active follow-up with clinic visits
- 7.1.2.4.3.2 End of active follow-up without clinic visits
- 7.1.2.5.1 Long-term follow-up (telephone follow-up)
- 7.1.2.5.2 End of long-term follow-up
- 7.3.2.2 Secondary efficacy endpoints:

Modification 13

Clarified the duration of the long-term follow-up period is a maximum of 7 years.

Sections affected include:

- Synopsis: Methodology
- 4.1.1 Study periods and duration
- Figure 4-1 Study design schematic
- 4.3 End of study
- Table 7-1 Schedule of assessments
- 7.1.2.5 Long-term follow-up for up to 7 years following last dose
- 7.1.2.5.1 Long-term follow-up (telephone follow-up)
- 7.1.2.6 End of study

Modification 14

Clarified that the end of study may occur when the last subject is transferred to a separate extended safety follow-up protocol.

Sections affected include:

- Synopsis: Methodology
- 4.1.1 Study periods and duration
- 4.3 End of study
- Table 7-1 Schedule of assessments
- 7.1.2.4.3.1 End of active follow-up with clinic visits
- 7.1.2.5 Long-term follow-up for up to 7 years following last dose
- 7.1.2.5.2 End of long-term follow-up

Modification 15

Described how the PK parameters will be handled during analysis to provide clarification.

Sections affected include:

- List of abbreviations
- 8.2 Analysis sets
- 8.4.4 Pharmacokinetic data

Modification 16

Clarified the eCRF will be used for recording data rather than using the terms CRF, eCRF, and Medidata Rave interchangeably.

Sections affected include:

- List of abbreviations
- 6.4.2 Radium-223 dose calculation
- Table 7-1 Schedule of assessments
- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.2 Visits 3, 5, and 7 (Cycles 1, 2, and 3, Day 15 ± 3 days) and unscheduled visits
- 7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.1.2.3.4 End of treatment visit
- 7.1.2.4.1 Active follow-up with clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.3.1 End of active follow-up with clinic visits

Modification 17

Clarified that the term bone scan as used in this protocol refers to a whole body technetium-99m bone scan.

Sections affected include:

- Definitions of terms
- 7.3.2.2 Secondary efficacy endpoints

Modification 18

Updated the number of study centers to 170 sites to reflect the additional sites required to recruit this study.

Sections affected include:

- 4.1 Design overview

Modification 19

Clarified the administration of study drug to provide missing information, including the duration of the bolus injection.

Sections affected include:

- 6.1 Treatments to be administered
- 6.4 Dosage and administration

Modification 20

Updated information regarding PRDs. Patient ready doses prepared by Cardinal Health for US sites have an extended expiry, as agreed by Bayer with FDA. Thus, Cardinal Health has additional time to ensure delivery prior to expiry and sites may have additional flexibility with actual dosing day (i.e., 1 more day) when logistical delays occur (i.e., either subject or PRD do not arrive as planned), as long as the PRD has not expired / dose is given prior to expiry date and time, assessments other than weight are repeated (to be within window prior to dose day / time), and measured activity of the PRD is within 10% of the 'ordered amount' (planned dose).

Sections affected include:

- 6.2 Identity of study treatment
- 6.4 Dosage and administration
- 6.4.1 Radium-223 dichloride dose handling
- 6.4.2 Radium-223 dose calculation
- 6.4.3 Study drug dose preparation
- Table 7-1 Schedule of assessments

Modification 21

Clarified that abiraterone acetate and prednisone / prednisolone will be centrally sourced and saline will be supplied locally.

Sections affected include:

- 6.2 Identity of study treatment

- 6.2.1 Study medication supply and packaging
- 6.2.1.4 Prednisone / prednisolone
- 6.6 Drug logistics and accountability

Modification 22

Clarified the processes for maintaining the blind.

Sections affected include:

- 6.2.1 Study medication supply and packaging
- 6.2.1.2 Saline
- 6.4.2 Radium-223 dose calculation
- 6.4.3 Study drug dose preparation
- 6.7 Treatment compliance

Modification 23

Updated the manufacturer of radium-223 dichloride from Algeta ASA to Bayer HealthCare.

Sections affected include:

- 6.2.1.1 Radium-223 dichloride

Modification 24

Clarified the storage conditions and expiry for radium-223 dichloride to reflect the most recent information.

Sections affected include:

- 6.2.1.1 Radium-223 dichloride
- 6.4.1 Radium-223 dichloride dose ordering and handling
- 6.4.3 Study drug dose preparation

Modification 25

Clarified the process for ordering radium-223 dichloride.

Sections affected include:

- 6.4.1 Radium-223 dichloride dose ordering and handling

Modification 26

Clarified body weight must be measured within 3 days prior to dosing and on the day of dosing for non-US sites and 3 to 5 days prior to dosing for US sites to account for the requirements of the US PRDs versus non-US sites, which will not use PRDs.

Sections affected include:

- 6.4.2 Radium-223 dose calculation
- Table 7-1 Schedule of assessments
- 7.1.2.1 Screening period (Visit 1)
- 7.1.2.3 Treatment period
- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)

Modification 27

Corrected an inconsistency in the required Hb level that must be met (> 8.0 g/dL) prior to radium-223 dichloride / placebo dosing.

Sections affected include:

- 6.9.2 Permitted concomitant therapy

Modification 28

Clarified the analgesic consumption diary and BPI-SF would be assessed daily for one week (6 days prior to the visit and the day of the visit), except at the screening visit when the BPI-SF will be assessed once using a paper version.

Sections affected include:

- 6.9.2 Permitted concomitant therapy
- Table 7-1 Schedule of assessments
- 7.1.2.1 Screening period (Visit 1)
- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.4 End of treatment visit
- 7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.3.1 End of active follow-up with clinic visits
- 7.1.2.4.3.2 End of active follow-up without clinic visits

Modification 29

Corrected the window for the dosing visits from ± 7 days to + 7 days to reflect the minimum period between 2 doses of radium-223 dichloride / placebo of 28 days.

Sections affected include:

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

Modification 30

Corrected the window for the active follow-up without clinic visits from ± 14 days to ± 7 days.

Sections affected include:

- Table 7-1 Schedule of assessments
- 7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)

Modification 31

Clarified that the HRQoL NCCN-FACT FPSI-17 and HRQoL EQ-5D forms will not be administered at the screening visit.

Sections affected include:

- Table 7-1 Schedule of assessments

Modification 32

Added completion of the resource utilization questionnaire to the active follow-up without clinic visits to capture this additional information.

Sections affected include:

- Table 7-1 Schedule of assessments
- 7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.3.2 End of active follow-up without clinic visits

Modification 33

Added completion of the analgesic consumption diary and recording 24 hour analgesic use to the end of active follow-up without clinic visits to be consistent with the active follow-up without clinic visits.

Sections affected include:

- Table 7-1 Schedule of assessments
- 7.1.2.4.3.2 End of active follow-up without clinic visits

Modification 34

Clarified that exploratory bone biomarkers will be assessed in serum and urine, and exploratory tumor-related biomarkers will be assessed in serum and plasma. Added the analysis of serum c-telopeptide, carboxyterminal telopeptide of type I collagen, and procollagen I N-terminal propeptide.

Sections affected include:

- Table 7-1 Schedule of assessments
- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone as IMP and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.1.2.3.4 End of treatment visit
- 7.6.3.1 Urine, serum, and plasma based biomarker analysis

Modification 35

Added collection of SSEs during the screening period.

Sections affected include:

- Table 7-1 Schedule of assessments
- 7.1.2.1 Screening period (Visit 1)

Modification 36

Clarified when radium-223 dichloride versus abiraterone and prednisone / prednisolone will be ordered to reflect the continuation of treatment with abiraterone and prednisone / prednisolone after the last dose of radium-223 dichloride / placebo.

Sections affected include:

- Table 7-1 Schedule of assessments

Modification 37

Clarified that death (i.e., survival status) will be collected throughout the study.

Sections affected include:

- Table 7-1 Schedule of assessments
- 7.1.2.1 Screening period (Visit 1)

- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.2 Visits 3, 5 and 7 (Cycles 1, 2, and 3, Day 15 ± 3 days) and unscheduled visits
- 7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone as IMP and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.1.2.3.4 End of treatment visit

Modification 38

Clarified that in the US, randomization should occur at least 7 days before Cycle 1, Day 1, whenever possible. This allows time for subjects to complete the BPI-SF completion for one week prior to dosing regardless of the time for shipment of study drug from the PRD.

Sections affected include:

- Table 7-1 Schedule of assessments
- 7.1.2.2 Randomization
- 7.4.1 Drug measurement

Modification 39

Corrected the study days to be in terms of the cycle number (e.g., Cycle 1, Day 8) and added the corresponding visits. The previous version inconsistently referred to Days 0, 7, etc. The first dose will be administered on Cycle 1, Day 1; therefore, 7 days after dosing is Cycle 1, Day 8 not Cycle 1, Day 7.

Sections affected include:

- Table 7-1 Schedule of assessments
- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.2 Visits 3, 5 and 7 (Cycles 1, 2, and 3, Day 15 ± 3 days) and unscheduled visits
- 7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone as IMP and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.6.3.1 Urine, serum, and plasma based biomarker analysis

Modification 40

Clarified that collection of cancer-related treatments includes androgen synthesis inhibitors / AR antagonists and excludes analgesics.

Sections affected include:

- Table 7-1 Schedule of assessments
- 7.1.2.1 Screening period (Visit 1)
- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.2 Visits 3, 5 and 7 (Cycles 1, 2, and 3, Day 15 ± 3 days) and unscheduled visits
- 7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone as IMP and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.1.2.3.4 End of treatment visit
- 7.1.2.4.1 Active follow-up with clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.3.1 End of active follow-up with clinic visits
- 7.1.2.4.3.2 End of active follow-up without clinic visits

Modification 41

Corrected that the handheld device will be provided to subjects at least 6 days prior to dosing not prior to randomization.

Sections affected include:

- Table 7-1 Schedule of assessments
- 7.1.2.1 Screening period (Visit 1)

Modification 42

Specified that biochemistry results should be evaluated before study drug administration if the results are available.

Sections affected include:

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

Modification 43

Clarified the resource utilization questionnaire will be completed by the sites not the subjects.

Sections affected include:

- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone as IMP and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.1.2.3.4 End of treatment visit
- 7.1.2.4.1 Active follow-up with clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.3.1 End of active follow-up with clinic visits
- 7.1.2.4.3.2 End of active follow-up without clinic visits

Modification 44

Clarified that both subjects and sites should record to which treatment they believe the subjects were randomized.

Sections affected include:

- 7.1.2.3.4 End of treatment visit

Modification 45

Clarified when the active follow-up period begins to be consistent with long-term follow-up.

Sections affected include:

- 7.1.2.4 Active follow-up

Modification 46

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

Sections affected include:

- 7.3.2.2 Secondary efficacy endpoints

Modification 47

Specified the time points for ALP response and PSA response to add clarity to the definitions of these terms.

Sections affected include:

- 7.3.2.3 Exploratory efficacy endpoints

Modification 48

Clarified the fasting requirements before or after abiraterone dosing prior to each PK visit.

Sections affected include:

- 7.4.1 Drug measurement

Modification 49

Corrected the expected study durations used for the sample size calculations. The durations were rounded to the nearest integer; therefore, displaying numbers to the first decimal point was inaccurate.

Sections affected include:

- 8.6 Determination of sample size

Modification 50

Clarified that subjects' race and ethnicity will only be collected where permitted by local regulations.

Sections affected include:

- 9.1 Data recording

Modification 51

Added the changes to the modified RECIST 1.1 criteria to provide further clarification of the modified RECIST criteria.

Sections affected include:

- 14.3 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Modification 52

Added the correction factor for Black subjects to the Modification of Diet in Renal Disease formula so GFR will be accurately calculated for these subjects.

Sections affected include:

- 14.4 Calculation for glomerular filtration rate

13.1.2 Changes to the protocol text

Changes to the protocol text done in Amendment 1 are provided in Section 13.1.2 of integrated protocol Version 2.0.

13.2 Amendment 2

Amendment 2 (dated 12 JUN 2015) is an amendment to Integrated Protocol version 2.0 dated 26 AUG 2014. Changes to the integrated protocol include:

- Update dosing and dose calibration of radium-223 dichloride to reflect revised NIST standardization for radium-223
- Removed cytological confirmation of adenocarcinoma of the prostate from inclusion criteria; histological confirmation only
- Clarified that the treatment period ended when a subject received abiraterone/prednisone as the standard of care (non-IMP) after an SSE
- Added an exclusion for immunotherapy (e.g., sipuleucel-T) within 4 weeks before the first dose of radium-223 dichloride
- Clarified duration of prohibited concomitant therapy is from Screening onwards
- Clarified potassium requirement for ECG collection
- Editorial updates

13.2.1 Overview of changes

Modification 1

Update of the radium-223 dichloride dosing and dose calibration to reflect the revised NIST standard.

Rationale:

The quantification of radium-223 radioactivity in Xofigo® is based on the primary standardization performed by the US National Institute of Standards and Technology (NIST). The NIST Standard Reference Material is used to calibrate the instruments in production and quality control of both the drug substance and drug product. Additionally, the calibrated instruments in production at the Institute for Energy Technology (Norway) are used to prepare the NIST traceable radium-223 reference material, which are then sent to the treatment sites (e.g., nuclear medicine laboratory physicians or technicians) for dial setting of their dose calibrators, to allow verification of the subject dose. A reassessment of the primary standardization was initiated by the NIST. A discrepancy of approximately 10% between the published NIST primary standardization (55) and current measurements was confirmed and a revised NIST primary reference standard has been issued (56). As a result of the revised NIST primary standardization, an adaption of the numerical description of subject dose and the description of radioactive concentration of the drug product solution

becomes necessary. This concerns Xofigo® for commercial use and product used in clinical trials.

After the implementation of the new standard (56), the numerical description of the subject dose will be adjusted from 50 kBq/kg to 55 kBq/kg, and the numerical description of the radioactivity in the vial will be changed from 1,000 kBq/mL to 1,100 kBq/mL. A respective variation application and substantial amendment to our Clinical Trial Applications have been initiated. The current standard (55), dial setting, and dose will remain in effect until a unique implementation date in Q2 2016 as agreed with FDA and the European Medicines Agency. All clinical sites using radium-223 dichloride will be notified in writing about the exact date of implementation prior to the effective date.

Justification for changing the dose to 55 kBq/kg body weight:

A systematic approximately 10% error in the radium-223 NIST standardization (55) means that the current subject dose and the dose documented as safe and efficacious throughout development is 55 kBq/kg body weight and not 50 kBq/kg body weight as declared during clinical trials and in the marketing authorization application / new drug application. However, as this is a systematic error, the actual dose has been the same all the time. In order to keep the actual dose for subjects identical to what has been documented and administered so far, also when implementing the new official standard, the nominal value of the subject dose will be changed to 55 kBq/kg body weight (56). This change keeps the same accuracy in the nominal value of the dose. Thus, there will be no actual change in the subject dose (amount of radioactivity); it will be only a change in the dose nominal value when corrected according to the new official radium-223 NIST standard. All sites will continue to use the current dial setting (55) for the activity measurements until the implementation date in Q2 2016.

Justification for changing the description of the radioactivity in the vial to 1,100 kBq/mL:

A systematic approximately 10% error in the radium-223 NIST standard (55) means that the Xofigo® solution for injection with a radioactivity concentration claim of 1,000 kBq/mL, which has been tested in pivotal clinical trials and is currently marketed, actually has a concentration of 1,100 kBq/mL. If the drug product concentration is adjusted to 1,100 kBq/mL, the total activity in the vial (6 mL) must be changed from 6,000 kBq/vial to 6,600 kBq/vial (changed from 6.0 MBq/vial to 6.6 MBq/vial in many countries). Xofigo® solution for injection produced according to the new NIST standardization (56), is the same product as before. NOTE: All product received by sites will be labelled with the current standard activity of 1000 kBq/mL until the implementation date in Q2 2016.

Now that the new radium-223 standard has been published, Bayer has applied for labeling and packaging changes, in accordance with the new standards, with each Health Authority for which Bayer holds a marketing application for radium-223 dichloride. Once all approvals have been received, the updated standard will be applied to all active protocols that include radium-223 dichloride, including this one, and the verification of the subject dose in treatment sites has to be performed using updated dial settings of dose calibrators.

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

NOTE: Throughout this document, the dose of radium-223 dichloride is given as 50 kBq/kg, which is based on the original NIST standardization (55); however, when NIST issues the updated radium-223 dichloride standardization, the dose administered will actually be 55 kBq/kg (based on a change to the reference standard [56] only), though the volume of radium-223 dichloride given to each subject will remain the same.

Sections affected include:

- Synopsis
- List of abbreviations
- 1.2.1.3 Dosing rationale
- 1.3 Study rationale
- 4.1.1 Study periods and duration
- 6.1 Treatments to be administered
- 6.2 Identity of study treatment
- 6.2.1.1 Radium-223 dichloride
- 6.4.1 Radium-223 dichloride dose calibration (new section)
- 6.4.3 Radium-223 dose calculation
- 12 Reference list

<u>Modification 2</u>

Removed cytological confirmation of adenocarcinoma of the prostate from inclusion criteria; histological confirmation only

Sections affected:

- Synopsis
- 5.1.1 Inclusion criteria

<u>Modification 3</u>

Clarified that the treatment period ended when a subject received abiraterone/prednisone as the standard of care (non-IMP) after an SSE

Section affected:

- 4.1.1 – Study periods and duration

Modification 4

Added an exclusion for immunotherapy (e.g., sipuleucel-T) within 4 weeks before randomization

Section affected:

- 5.1.2 Exclusion criteria

Modification 5

Clarified duration of prohibited concomitant therapy and added a prohibited medication

Section affected:

- 6.9.1 Prohibited concomitant therapy

Modification 6

Clarified potassium requirement for ECG collection

Sections affected:

- Section 7.1.2.1 Screening period (Visit 1)
- Section 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- Section 7.1.2.3.3 Visits 11 and 12 + (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone as IMP and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- Section 7.1.2.3.4 End of treatment visit

Modification 7

Editorial update to remove language deemed unclear

Sections affected:

- Section 7.1.1 Tabulated overview – Table 7-1 – footnote “s”
- Section 7.1.2.1 Screening period (Visit 1)
- Section 7.1.2.3 Treatment period, and Section 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)

13.2.2 Changes to the protocol text

Changes to the protocol text done in Amendment 2 are provided in Section 13.2.2 of integrated protocol Version 3.0.

13.3 Amendment 4

Amendment 4 (dated 13 SEP 2016) is an amendment to Integrated Protocol version 3.0 dated 12 JUN 2015. Changes to the integrated protocol include:

- Update to reflect recent Bayer AG legal entity name change

- Update of GCL name
- Clarification of continuation of medical castration
- Clarification of documentation of radiological progression
- Clarification timing of visits, scans, EOT visit, and the collection of anti-cancer therapies, AEs, and SAEs
- Clarification of study drug handling if administration is postponed more than 3 days
- Removal of obsolete NIST language
- Clarification of treatment unblinding procedures
- Removal of bisphosphonate timing requirements

13.3.1 Overview of changes

Modification 1

Update to reflect recent Bayer AG legal entity name change.

Rationale:

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

Sections affected include:

- Headers
- Title Page

Modification 2

Update of GCL name.

Rationale:

Change reflects the current protocol signatory.

Sections affected include:

- Signature of the sponsor's medically responsible person

Modification 3

Clarification of continuation of medical castration.

Rationale:

Clarification for sites that medical castration should be maintained during the entire study and should not be discontinued after enrollment.

Sections affected include:

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

Modification 4

Clarification of documentation of radiological progression.

Rationale:

Clarification for sites that even if a subject has an SSE, the site is still required to document radiological progression. This change also clarifies when subjects can progress to the next study period.

Sections affected include:

- Synopsis – Methodology
- 4.1.1 – Study periods and duration
- Figure 4-1 – Study design schematic
- 7.1.2.4 – Active follow-up
- 7.1.2.4.1 – Active follow-up with clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.5 – Long-term follow-up for up to 7 years following last dose

Modification 5

Clarification timing of visits, scans, EOT visit, and the collection of anti-cancer therapies, AEs, and SAEs.

Rationale:

Clarification for sites on the timing of the EOT visit and prevention of unnecessary AE and SAE reporting in subjects who have started new anti-cancer therapy and clarification of the need to continue to collect subject anti-cancer therapy data. Additionally, clarified the timing of active follow-up visits and scans.

Sections affected include:

- Synopsis – Methodology
- 4.1.1 – Study periods and duration
- 7.1.1 – Tabulated overview: Table 7-1 Schedule of assessments
- 7.1.2.3 – Treatment period

- 7.1.2.3.3 - Visits 11 and 12+ (Cycles 7 and 8, Day 1, and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone as IMP and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.1.2.3.4 – End of treatment visit
- 7.1.2.4.3.1 – End of active follow-up with clinic visits
- 7.1.2.4.3.2 – End of active follow-up without clinic visits
- 7.1.2.4 – Active follow-up
- 7.1.2.4.1 - Active follow-up with clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.2 – Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.5 – long-term follow-up for up to 7 years following last dose
- 7.1.2.5.1 – Long-term follow-up (telephone follow-up)
- 7.1.2.5.2 – End of long-term follow-up
- 7.5.1.3 – Assessments and documentation of adverse events

Modification 6

Clarification of study drug handling if administration is postponed more than 3 days.

Rationale:

If administration of radium-223 dichloride is postponed more than 3 days, the remaining activity in the product may not be sufficient for treatment by protocol standards and the site may need to re-order the study drug.

Sections affected include:

- 6.2.1.1 – Radium-223 dichloride
- 6.2.1.2 – Saline

Modification 7

Removal of obsolete NIST language.

Rationale:

As the NIST standards have now been implemented, language referring to future planning for the NIST implementation has been removed.

Sections affected include:

- 6.4.1 – Radium-223 dichloride dose calibration

Modification 8

Clarification of treatment unblinding procedures.

Rationale:

Due to an SOP update, protocol language has been clarified to reflect that investigators are not required to contact the medical monitor before unblinding subject treatment.

Sections affected include:

- 6.5 – Blinding

Modification 9

Removal of bisphosphonate timing requirements.

Rationale:

As there is no data supporting a requirement for bisphosphonate to be administered with a 2-hour separation from study drug, this language has been removed.

Sections affected include:

- 6.9.1 – Prohibited concomitant therapy

13.3.2 Changes to the protocol text

Changes to the protocol text done in Amendment 4 are provided in Section 13.3.2 of integrated protocol Version 4.0.

13.4 Amendment 6

Amendment 6 (dated 03 APR 2018) is an amendment to Integrated Protocol Version 4.0, dated 13 SEP 2016. Changes to the integrated protocol include:

- New request that bone fractures and bone associated events (e.g., osteoporosis) need to be reported as (S)AEs, including during long-term follow-up, regardless of the investigator's causality assessment.
- Addition of independent radiological review of fractures.
- Based on the available data on radium-223 dichloride, initiation of BHA is now allowed.
- Addition that radium-223 dichloride should not be given in combination with abiraterone plus prednisone/prednisolone during follow-up.
- Additional minor clarifications.

13.4.1 Overview of changes

Rationale:

The study was unblinded early based on the IDMC recommendation according to an ad hoc independent analysis where more treatment emergent fractures, SSE-FS, and total deaths events were observed in the active treatment arm compared with the placebo arm. Based on these data, European Health Authorities requested that all bone fractures and bone associated

events (e.g., osteoporosis) occurring during study and in the follow-up period should be documented regardless of the investigator's causality assessment. In addition, the FDA requested a radiological review of all fracture imaging scans. The central radiological review of all fracture scans will evaluate the correlation between bone metastasis and fractures, and support the root cause analysis of the observed increased incidence of fractures in the experimental treatment arm.

Based on the available data on radium-223 dichloride, the option of starting a BHA including bisphosphonates or denosumab should be considered, taking into consideration applicable guidelines.

13.4.1.1 Modification 1

Bone fractures and bone associated events (e.g., osteoporosis) need to be reported as (S)AEs, including during long-term follow-up, regardless of causality to study treatment.

Sections affected include:

- Synopsis
- 4.1.1 Study periods and duration
- Schedule of assessments
- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.2 Visits 3, 5, and 7 (Cycles 1, 2, and 3, Day 15 ± 3 days) and unscheduled visits
- 7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone as IMP and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.1.2.3.4 End of treatment visit
- 7.1.2.4.1 Active follow-up with clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.3.1 End of active follow-up with clinic visits
- 7.1.2.4.3.2 End of active follow-up without clinic visits
- 7.1.2.5.1 Long-term follow-up (telephone follow-up)
- 7.1.2.5.2 End of long-term follow-up
- 7.5.1.3 Assessments and documentation of adverse events
- 7.5.1.4 Reporting of serious adverse events

13.4.1.2 Modification 2

Addition of independent radiological review of fractures.

Sections affected include:

- Synopsis

- 3.2 Independent radiological review
- 4.1.1 Study periods and duration
- Schedule of assessments
- 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Cycles 1 through 6, Day 1 + 7 days at each visit)
- 7.1.2.3.2 Visits 3, 5, and 7 (Cycles 1, 2, and 3, Day 15 ± 3 days) and unscheduled visits;
- 7.1.2.3.3 Visits 11 and 12+ (Cycles 7 and 8, Day 1 and every 4 weeks thereafter ± 7 days) up until discontinuation of abiraterone as IMP and prednisone / prednisolone or until 6 months post last radium-223 dichloride / placebo administration, whichever occurs later
- 7.1.2.3.4 End of treatment visit
- 7.1.2.4.1 Active follow-up with clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.4.3.1 End of active follow-up with clinic visits
- 7.1.2.4.3.2 End of active follow-up without clinic visits
- 7.1.2.5.1 Long-term follow-up (telephone follow-up)
- 7.1.2.5.2 End of long-term follow-up
- 7.5.1.3 Assessments and documentation of adverse events
- 7.5.1.4 Reporting of serious adverse events

13.4.1.3 Modification 3

Based on the available data on radium-223 dichloride, new initiation of BHAs is now allowed in this study, and the option of starting BHA treatment should be considered, taking into consideration applicable guidelines.

Sections affected include:

- List of abbreviations
- 6.9.1 Prohibited concomitant therapy
- 6.9.2 Permitted concomitant therapy

13.4.1.4 Modification 4

The study was unblinded early based on the IDMC recommendation following an ad hoc independent analysis where more treatment emergent fractures, SSE-FS, and total deaths events were observed in the active treatment arm compared with the placebo arm. Based on the available data, the benefit-risk of radium-223 dichloride in combination with abiraterone acetate plus prednisone/prednisolone in metastatic CRPC is considered unfavorable.

Sections affected include:

- Synopsis

- 6.8 Post-study treatment therapy
- 6.9.1 Prohibited concomitant therapy

13.4.1.5 Minor clarifications

Clarification of the timeframe of reporting requirements of (S)AEs following the treatment period, for consistency across the document.

Sections affected include:

- Schedule of assessments
- 7.1.2.3.4 End of treatment visit
- 7.5.1.4 Reporting of serious adverse events

Clarification that subjects in the "active follow-up without clinic visits" period will still be followed for radiological progression if they did not have progressive disease in the previous period and if they could have scans as part of standard of care.

Sections affected include:

- Synopsis
- 4.1.1 Study periods and duration
- Figure 4–1 Study design schematic
- Schedule of assessments
- 7.1.2.4.2 Active follow-up without clinic visits assessments (Every 12 weeks ± 7 days at each visit)
- 7.1.2.5 Long-term follow-up for up to 7 years following last dose

For Word-related technical reasons, numbered footnotes have been replaced with a summary of changes at the start of each amended section.

13.4.2 Changes to the protocol text

Changes to the protocol text done in Amendment 6 are provided in Section 13.4.2 of integrated protocol Version 5.0.

13.5 Amendment 7

Amendment 7 is a global amendment dated 26 NOV 2019.

13.5.1 Overview of changes

Overall rationale for the amendment

At the time of the final OS analysis, after approximately 500 death events, approximately 70 subjects are still receiving study medication (abiraterone acetate plus prednisone or prednisolone).

To continue providing study medication to these subjects, the protocol remains open with all safety-related endpoints, including long term follow-up, still being collected. However, to

reduce the burden to study subjects, evaluation of efficacy and exploratory endpoints, except for SSE and OS, will be discontinued following the final OS analysis.

The criteria for discontinuation of abiraterone acetate plus prednisone / prednisolone was updated to follow standard clinical practice. Subjects discontinuing study treatment will enter long-term follow-up or, once a separate extended safety follow-up protocol has been implemented, will be directly transitioned to this extended safety follow-up study, in order to complete 7 years of safety follow-up.

High-level descriptions and rationales of the changes and the affected sections are listed below.

Sections	Description of change	Rationale
Synopsis 2. Study objectives 4.1.1 Study periods and duration 4.1.2 Study endpoints 5.2.1.1 Withdrawal from treatment period (collection of FU data) 7.1.1 Tabulated overview 7.1.2.3.2 Visits 3, 5, and 7 [...] 7.1.2.3.3 Visits 11 and 12+ […] 7.1.2.3.4 End of treatment visit	Evaluation of efficacy and exploratory endpoints will be discontinued (except for SSE and OS)	To reduce the burden to study subjects, evaluation of efficacy and exploratory endpoints will be discontinued, except for SSE and OS. To continue providing study medication to study subjects, the protocol remains open with all safety related endpoints, including long term follow-up, still being collected.
7.1.2.4 Active follow-up 7.1.2.5.1 Long-term FU (telephone FU) 7.1.2.5.2 End of long-term FU 7.3.1 Efficacy variables 7.3.2.2 Secondary efficacy variables 7.3.2.3 Exploratory efficacy variables 7.4 Pharmacokinetics (selected sites only) 7.5.1.3 Assessments and documentation of adverse events 7.5.1.4 Reporting of serious adverse events 7.6 Other procedures and variables 7.7 Appropriateness of procedures / measurements 8.3 Efficacy variables 8.4.4 Pharmacokinetic data	Updated planned analyses and study procedures • Discontinuation of pain, QoL assessments, and biomarker collection • Images will be read only locally	Planned analyses and study procedures were updated to reflect changes in study status. The changes are appropriate for safety follow-up and limited safety.

Sections	Description of change	Rationale
Synopsis 4.1.1 Study periods and duration 5.2.1 Withdrawal 7.1.1 Tabulated overview 7.1.2.3.4 End of treatment visit 7.1.2.4 Active follow-up 7.1.2.5 Long-term follow-up 7.1.2.5.2 End of long-term follow-up	Removal of the active follow-up periods Updated criteria to transition subjects to separate extended safety follow-up study	As several efficacy endpoints are no longer being collected, the active follow-up periods were removed. Therefore, subjects discontinuing study treatment will either enter long term follow-up or will be directly transitioned to the separate extended safety follow-up study, as both of them allow for the collection of safety information and OS.
Synopsis 4.1.1 Study periods and duration 4.3 End of study 7.1.2.6 End of study	Modification of the definition of the end of study (EOS)	The definition of EOS was modified to reflect the changes in study status. EOS will occur at the time the last patient on treatment discontinues oral treatment and completes end of treatment visit or at the time the last subject is transitioned to a separate extended safety follow-up study, whichever occurs later. In addition, guidance was included on reporting of safety-related events for sites and subjects not transitioning to extended safety follow-up study.
Synopsis 4.1.1 Study periods and duration 5.2.1.1 Withdrawal from treatment period (collection of follow-up data) 6.2.1.3 Abiraterone acetate	Updated criteria for discontinuation of study drug Minor clarification on eCRF use	Discontinuation of abiraterone + prednisolone shall also follow standard clinical practice, i.e., subjects presenting radiological progression (either by RECIST or bone progression by PCWG2), SSE, clinical progression (clinical deterioration or lack of clinical benefit, assessed by investigator), or that start a new anti-cancer therapy should be discontinued from study treatment. Abiraterone use should be recorded on the systemic anti-cancer therapy CRF.
Synopsis 3.1 Independent Data Monitoring Committee 3.2 Independent radiological review	Clarification on the role of IDMC and independent radiological review	After primary analysis, IDMC and independent radiological review were no longer applicable.

Sections	Description of change	Rationale
7.1.1 Tabulated overview 7.1.2.3.1 Visits 2, 4, 6, 8, 9, 10 […] 7.1.2.3.3 Visits 11 and 12+ [...] 7.1.2.3.4 End of treatment visit	Serum testosterone measurement and ECG will only be done at the discretion of the investigator	To reduce patient burden and to reflect standard of care (local practice), after implementation of Amendment 7 measurements after screening are only done at the discretion of the investigator.
6.5 Blinding 8.5 Planned interim analyses	Clarification on the blinding of the study and on the analysis performed after last subject last visit	Following the IDMC's recommendation, study was prematurely unblinded in 2017 and subject-level unblinding information has been communicated to the sites. After last subject last visit has occurred, a descriptive updated analysis will be performed.
7.1.1 Tabulated overview 7.1.2.3.3 Visits 11 and 12+ […]	The language related to the schedule of radiological tumor assessments was updated.	To consider local regulations in radiological imaging.
Title page	Sponsor's medical expert was changed.	Administrative change.
Signature of the sponsor's medically responsible person	Title of signatory was changed	Administrative change.
13.1.2, 13.2.2, 13.3.2 and 13.4.2 Changes to the protocol text Throughout	The detailed old vs. new text comparisons for protocol amendments 1, 2, 4, and 6 were replaced with a reference to the respective integrated protocol document. Old annotations from previous amendments were removed.	To improve readability, and to reduce complexity of the protocol.

13.5.2 Changes to the protocol text

Changes to the protocol text done in Amendment 7 are provided in a separate tracked-changes document.

13.6 Amendment 8

Amendment 8 is a global amendment dated 13 JAN 2023.

13.6.1 Overview of changes

Overall rationale for the amendment

The rationale for the current protocol amendment is to accommodate the subjects who are still on oral study treatment (abiraterone acetate plus prednisone / prednisolone) after the study has been completed. The original EOS definition did not foresee that after completing all planned analyses, a few subjects would remain on backbone study treatment.

After all the planned analyses of the protocol, including the 7 years of safety follow-up, have been completed, the study will be closed and for the few subjects on backbone treatment, the options for treatment continuation such as a switch to commercial drug supply, a continued

access program, or any other means of continued drug supply will be discussed and agreed between the investigator, sponsor, and the subject in compliance with local regulations.

High-level descriptions and rationales of the changes and the affected sections are listed below.

Section name and number	Description of change	Rationale
Title page	Updated date and version number per current amendment. Medical expert details were updated	Administrative changes.
Synopsis 4.3 End of study 7.1.2.6 End of study 4.1.1 Study periods and duration (under the heading long-term follow-up)	Modification of the definition of the end of study (EOS) including potential options for treatment continuation.	The definition of EOS was modified to reflect the changes in study status. Original EOS definition did not foresee that after completing all planned analyses, a few subjects would still be on backbone study treatment. The EOS is defined as the date of the last subject last visit (LSLV) in the study. The EOS will occur at the time the last subject on study completes 7 years of follow-up unless the subject died, withdraws consent or is lost to FU.
6.8 Post-study treatment therapy 7.1.2.5 Long-term follow-up 7.1.2.6 End of study	Modification of text about the treatment options according to the revised EOS definition.	For including potential options for treatment continuation as per revised EOS definition.
Reference to the latest protocol amendment and version number throughout the document	Old annotations/reference of/from previous amendments were removed and updated with amendment number 8 and version number 7	Consistency and template requirements.

13.6.2 Changes to the protocol text

Changes to the protocol text done in Amendment 8 are provided in a separate tracked changes document.

14. Appendices

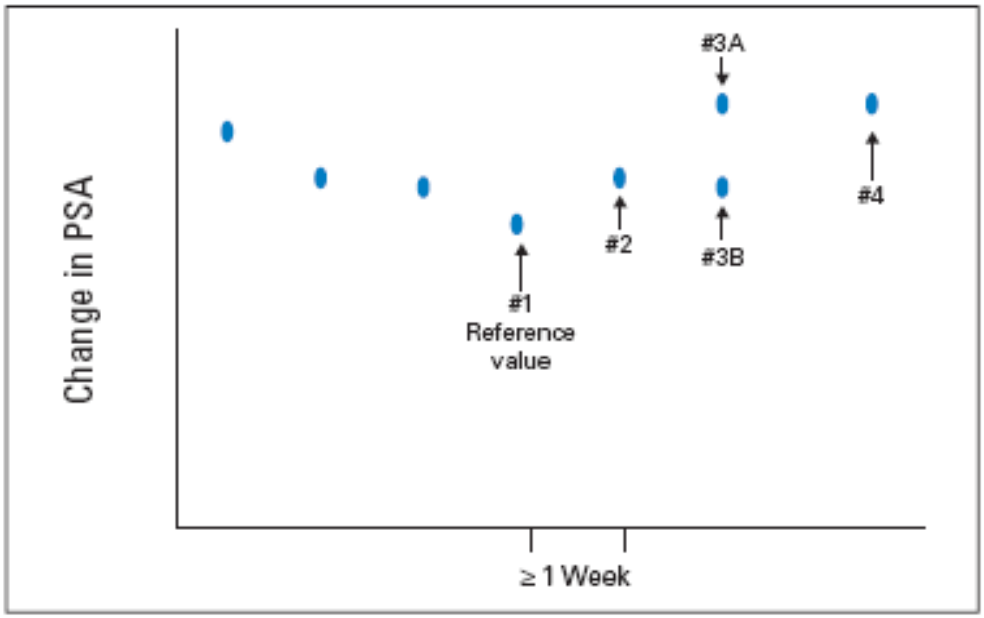
14.1 National Cancer Institute-Common Terminology Criteria, version 4.03

This study will utilize the NCI-CTCAE v4.03 for toxicity and SAE reporting. A copy of the CTCAE v4.03 can be downloaded from the website: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. All appropriate treatment areas should have access to a copy of the CTCAE v4.03.

14.2 Prostate Cancer Working Group 2 Criteria

Progressive disease after androgen deprivation eligibility criteria:

The reference value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point 3 (value #3A) is greater than that at point 2, then eligibility has been met. If the PSA is not greater than point 2 (value #3B), but value #4 is, the subject is eligible assuming that other criteria are met, if values #3A or #4 are 2 ng/mL or higher.



Eligibility based on PSA

14.3 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Response and progression will be evaluated in this study using a modified version of the bone lesions identified on whole body technetium-99 bone scans will be recorded separately from soft tissue lesions detected on CT / MRI. CT / MRI will not be used to identify bone lesions. Radiological progression of bone lesions will be determined according to the radiological criteria of the PCWG2 (see Section 7.3.2.2). CT / MRI will be used to determine progression according to RECIST 1.1 (i.e., increase in tumor burden and appearance of new lesions with the exception of bone lesions). The overall time point response and resulting date of progression according to modified RECIST 1.1, will take into account disease assessed by bone scan and CT / MRI. For exploratory purposes, the date of progression by bone scan only will also be determined.

Table 14–1: Overall time point response

Response	Response characteristics
Complete response	Disappearance of all clinical and radiological evidence of tumor (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm.
Partial response	At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions and no appearance of new lesions.
Progressive disease	At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non-target lesions or the appearance of one or more new lesions will also constitute progressive disease.
Stable disease	Steady state of disease. Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease; no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Modified RECIST 1.1

Soft tissue disease (abnormal lymph nodes) and visceral lesions will be detected and monitored on chest, abdomen, and pelvic CT / MRI according to modified RECIST 1.1 criteria. Bone lesions will not be detected and followed on CT / MRI and will not be evaluated by RECIST 1.1. The described modifications in Table 14–2 represent an adaptation of the published criteria based on current radiology practices. A rationale for the modified criteria is provided. The modified criteria may include further definitions of rules, assumptions and/or clarifications of the original RECIST 1.1.

Table 14–2: Modified RECIST 1.1 criteria

Original RECIST 1.1 reference	Modified criteria	Rationale
Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability.	Bone lesions will only be evaluated by bone scan using a modified PCWG2 criteria defined in protocol. Bone lesions detected by CT / MRI cannot be selected as target or non-target lesions (to be followed quantitatively and qualitatively in respective order).	This approach has been successfully used in the double-blind phase III study (COU-AA-302) in the same patient population.
When more than one measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ)… should be identified as target lesions.	Up to 5 target lesions may be selected at baseline and followed quantitatively in all organs including lymph nodes (lymph node system constituting one organ).	This is to follow the PCWG2 recommendation, as lymph nodes are predominant site of metastasis except bone.

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; PCWG2 = Prostate Cancer Working Group 2; RECIST = Response Evaluation Criteria in Solid Tumors.

14.4 Calculation for glomerular filtration rate

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated GFR, calculated using the abbreviated Modification of Diet in Renal Disease study formula.

This equation of 4 variables (serum creatinine level, age, sex, and ethnicity) is recommended by the National Kidney Foundation for use in individuals 18 years or older. The formula is as follows:

GFR (mL / min / 1.73m^2) = k x 186 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (1.210 if Black)

Where k = 1 (men) or 0.742 (women), GFR indicates glomerular filtration rate, and serum creatinine is measured in mg/dL.

Subjects with a baseline GFR < 30 mL/min calculated by this method will not be allowed to participate in the study.

14.5 New York Heart Association 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.

14.6 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)

14.7 NCCN-FACT FPSI-17

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

			Not at all	A little bit	Some what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	P7	I have difficulty urinating	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	NCCN3	I have weakness in my legs	0	1	2	3	4
	P3	My pain keeps me from doing things I want to do	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	P6	I have trouble moving my bowels	0	1	2	3	4
	GS7	I am satisfied with my sex life	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale
English (Universal), Copyright 2001 03 March 2010

14.8 EQ-5D

Health Questionnaire

English version for the UK
(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

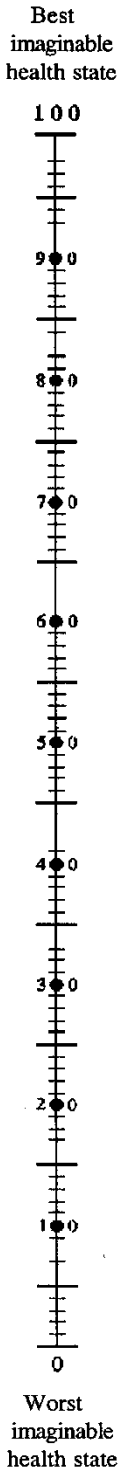
I am extremely anxious or depressed ❑

EQ-VAS

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



14.9 BPI-SF

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

Brief Pain Inventory (Short Form)

Date:____/____/____ Time:_____

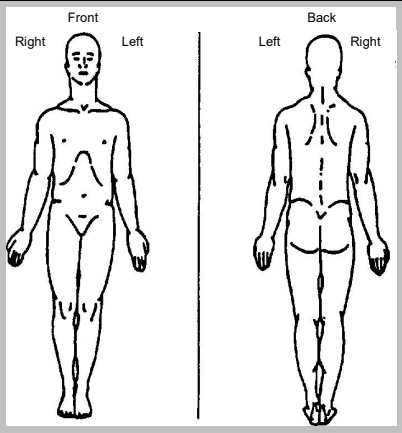
Name:_____ _____ _____

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

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

[redacted]___/___/____ [redacted]_____

[redacted]_____ _____ _____

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 [redacted] you have received.

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

14.10 Resource utilization questionnaire

Resource Utilization Questionnaire

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

During the past 4 weeks:

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		

---

5. Has the subject visited or been visited by a physician? ☐ No ☐ Yes

If yes: how many times? ☐☐