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APPLICATION NUMBER:

203971Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203971
Priority or Standard	Priority
Submit Date(s)	12/14/2012
Received Date(s)	12/14/2012
PDUFA Goal Date	6/14/2012
Division / Office	CDER/OHOP Division of Oncology Products - 1
Reviewer Name(s)	Paul G. Kluetz, M.D. - Efficacy William Pierce, Pharm.D. - Safety
Lead Clinical Reviewer	V. Ellen Maher, M.D.
Review Completion Date	
Established Name	radium Ra 223 dichloride
(Proposed) Trade Name	XOFIGO®
Therapeutic Class	Alpha-Emitting Radiopharmaceutical
Applicant	Bayer Pharmaceuticals
Formulation(s)	Intravenous (IV) solution
Dosing Regimen	50 kBq/kg administered as slow IV bolus 6 times at intervals of 4 weeks
Proposed Indication(s)	Treatment of castration-resistant prostate cancer patients with bone metastases
Intended Population(s)	Castration-resistant prostate cancer patients with bone metastases

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The primary clinical reviewers recommend regular approval of NDA 203971 for the indication: "treatment of symptomatic castration resistant prostate cancer patients with bone metastases and no evidence of visceral metastatic disease." This recommendation is based on substantial evidence of clinical benefit including a statistically significant and clinically meaningful improvement in overall survival and symptomatic skeletal events with an acceptable safety profile.

The recommended indication has been changed from the Applicant's proposed indication to more accurately reflect the patient population that was enrolled in the key randomized clinical trial which formed the basis for this submission.

1.2 Risk Benefit Assessment

NDA 203971 is primarily supported by data from trial BC1-06 (ALSYMPCA); a randomized, double-blind, placebo-controlled, international phase 3 trial enrolling patients with castration resistant prostate cancer and symptomatic bone metastases. Patients with visceral metastatic disease were excluded. The primary endpoint was overall survival (OS) with one pre-specified interim analysis. A key secondary endpoint was time to symptomatic skeletal events.

Efficacy:

At the time of the primary interim analysis, 809 patients were randomized 2:1 to receive radium-223 (Ra-223) at 50kBq/kg intravenously every 28 days for 6 injections plus best supportive care (N=541) or placebo given at the same frequency plus best supportive care (N=268). Opiate pain medications were used for cancer-related pain in 54% of patients, non-opiate pain medications in 44% and no pain medications in 2%. Patients were stratified by baseline alkaline phosphatase (ALP), current bisphosphonate use, and prior docetaxel exposure. Current bisphosphonate use was reported by 41% of patients and 58% had received prior docetaxel.

At the pre-specified interim analysis, the primary endpoint of overall survival met the O'Brien-Fleming efficacy boundary for statistical significance revealing a decrease in the risk of death in the Ra-223 arm with a hazard ratio of 0.695 (95% CI 0.552, 0.875), $p=0.00185$. The median overall survival was 14.0 months compared with 11.2 months for Ra-223 and placebo respectively. The result was supported by consistent findings in pre-specified OS subgroup analyses. Multiple sensitivity analyses to adjust for slight imbalances in baseline disease characteristics continued to show a benefit in favor of Ra-223. The time to symptomatic skeletal events (SSE) was also delayed in the Ra-223 arm with a hazard ratio of 0.610 (95% CI 0.461, 0.807), $p=0.00046$. The median time to SSE was 13.5 months compared with 8.4 months for Ra-223 and placebo respectively. The median time to first SSE when adjusting for informative

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censoring by including deaths as events was 8.2 months compared with 6.1 months in the Ra-223 versus placebo arm, respectively. The incidence of spinal cord compression (4% vs. 7%) and symptomatic pathologic bone fracture (5% vs. 7%) was lower in the Ra-223 arm compared to placebo, respectively. An updated analysis after enrollment of 921 patients revealed a persistent benefit for both overall survival and time to SSE favoring Ra-223. Other markers of disease activity including time to alkaline phosphatase progression and time to PSA progression were also statistically in favor of the Ra-223 arm. While limited by infrequent assessments and a high degree of missing data, patient reported outcomes data did not reveal a detriment in quality of life measures in the Ra-223 arm when compared with placebo.

Safety:

In the BC1-06 trial, at the time of the primary safety analysis (safety cutoff date of July 15, 2011), 600 patients had been treated with Ra-223 plus best supportive care and 301 patients had been treated with placebo plus best supportive care. The median duration of treatment was 20 weeks for Ra-223 (6 injections) and 18 weeks (5 injections) for placebo. The most common adverse reactions (ARs) (>10%) in patients receiving Ra-223 were nausea, diarrhea, vomiting and, peripheral edema. The most common hematologic laboratory abnormalities (> 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Dehydration occurred in 3.3% of the patients on Ra-223 and 1.3% patients on placebo; oral intake and fluid status should be monitored carefully for patients treated with Ra-223. Since fecal excretion is the major route of elimination and influenced by intestinal transit times, bowel movement frequency should also be carefully monitored during treatment with Ra-223.

On the Ra-223 arm, 2.3% of patients experienced bone marrow failure, with two bone marrow failure deaths (0.3%), compared to no bone marrow failure in patients treated with placebo. In patients experiencing bone marrow failure, there was a small increase in deaths related to vascular hemorrhage in Ra-223-treated patients (1.2%) compared to patients treated with placebo (0.3%). A majority of the patients who experienced bone marrow failure required blood transfusions and the bone marrow suppression was ongoing at the time of death. In the randomized controlled trial, blood transfusion and erythropoietin were used to manage myelosuppression, and G-CSF was used to manage persistent or febrile neutropenia. More patients treated with Ra-223 required blood transfusions (42% vs. 39%; respectively), erythropoietin (3.2% vs. 1.7%; respectively), and G-CSF (1.5% vs. 0%; respectively) treatment. In the randomized clinical trial, 16% of the patients in the Ra-223 group and 18% of the patients in the placebo group received cytotoxic chemotherapy after completion of study treatments. Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Ra-223 tolerate subsequent cytotoxic chemotherapy.

Due to its mechanism of action, and as seen in nonclinical toxicology data, Ra-223 may induce secondary malignancies. Epidemiology studies of short-lived, alpha-emitting, Ra-223-224 have demonstrated an increased risk of bone sarcoma and possible association with other secondary malignancies. In the randomized trial, less than 3% of the patients were followed for more than three years after initiation of study treatment. The expected latency period for secondary malignancies greatly exceeds the duration of follow up in the Ra-223 clinical trial database. The

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overall incidence of secondary malignancies in the randomized trial was lower on the Ra-223 arm compared to placebo (0.8% vs. 1.7%; respectively). The total incidence of solid non-cutaneous malignancies in the Ra-223 database is approximately 0.4%.

The administration of Ra-223 is associated with potential risks for medical staff, care givers and members of the patient's family from radiation or contamination from spills of body fluids such as feces or urine. Therefore, radiation protection precautions must be taken in accordance with national and local regulations. Following the normal working procedures for the handling of radiopharmaceuticals and use of universal precautions for patient care is expected to be sufficient given the physical properties of the Ra-223. Due to the fecal elimination pathway of Ra-223, patients should use a toilet and the toilet should be flushed several times after each use whenever possible. Clothing soiled with Ra-223 or patient fecal matter or urine should be washed promptly and separately from other clothing. In the event of spillage of Ra-223, the local radiation protection advisor should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area.

Risk:Benefit Analysis:

A statistically significant and meaningful improvement in overall survival provides substantial evidence for the efficacy of Ra-223. This is supported by an improvement in the time to symptomatic skeletal events. The application contains an adequate safety database revealing relatively modest increases in hematologic, gastrointestinal, and general adverse reactions for patients treated with Ra-223. The risk for longer term safety concerns such as bone marrow failure, secondary malignancies and the ability to tolerate subsequent cytotoxic chemotherapies will be investigated further through post-marketing requirements. Based on the totality of the data presented in this submission, the reviewers conclude that the benefit:risk of Ra-223 is favorable for the population studied in trial BC1-06: Symptomatic castration resistant prostate cancer patients with bone metastases and no evidence of visceral metastatic disease.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team did not identify substantial safety issues that would warrant a REMS. The Division of Risk Management consultation concurred with this assessment.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarketing Requirements:

There is concern for delayed toxicities with this radiation product including secondary malignancies, bone marrow failure, and intolerance to subsequent cytotoxic chemotherapy. A long-term follow-up study is being negotiated as a post-marketing required trial. Please see the final approval letter for details regarding the final trial size and design.

Postmarketing Commitments:

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During the review, inferior efficacy results in the lowest weight quartile by clinical pharmacology suggested a suboptimal dosing strategy. This was supported by the limited data from the BC1-04 trial suggesting improved efficacy at the 80 kBq/kg dose with similar safety. Because of these findings, a post-marketing commitment to evaluate alternative dosing strategies in order to maximize treatment effect is being drafted. Please see the final approval letter for details regarding the final trial size and design.

2 Introduction and Regulatory Background

Approximately 240,000 men in the United States are predicted to be diagnosed with prostate cancer in 2013. It is the most common non-cutaneous malignancy in U.S. men and the second leading cause of death with over 28,000 deaths in 2012.¹ While most patients are diagnosed at an early localized stage, approximately 15-30% of patients will recur following curative surgical or radiation therapy and the majority of these patients will be identified by PSA rise alone. Androgen deprivation therapy (ADT) with either surgical castration or gonadotropin releasing hormone (GnRH) analogs are commonly initiated to control disease in those with metastases or with non-metastatic disease at high risk (such as those with rapid PSA doubling time). Unfortunately, nearly all patients will eventually progress on ADT. When patients recur on ADT in the setting of "castrate" levels of testosterone, patients are termed "castration resistant". Ra-223 is intended for those patients with castration resistant prostate cancer with symptomatic bone metastases.

2.1 Product Information

Radium-223 dichloride solution for injection is a therapeutic alpha-particle emitting radiopharmaceutical. Throughout development, the compound has also been termed, "alpharadin" and may be referred to as such in some of the Applicant tables. The abbreviated name Ra-223 will be used preferentially throughout this review.

The predominance of alpha emission seen with Ra-223 differs from available bone-targeted radioisotopes which largely utilize beta emission. Alpha emitters have a higher energy and shorter ionization path (<100 μm) than existing beta emitting radiopharmaceuticals. Ra-223 dichloride has a physical half-life of 11.4 days. The majority of energy emitted by the decay of Ra-223 is alpha particles with energy ranging from 5.0 to 7.5 MeV.

Table 1: Ra-223 Energy Fractions

	Fraction of total energy emitted	Energy (MeV)
Alpha-particles (helium nuclei)	95.3%	Range 5.0 to 7.5
Beta-particles (electrons)	3.6%	0.445 and 0.492 (average)
Gamma-radiation (electromagnetic waves)	1.1%	Range 0.01 to 1.27

Source: Clinical Overview submitted by Applicant.

¹ Cancer Facts and Figures, American Cancer Society, accessed online 1/4/2012: <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf>

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Ra-223 accumulates in areas of high bone turnover by forming a complex with hydroxyapatite. Because bone metastases frequently demonstrate increased bone metabolism, Ra-223 is taken up preferentially in areas of bone metastases. Ra-223 is formulated as a ready-to-use solution containing Ra-223 dichloride ($^{223}\text{RaCl}_2$) to be administered according to the following recommendations:

- Clinical dose: 50 kilobecquerel (kBq) (= 0.00135 mCi) per kilogram body weight
- Regimen: every 4 weeks (q4w) for 6 cycles
- Administration: slow intravenous (i.v.) injection (generally up to 1 minute)

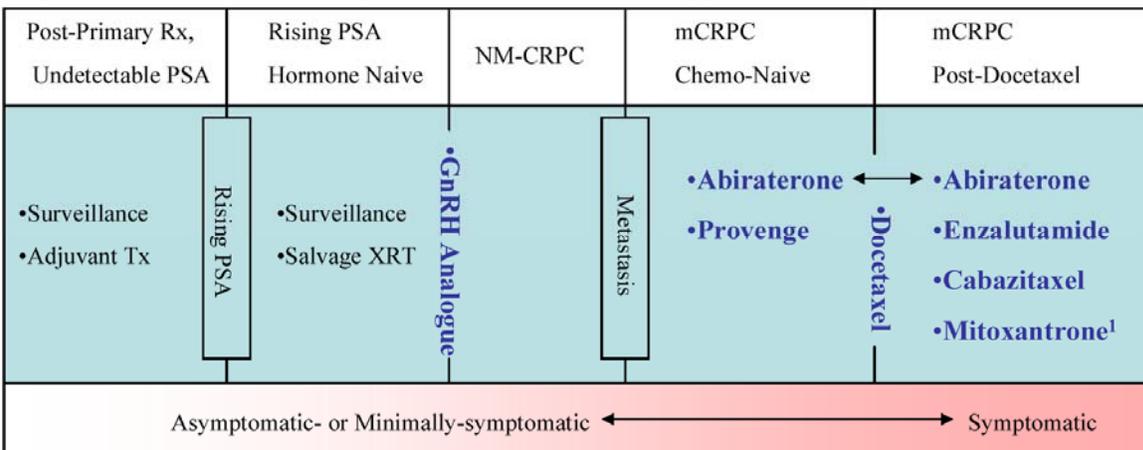
2.2 Tables of Currently Available Treatments for Proposed Indications

For the purposes of this discussion, **systemic therapies** are those which are not targeted to a specific organ and would be considered to have activity to all areas of disease within the body (with the exception of the CNS depending on blood-brain barrier permeability). **Bone-targeted therapies** are considered active predominately in the bone leaving lymph node and visceral metastases untreated.

Systemic Therapies:

The FDA approved systemic therapies for the treatment of metastatic castration resistant prostate cancer (mCRPC) are illustrated in dark blue in Figure 1 below:

Figure 1: Prostate Cancer Systemic Treatment FDA Approvals



¹ Mitoxantrone approved in 1996 for treatment of pain related to advanced hormone refractory prostate cancer. mCRPC: Metastatic Castration Resistant Prostate Cancer
nmCRPC: Non-Metastatic Castration Resistant Prostate Cancer

Since 2004, there have been 6 indications for 5 drug and biologic products approved for the treatment of metastatic castration resistant prostate cancer (mCRPC):

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- Docetaxel (2004): mCRPC
- Provenge (2010): asymptomatic or minimally symptomatic mCRPC
- Cabazitaxel (2010): mCRPC previously treated with docetaxel
- Abiraterone (2011): mCRPC previously treated with docetaxel.
- Enzalutamide (2012): mCRPC previously treated with docetaxel
- Abiraterone (2012): indication expanded to include chemotherapy-naive mCRPC

All five systemic therapies approved for metastatic prostate cancer in the last 10 years have been initially approved based on overall survival, a direct measure of clinical benefit. Mitoxantrone was approved in 1996 based on a composite pain endpoint, also considered a measure of direct clinical benefit.

Table 2: Endpoints for Metastatic Prostate Cancer Approvals

Drug	Endpoint	Magnitude (Months)	HR (95%CI)
mCRPC			
Mitoxantrone+Pred	Pain	29% vs 12% (p=0.011)	n/a
Docetaxel+Pred	OS	2.4 (18.9 vs 16.5)	0.76 (0.62, 0.94)
Provenge	OS	4.1 (25.8 vs 21.7)	0.78 (0.61, 0.98)
Zytiga+Pred	OS	3.9 (14.8 vs 10.9)	0.65 (0.54, 0.77)
	rPFS	(NR vs. 8.3)	0.43 (0.35, 0.52)
mCRPC after Failure of Docetaxel			
Cabazitaxel+Pred	OS	2.4 (15.1 vs 12.7)	0.70 (0.59, 0.83)
MDV3100	OS	4.8 (18.4 vs 13.6)	0.63 (0.53, 0.75)

Note: GnRH analogues have been approved based on reduction in serum testosterone.

Note: Abiraterone approval based on rPFS granted in the setting of a known overall survival benefit in the post-chemotherapy setting.

Bone Targeted Therapies:

In contrast to the systemic therapies mentioned above, bone-targeted agents have their activity limited to the bone. The available bone-targeted therapies for prostate cancer are shown in Table 3 below.

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Table 3: Available Bone-Targeted Therapies for Prostate Cancer

Drug	Endpoint	Magnitude (months)	HR
Inhibitors of Osteoclast Bone Resorption			
Zoledronic Acid	Time To SRE*	NR (NR vs 10.6)	0.67 (0.49-0.91)
Denosumab†	Time To SRE	3.6 (20.7 vs 17.1)	0.43 (0.35-0.52)
Bone-Seeking Radiopharmaceuticals			
Strontium Chloride, Sr-89 (Metastron)	Reduction in Pain Score	Improvement in % of patients with pain score reduction and % of patients with resolution of pain	
Samarium-153 (Quadramet)	Reduction in Pain Score	Improvement in patient reported VAS for pain and decrease in analgesic use.	

* SRE composite endpoint: Pathologic Fracture, EBRT, Surgery, Cord Compression, or Change in Systemic Therapy for Pain.

† Active comparator trial Denosumab (XGEVA) vs. Zometa was noninferior and met statistical significance for superiority. SRE was defined as pathologic fracture, EBRT, Surgery or Spinal Cord Compression.

Osteoclast-targeted therapies zoledronic acid (Zometa) and denosumab (Xgeva) were approved based on a delay in the time to skeletal related events. In addition, two bone-seeking radioisotopes were approved for the palliation of bone pain from metastatic disease; Strontium-89 approved in 1993 and samarium-153 approved in 1997.

Strontium-89 (Metastron) Approved in 1993:

Strontium is indicated for the relief of bone pain in patients with painful skeletal metastases. Key characteristics of Strontium-89 include:

- Pure Beta emitter maximum range in tissue is approximately 8mm
- Max energy is 1.46 MeV
- Half life 50.5 days
- Excretion 2/3 urine, 1/3 fecal (higher urine excretion in patients with lower bone disease)
- Platelet Nadir between 12 and 16 weeks. (typically about 30% reduction)

Strontium was approved based on a placebo controlled trial of 126 patients. The trial demonstrated a reduction in pain score without an increase in analgesic intake and without supplemental radiotherapy at the index site of metastases.

Table 4: Strontium Efficacy: Patients with reduction in pain score

	Months Post-Treatment					
	1	2	3	4	5	6
Metastron	71.4% (n=42)	78.9% (n=38)	60.6% (n=33)	59.3% (n=27)	36.4% (n=22)	63.6% (n=22)
Placebo	61.4% (n=44)	57.1% (n=35)	55.9% (n=34)	25.0% (n=24)	31.8% (n=22)	35.0% (n=20)

Source: FDA Label

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Samarium-153 (QUADRAMET®)

Samarium-153 is indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan. Key characteristics of Samarium-153 include:

- Beta and Gamma emitter maximum range in tissue 3.0mm and bone 1.7mm
- Max Beta energy is 0.233 MeV
- Radioactive half life is 46.3 hours
- Excretion in Urine
- Bone Marrow suppression nadir to 40-50% baseline in 95% patients within 3 to 5 weeks

Samarium-153 approval was based on 270 patients in two randomized clinical trials of patients with prostate cancer (86%) and other cancers with radiographic evidence of bone metastases and pain. A reduction in weekly pain score was demonstrated as seen in Table 5:

Table 5: Samarium-153 Efficacy Results; Comparison of Weekly Pain Scores

	STUDY A (n = 73) (b)		STUDY B (n = 150) (c)	
WEEK	Placebo N=36	1.0 mCi/kg N=37	Placebo N=50	1.0 mCi/kg N=100
Baseline	26.5 (11.8)	28.7 (12.3)	28.5 (14.1)	28.1 (12.9)
1	26.1 (10.3)	27.6 (14.1)	27.9 (14.6)	25.8 (13.1)
2	24.4 (10.4)	23.8 (13.7)	28.1 (15.4)	20.6 (13.9)*
3	24.3 (11.0)	20.5 (11.5)*	25.8 (16.1)	20.1 (13.3)*
4	24.7 (12.1)	18.8 (10.8)*	24.7 (15.3)	19.9 (13.7)*

(*) Statistically significant difference in change from baseline in comparison to placebo
Source: FDA Label for Samarium-153 (QUADRAMET®)

Available Therapy Summary:

In summary, the initial approvals of available therapies for the treatment of metastatic prostate cancer have largely relied on improvements in either overall survival, skeletal related events or pain. All three of these endpoints can be considered direct measures of clinical benefit in a well-conducted, blinded randomized clinical trial setting. In contrast to the available bone-seeking beta-emitting radioisotopes, Strontium and Samarium, Ra-223 is the first alpha-emitting bone-targeted therapy and also the first radio-pharmaceutical to seek FDA approval based on an overall survival benefit.

2.3 Availability of Proposed Active Ingredient in the United States

Ra-223 dichloride is not currently marketed in the U.S. There are several ongoing clinical trials including a large expanded access protocol 15955 (Table 11).

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2.4 Important Safety Issues With Consideration to Related Drugs

There are currently no therapeutic alpha-emitting radionuclides approved in the United States. The most relevant approved products are bone-targeted, beta-emitting, radioisotopes used for palliation of bone pain from metastatic disease. The most significant toxicity related to beta-emitting strontium-89 and samarium-153 is bone marrow suppression. The safety profile of an alpha particle emitter (alpha particles can penetrate 10 microns of tissue) is expected to differ from these beta emitters. The administration of any radionuclide is associated with potential risks for other persons from radiation or contamination from spills of body fluids such as feces or urine. Therefore, radiation protection precautions must be taken in accordance with national and local regulations. Universal precautions are expected to adequately protect healthcare providers and caregivers since the alpha particles will not penetrate a glove.

There is no significant exposure data available for Ra-223 from other human experience. Historical toxicity findings related to a similar isotope, radium-224 ($t_{1/2}$ = 3.6 days), are relevant to Ra-223 ($t_{1/2}$ = 11.4 days) given that both radium -223 and -224 are relatively short-lived alpha-emitting radioactive particles. Based on the radium-224 experience, potentially serious or life-threatening toxicities for Ra-223 may include bone marrow failure, bone sarcoma, secondary malignancies, and osteonecrosis. Epidemiology studies also suggest the incidence of other malignancies, including solid tumors and leukemia, may be increased with short-lived alpha-emitting radionuclides. The exposure levels required to induce these toxicities or to increase the risk of secondary cancers is controversial and not clearly defined.

For additional details see section 7.2.6.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Ra-223 has been developed under IND 67,521 originally submitted by Algeta ASA on December 20, 2007. Prior to IND submission there were multiple pre-IND meetings held starting in July of 2004 which focused predominately on challenges related to dosimetry and the novel alpha-emitting mechanism of action. Bayer became the sponsor of the IND upon transfer of obligations dated May 27, 2011. The following is a table summarizing the key regulatory history of the development of Ra-223:

Table 6: Key Regulatory Interactions

July 2004	Pre-IND: Agency requests protocol design of biodosimetry, rationale and justification of starting dose and long and short term safety monitoring plan.
Feb 2005	Pre-IND telcon to discuss Phase I trial
Jun 2005	Pre-IND telcon on required preclinical studies and clinical development
Feb 2006	pre-IND telcon RE: long-term radiation nonclinical toxicology program
Feb 2007	Type C Mtg discussion regarding NIST calibration measurement program and design of phase 1b dosimetry (Study BC1-05)
Jul 2007	Follow-up Telcon from Type C above
Dec 2007	Algeta ASA submits new IND 67,521

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Jan 2009	End of Phase 2 Meeting
May 2011	Sponsorship transferred from Algeta ASA to Bayer Pharmaceuticals
Aug 2011	Fast Track Designation Granted
Oct 2011	pre-NDA meeting held
Jul 2012	Type C to discuss CMC aspects of drug substance characterization

Key Minutes of 2009 End of Phase 2 Meeting:

- Nonclinical:
FDA agreed that carcinogenicity, genotoxicity, development and reproductive toxicology studies would not be required.
- Phase 3 Study Design:
The current design of the study is adequate for demonstrating the clinical benefit of Radium-223 (Ra-223).
- Statistical Analysis Plan
FDA recommended the use of a log-rank test rather than Cox model for the primary efficacy analysis. FDA requested that the Applicant pre-specify the criteria for any increase in sample size
- Late Radiation Toxicity:
The agency stressed the importance of follow up for late radiation toxicity
- Definition of Symptomatic for Inclusion Criteria:
FDA noted patients who receive ERBT for bone pain should not be considered symptomatic if they do not have pain or analgesic use at screening.

Reviewer Comment: Only 16/809 patients in the primary analysis had a WHO analgesic score of 0 at baseline (no pain medication). See baseline characteristics in Efficacy section.

Key Minutes of 2011 pre-NDA Meeting:

Clinical:

- FDA asked for more information regarding the Quality Verification Program and under-reporting of AEs.

3 Ethics and Good Clinical Practices

It is documented in the submitted study report that the protocol and all protocol amendments were reviewed and approved by independent ethics committees (IEC) or institutional review boards (IRBs). The study was said to be conducted in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP, ICH E6). An IEC/IRB approved informed consent

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document was required to be voluntarily signed by all subjects. An independent data monitoring committee (IDMC) was established to review safety data at regular intervals as well as the primary efficacy variable OS at the pre-planned interim analysis. The Applicant states the IDMC members had no affiliation with the investigators or sponsor.

3.1 Submission Quality and Integrity

FDA reviewers noted a longer than normal time period between the pre-NDA meeting and the submission of the NDA. When queried regarding the reason of this delay, the Applicant responded that the delay was primarily due to commercial manufacturing challenges as well as additional data cleaning including a Quality Verification Program (QVP) for the BC1-06 trial.

After careful review of submitted data, multiple information requests, clinical site inspections and discussions with the Applicant, the overall quality and integrity of the submitted data was found to be acceptable. Both raw and analysis datasets were provided for trial BC1-06 at both the interim (primary analysis) cutoff as well as the updated analysis which provided reviewers with the ability to verify analyses submitted in the clinical study report. Additional case report forms, narratives and analyses were requested and obtained throughout the review further verifying key safety and efficacy findings.

3.2 Compliance with Good Clinical Practices

Quality Verification Program (QVP)

After a routine planned audit conducted by Bayer, Algeta (b) (4) up to the end of 2010, a potential under reporting of adverse events was observed. This prompted the initiation of a Quality Verification Program. The Quality Verification Program summary report (R-8744) v.1.0 dated 11/24/2012 was submitted by the Applicant. The QVP was intended to confirm the quality of data with respect to adverse events, patient eligibility and CRA access to electronic source data.

Timeline:

- January 2011 Step I Initiated
- March 2011 Step II Initiated

Site Selection for Step 1 was Risk-Based using the following criteria:

- Audit findings
- High recruiting sites
- Data entry back log
- Monitoring back log
- Query processing (high # of queries)
- Sites with higher or lower reported A.E.s per patients than study average
- Geographic spread was considered

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Scope:

AE / SAE Reporting

- The AE/SAE reporting audit was conducted by performing frontwards and backwards CRF-to-source data verification.
- Approximately 75% of the patients randomized by 10/13/2010 in both the ITT (595/809) and Safety population (561/762) were reviewed for AE/SAE reporting

Source Data Verification

- 31 patients had 100% source document verification during audit. This included eligibility, process in place to ensure blinding, procedure in place for documentation of extent of disease, and informed consent. Another 62 patients had targeted source document verification (selected eligibility criteria, medical history, prior therapy, concomitant medications and adverse events. Thus, 93/809 patients (11%) of patients had some level of source data verification. Just over 50% of sites were reviewed.
- Site Selection: Sixty seven of 128 (52%) sites were reviewed. All 67 sites were reviewed for CRA access to source data.

Results:

AE / SAE REPORTING

- 9 under-reported treatment-emergent SAEs in 8 patients
- 3 under-reported SAEs occurring prior to treatment in 3 patients
- Approximately 1 under-reported AE per patient (565 under-reported AE/SAE out of 561 patients).
- A total of 565 under-reported out of 5,140 AEs (11%)

SOURCE DATA VERIFICATION

- 93 patients were selected for either 100% (31) or targeted (62) source verification. The predominant discrepancies were related to concomitant medications (38 patients) and medical history (32 patients). The Applicant notes that none of these findings were likely to affect eligibility, the safety of subjects or the assessment of efficacy.

QVP Conclusion:

The report concludes that there were no obvious patterns or unexpected findings in the types of adverse events under-reported. While there were some countries with higher under-reporting, there were differences between sites within those countries and in general there was no regional, site or CRA pattern noted or bias of under-reporting for either treatment arm. CRO study teams were retrained and 31 sites were identified as needing further quality oversight and the QVP was extended for them into the post-interim analysis phase of data collection.

Reviewer Comment: In order to address concerns regarding the accuracy of CRFs and primary analysis datasets with respect to overall survival and skeletal related events, a

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teleconference between the FDA and the Applicant was held on January 18, 2013 in which the Applicant reviewed the quality verification program. Following this teleconference, additional CRFs based on longest OS in Ra-223 arm and shortest OS in placebo arm as well as additional CRFs selected at random were obtained and cross-checked to ensure accurate CRF to Dataset conversion for SRE and OS dates. Focus on source verification of primary efficacy event dates was also performed at the clinical site inspections.

Following careful consideration of the results of the teleconference and further CRF analysis, as well as the clinical site inspections with source verification performed by the FDA Office of Scientific Investigation, the review team concludes that the integrity of the efficacy and safety data for trial BC1-06 is adequate.

Site Closures:

There were 7 sites that were permanently closed to randomization and the reasons for closure were reviewed. (Study Center Numbers 209, 028, 170, 173, 181, 155 and 071). Site 028 in Belgium was noted to have high proportion of early deaths. Despite closure of these sites, all patients were included in both ITT and safety populations. The list of site closures was brought to the attention of the Division of Scientific Investigations to assist in their review.

Reviewer Comment: The Applicant was asked whether any of the site closures were reported to the FDA under the IND. The Applicant responded that these were not considered premature site closures, but rather enrollment holds and thus they did not feel they were required to report them. No single site enrolled more than 12 patients and all the above sites together enrolled only 6.4% of the interim analysis population..

Clinical Database - CIOMS Discrepancies

The Applicant conducted a routine quality control medical review of the contents of the Council for International Organizations of Medical Sciences (CIOMS) forms and the narratives and compared them with the patient profiles in the clinical database to evaluate for discrepancies. This was conducted by sponsor medical experts. Patients who were reviewed included deaths during treatment or within 30 days of last treatment, SAEs, or AEs leading to discontinuation. The majority of inconsistencies were with concomitant medications that were not entered into the database. Additional skeletal related events were also found via review of the adverse event datasets.

Reviewer Comment:

These discrepancies were reviewed and do not appear to materially affect the efficacy or safety findings with the exception of those which would be considered skeletal related events. The additional 38 unreported skeletal related events were included in a post-hoc exploratory analysis by the Applicant with slightly improved hazard ratio favoring the Ra-223 arm. Further details regarding the additional SRE events are found in the Efficacy section of the clinical review.

Protocol Deviations:

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A total of 232 patients had protocol violations as defined by the protocol. There were 95/268 (35.4%) protocol violations in the placebo arm compared with 137/541 (25.3%) violations in the Ra-223 arm. The most common protocol violation was receiving less than 3 doses of study treatment which was required in order to be included in the per-protocol (PP) population. Protocol deviations by arm are listed in Table 7 below:

Table 7: Protocol deviations for BC1-06

Protocol Deviations:	Ra-223		Placebo	
	N=541		N=268	
Any Protocol Deviation:	137	25.3%	95	35.4%
< 3 doses	110	20.3%	74	27.6%
Inclusion: PSA Progression	17	3.1%	7	2.6%
Inclusion: Testosterone <50	14	2.6%	7	2.6%
Inclusion: Confirmed AdenoCa of Prostate	8	1.5%	2	0.7%
Exclusion: Visceral Metastases	6	1.1%	3	1.1%
Exclusion: >3cm Lymphadenopathy	3	<1%	0	0.0%
Inclusion: Orchiectomy or Continuous LHRH	2	<1%	2	<1%
OTHER*	1	<1%	5	1.9%

Source: Analysis dataset [PV] cutoff 10/2010.

* Radium arm: 1 had other malignancy within 5 years.

* Placebo arm: 3 patients treated with cytotoxic chemotherapy within 4 weeks, 1 patient lacked multiple skeletal metastases and 1 patient received incorrect study treatment.

Reviewer Comment: The discrepancy seen between the arms in protocol deviations is primarily due to the placebo group receiving less than 3 doses of study medication. This appears to be secondary to patients being discontinued for disease progression or death prior to receiving their 3rd placebo dose. Early deaths from both arms were noted in the IDMC minutes and it was stated that adherence to the protocol inclusion/exclusion criteria, particularly with respect to performance status and life expectancy, should be reiterated to Investigators. This appears to have made a difference. Of the 314 death events in the primary analysis (10/2010 data cutoff), 19/314 (6%) occurred within 60 days of randomization (11 Radium and 8 placebo). In the subsequent 2011 analysis, of the additional 214 death events there were only 4 deaths that had occurred within 60 days of randomization (1.9%) indicating that early deaths were less common as the trial progressed. The remainder of the protocol deviations were relatively well balanced between the arms and unlikely to bias the study results.

Clinical Site Inspections:

Based on efficacy and safety reporting as well as protocol deviations for each clinical site, 4 study sites were identified for clinical site inspections performed by the Office of Scientific Investigations (OSI).

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Table 8: Clinical Inspection Sites Trial BC1-06

Site # (Name, Address, Phone number, email, fax#)	Number of Subjects	Indication
Site ID: 006 Kreftpolikliniken, Haukeland University Hospital Bergen 5021 Norway	45	Highest Accrual.
Site ID: 035 Cancer Centre, Belfast Hospital Lisburn Road Belfast BT9 7AB UK	32	High Accrual, Low reporting of Grade 3-4 AE
Site ID: 033 The Royal Marsden Surrey SM2 5PT UK	27	High Accrual, Global Principal Investigator Site Large OS benefit favoring Investigational Arm
Site ID: 002 Ullevål University Hospital Kirkeveien 166 Oslo N-0407 Norway	17	Large OS benefit favoring Investigational Arm, High Accrual

In addition to clinical sites, the Applicant, Bayer, was inspected. Source verification of key efficacy endpoints were conducted including overall survival and symptomatic skeletal events. Of note, site 006, 033 and 035 were identified by the Applicant based on their risk based approach for the Quality Verification Program. Site 002 was not a part of the QVP.

The clinical and Applicant site inspections did not reveal any significant concerns at the time of this review, however final inspection report is pending.

3.3 Financial Disclosures

A financial disclosure reporting threshold of \$25,000 per investigator was used. The overall financial disclosure information was reviewed. The study coordinating investigator (b) (6) was noted to have received a total of \$60,983 collectively from Bayer and Algeta in the form of consulting and honoraria fees. The Applicant notes the following steps to minimize potential bias from this relationship:

1. The investigator enrolled only (b) (6) of the total study population randomized
2. The interpretation of the outcome for the primary endpoint of OS is not subject to bias
3. There were a total of 136 sites enrolling patients into the trial.

Reviewer Comment: The subset of patients enrolled by the study coordinating investigator (b) (6) were reviewed. An analysis of the main efficacy endpoint (OS) was performed by the statistical reviewer for the patients enrolled at this site at the time of the interim analysis. While this subgroup did appear to have a more favorable outcome than the overall trial, the number of

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patients was small compared with the overall trial population (b) (6). Exclusion of (b) (6) data from the OS dataset did not materially affect the study results. It is the reviewer's determination that there is insufficient evidence to conclude that financial conflict materially affected the outcome of the pivotal trial BC1-06.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

During the review, it was noted that the calibration of the radiation dose for Ra-223 may be a potential safety/efficacy issue. An information request was sent to the Applicant regarding the concern that given the novel alpha-emission characteristics of Ra-223, commercial U.S. radio-pharmacies (outside of clinical trial conditions) may not be able to accurately measure the correct dose using standard dose calibrators. Data regarding the type of calibrators used in the clinical trial BC1-06 and their suitability to generalize to standard U.S. practice were requested. The Applicant responded with this data and in addition, applicable NIST reports on Ra-223 measurement and NIST traceable sources were submitted. A teleconference was also held during the review to discuss these issues with CMC and the clinical team.

Following review of this data by CMC and the clinical reviewer it was determined that the dose calibration method proposed by the Applicant would be acceptable with appropriate labeling.

Please see the FDA primary CMC review for details.

4.2 Clinical Microbiology

The FDA microbiology review notes the radioactive product is filled (b) (4). The FDA Microbiology reviewer recommends approval from a quality microbiology standpoint.

4.4 Clinical Pharmacology

Single- and multiple-dose pharmacokinetic, biodistribution and dosimetry data were obtained from 3 phase-1 studies and 3 phase-2 studies (see Table 10) at doses ranging from 46 to 250 kBq/kg body weight. For a full discussion of the clinical pharmacology package please see the primary FDA clinical pharmacology review. Briefly, Ra-223 is rapidly cleared from the blood with only 20% at 15 minutes, 4% at 4 hours and <1% at 24 hours of post-injection activity present in the blood. Fecal excretion is the major route of elimination. There is no significant renal or hepatic clearance. There was no significant uptake in the heart, liver, kidneys urinary bladder or spleen at 4 hours.

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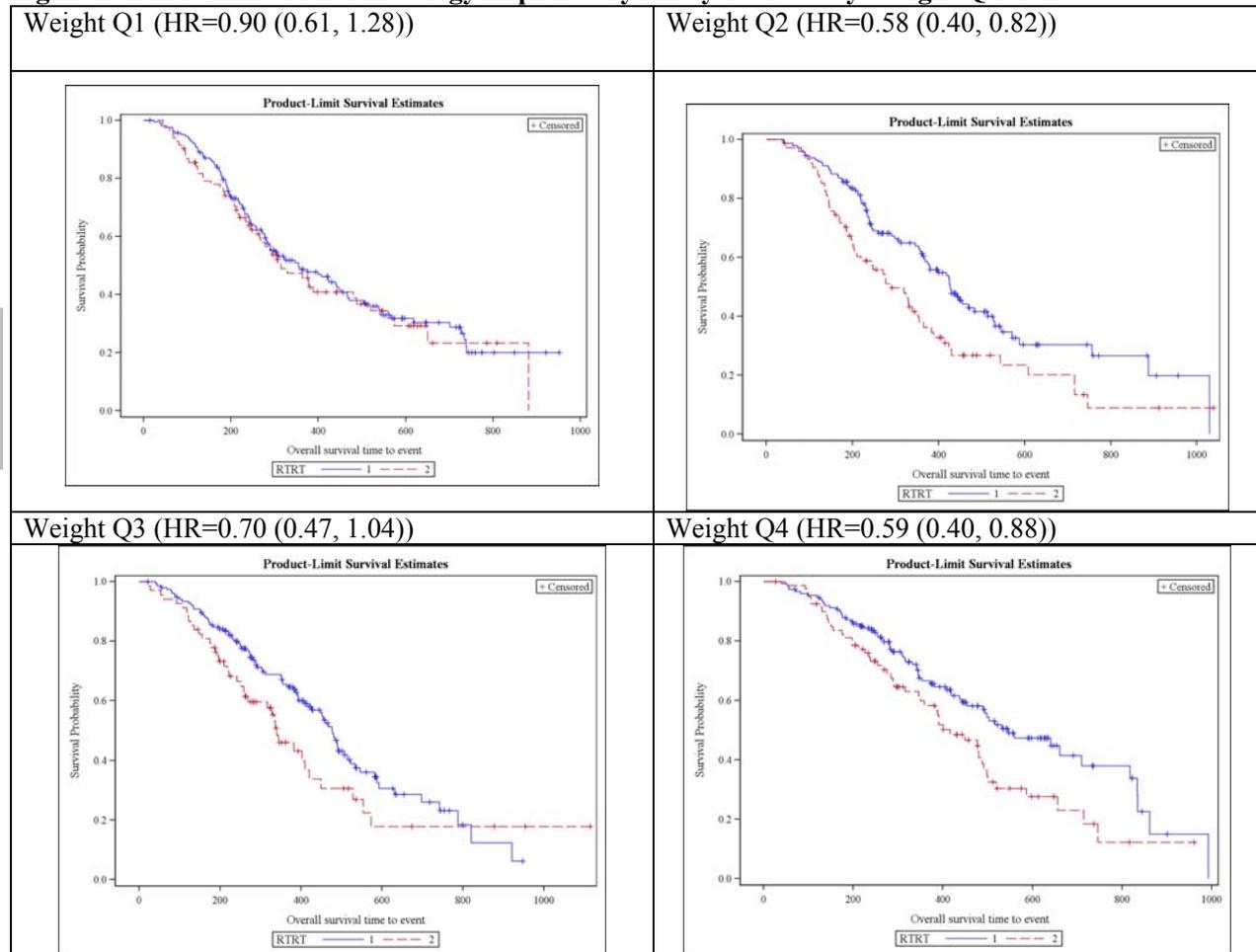
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Reviewer Comment: There is a concern regarding secondary exposure to the patient and/or caregivers through radioactivity present in feces during the first several days after injection. The concern is mitigated by the very short path length of the alpha-emission based radioactivity. Additionally, given fecal elimination, constipation and decreased fecal transit as well as environmental exposure were discussed throughout the review and were considered during labeling. Analysis of adverse events for those with and without constipation was performed and did not reveal a substantial increase in adverse events. See safety results for details.

Weight Based Dosing:

It was noted by clinical pharmacology that when analyzing the population by weight quartiles, the lowest weight quartile appeared to demonstrate substantially lower efficacy in an exploratory post-hoc analysis of overall survival. (Figure 2)

Figure 2: FDA Clinical Pharmacology Exploratory Analysis of OS by Weight Quartile



Source: FDA Clinical Pharmacology Reviewer Analysis, BC1-06 performed on updated analysis dataset (N=921) adjusted by ALP, Docetaxel and Baseline ECOG. Red line placebo, Blue line Ra-223.

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Analysis of the time to PSA progression also revealed an inferior result in the lowest weight quartile when compared to the higher weight quartiles and the overall results. Interestingly, the time to alkaline phosphatase progression was significantly in favor of Ra-223 in all weight quartiles. (Table 9)

Table 9: Time to PSA and ALP Progression by Weight Quartile (Updated Analysis)

	Body Weight Quartile 1 Weight <= 73 kg		Body Weight Quartile 2 73kg < Weight <= 82 kg		Body Weight Quartile 3 82kg < Weight <= 91 kg	
	Ra-223 (N=160)	Placebo (N=81)	Ra-223 (N=146)	Placebo (N=75)	Ra-223 (N=154)	Placebo (N=68)
PSA						
Subjects randomized	160	81	146	75	154	68
Experienced	105 (65.6%)	47 (58.0%)	85 (58.2%)	46 (61.3%)	104 (67.5%)	45 (66.2%)
Censored	55 (34.4%)	34 (42.0%)	61 (41.8%)	29 (38.7%)	50 (32.5%)	23 (33.8%)
Time to PSA progression ^a Median (95% CI)	3.5 (3.3, 3.8)	3.5 (3.4, 4.1)	3.5 (3.4, 4.0)	3.4 (3.2, 3.5)	3.5 (3.4, 3.8)	3.4 (3.3, 3.5)
p value ^b	0.9735		0.0008		0.0364	
Hazard ratio (95% CI) ^c	1.006 (0.701, 1.443)		0.528 (0.361, 0.770)		0.674 (0.464, 0.977)	
ALP						
Subjects randomized	160	81	146	75	154	68
Experienced	23 (14.4%)	40 (49.4%)	28 (19.2%)	31 (41.3%)	24 (15.6%)	35 (51.5%)
Censored	137 (85.6%)	41 (50.6%)	118 (80.8%)	44 (58.7%)	130 (84.4%)	33 (48.5%)
Time to total ALP progression ^d Median (95% CI)	7.4 (7.1, 7.4)	4.1 (3.5, 5.0)	NE	3.9 (3.4, 5.3)	NE (6.6, NE)	3.7 (3.3, 4.3)
p value ^b	< 0.0001		< 0.0001		< 0.0001	
Hazard ratio (95% CI) ^c	0.127 (0.070, 0.229)		0.215 (0.122, 0.378)		0.128 (0.071, 0.232)	

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	Body Weight Quartile 4 Weight > 91 kg		Overall	
	Ra-223 (N=150)	Placebo (N=81)	Ra-223 (N=614)	Placebo (N=307)
PSA				
Subjects randomized	150	81	614	307
Experienced	91 (60.7%)	53 (65.4%)	388 (63.2%)	193 (62.9%)
Censored	59 (39.3%)	28 (34.6%)	226 (36.8%)	114 (37.1%)
Time to PSA progression ^a Median (95% CI)	4.1 (3.6, 5.0)	3.4 (3.3, 3.5)	3.6 (3.5, 3.8)	3.4 (3.3, 3.5)
p value ^b	< 0.0001		< 0.0001	
Hazard ratio (95% CI) ^c	0.444 (0.307, 0.644)		0.643 (0.539, 0.768)	
ALP				
Subjects randomized	150	81	614	307
Experienced	31 (20.7%)	43 (53.1%)	106 (17.3%)	151 (49.2%)
Censored	119 (79.3%)	38 (46.9%)	508 (82.7%)	156 (50.8%)
Time to total ALP progression ^d Median (95% CI)	NE (6.4, NE)	3.7 (3.5, 4.2)	7.4 (7.1, NE)	3.8 (3.6, 4.2)
p value ^b	< 0.0001		< 0.0001	
Hazard ratio (95% CI) ^c	0.197 (0.120, 0.322)		0.167 (0.129, 0.217)	

Source: FDA statistical reviewer using data cutoff 7/15/2011 (updated analysis datasets)

^a Time to PSA progression is calculated as months from date of randomization to date of PSA progression. PSA progression was defined as:

- in subjects with no PSA decline from baseline as: $\geq 25\%$ increase from the baseline value and an increase in absolute value of ≥ 2 ng/mL, at least 12 weeks from baseline
- in subjects with an initial PSA decline from baseline as: $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir value, which was confirmed by a second value obtained ≥ 3 weeks later

^b p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.

^c Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior used of docetaxel. Hazard ratio < 1 favors Ra-223dichloride.

^d Time to total ALP progression is calculated as months from date of randomization to date of total ALP progression.

Total ALP progression was defined as:

- in subjects with no total ALP decline from baseline as: $\geq 25\%$ increase from the baseline value, at least 12 weeks from baseline
- in subjects with an initial total ALP decline from baseline as: $\geq 25\%$ increase above the nadir value, which was confirmed by a second value obtained ≥ 3 weeks later.

Note: Subjects who did not experience an event were censored at the last disease assessment date.

Note: Cut-off date July 15, 2011.

Note: Dataset used in this analysis: [PSAALP]

It is also notable that the BC1-04 dose-finding study revealed a higher confirmed PSA response at the higher 80 kBq/kg dose level. (see section 5.3 Discussion of Individual Studies/Clinical Trials) For further details regarding the clinical pharmacology of Ra-223, please see the full Clinical Pharmacology review.

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Reviewer Comment: Based on the analysis of overall survival by weight quartile, as well as PSA response results from the dose finding study BC1-04, the dosing strategy for Ra-223 may not be optimal. A post-marketing commitment is being drafted in order to optimize dosing of Ra-223.

4.4.1 Mechanism of Action

Ra-223 is an alpha-emitting radionuclide. The divalent cation Ra-223 is the active moiety and is selectively taken up in areas of increased bone turnover (such as bone metastases) where it forms a complex with hydroxyapatite. Ra-223 is unique compared with other available therapeutic radiopharmaceuticals in that 95.3% of its total energy emitted is via alpha-particles (helium nuclei). Alpha emitters have higher radiation transfer than beta emitters and induce double-strand DNA breaks which sets Ra-223 apart from existing radiopharmaceuticals. (Figure 3) Alpha particles also have a very short track length providing dense ionizing radiation in a narrow range with the theoretical benefit of less toxicity to adjacent healthy bone marrow.

Figure 3: Physical Characteristics of Ra-223 and other Radiopharmaceuticals

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Source: Adapted from Goyal et al., Cancer Letters (2012) 135-146.

4.4.2 Pharmacodynamics

Clinical trial BC1-04 assessed a total of 122 patients randomized to three doses of Ra-223: 25-, 50-, and 80 kBq/kg. There was a significant dose response noted with 0%, 5.6% and 12.8% of patients demonstrating a confirmed 50% PSA decline for the 25-, 50- and 80 kBq/kg doses respectively. In the phase 3 trial, BC1-06, patients with higher actual body weight (i.e., higher total dose) appear to exhibit better OS improvement while experiencing no substantial increase in the incidence of Grade 3 or worse (Grade 3+) adverse events (AEs). The dose - response relationship for efficacy (e.g., OS improvement) is even more clear, when ideal body weight (IBW) normalized dose $[(\text{actual body weight} * 50 \text{ kBq/kg}) / \text{ideal body weight}]$ is used as the variable for dose. The OS benefit seems to be limited in patients whose actual body weight is less than their ideal body weight. A case has been made by the FDA clinical pharmacology review team that a dose higher than 50 kBq/kg should be further evaluated and the clinical reviewers agree with this recommendation. See the FDA clinical pharmacology review for details on the pharmacodynamics of Ra-223.

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4.4.3 Pharmacokinetics

After intravenous injection, Ra-223 is rapidly cleared from blood and distributed to bone and intestine, with $4 \pm 1\%$, $61 \pm 10\%$, and $49 \pm 16\%$ in blood, bone, and intestine, respectively, at 4 hours post injection. Approximately 63% of administered radioactivity was excreted from the body within 7 days, primarily via fecal route. See the FDA clinical pharmacology review for details on the pharmacokinetics of Ra-223.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Completed studies included in support of the proposed indication:

Table 10: Table of Completed Clinical Trials Supporting Ra-223

Trial Name	Title	# Subjects	Population
ATI BC-1 / 15522	Phase 1: Single Dose, Dose Escalation. Repeat dose in some subjects.	31	21 prostate, 10 breast cancer with bone metastases
BC1-05 / 15302	Phase 1: Radiation Dosimetry and PK Repeat Dose.	6	CRPC with bone metastases
BC1-08 / 15303	Phase 1: Single Dose Safety, Long Term Radiation Toxicity, Biodistribution	10	CRPC with bone metastases
BC1-02 / 15280	Phase 2: Randomized 1:1 Placebo controlled 50 kBq q4 weeks x 4	64	Prostate Cancer with bone metastases
BC1-03 / 15305	Phase 2: Randomized 4 doses (5, 25, 50, 100 kBq) Single Dose	100	CRPC with bone metastases
BC1-04 / 15304	Phase 2: Randomized multiple dose cohorts 25, 50, 80 kBq q 6 weeks	122	CRPC with bone metastases
BC1-06 / 15245 "ALSYMPCA"	Phase 3 (Pivotal): Randomized placebo-controlled 50 kBq q 4 weeks x 6 doses	921 (809 ITT at Interim Analysis)	CRPC with symptomatic bone metastases

In addition, there are several ongoing clinical trials. (Table 11)

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Table 11: Ongoing Clinical Trials of Ra-223, Study Reports Not Available

Trial Name	Title	# Subjects	Population
15354	Phase 1: Open label study of safety, biodistribution, dosimetry, PK in Japanese mCRPC patients (50kBq/kg and 100 kBq/kg)	Up to 18	Japanese CRPC with bone metastases
BC1-10 / 15469	Phase 1: Radiation Dosimetry and PK Repeat Dose.	Up to 6	CRPC with bone metastases
15995	Phase 2: Ra-223 Dichloride Early Access Program (EAP) 50 kBq/kg q 4 weeks x 6 doses	Based on Demand	CRPC with symptomatic bone metastases
BC1-09 / 15468	Phase 2: Open-label treatment with 50 kBq/kg q 4 weeks x 4 doses	Up to 20	Breast cancer patients with bone metastases no longer considered suitable for endocrine therapy
16216	Phase 3b: Open label, prospective 50 kBq/kg q 4 weeks x 6 doses	Based on Demand	CRPC with bone metastases (do not need to be symptomatic)

5.2 Review Strategy

The clinical study reports, supportive analyses and risk:benefit assessment submitted by the Applicant were reviewed. Key datasets from the safety and efficacy analyses were re-analyzed by both the clinical and statistical reviewers. The reliability and integrity of the data were assessed based on information obtained from OSI site visits, conflict of interest data, protocol deviations and via random cross-validation of datasets with CRF forms and patient narratives. Sensitivity analyses and subgroup analyses were performed as necessary.

5.3 Discussion of Individual Studies/Clinical Trials

Study BC1-02: Randomized phase 2 placebo controlled study (N=64) of a single dose of EBRT followed within 7 days by either Ra-223 given at 50kBq/kg every 4 weeks for 4 doses or placebo for 4 doses. Patients had adenocarcinoma of the prostate and were referred for palliative EBRT for painful bone metastases.

The primary objective was time to skeletal related event (SRE) and change in bone-specific alkaline phosphatase levels.

Skeletal Related Events (SRE) were defined as:

1. Increase in skeletal pain in areas defined at baseline
2. New areas of skeletal pain
3. Increase in analgesic consumption
4. Neurological symptoms secondary to skeletal manifestations of prostate cancer

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5. New pathologic bone fractures
6. Tumor related orthopedic surgical intervention
7. Subsequent external beam radiotherapy
8. Use of radioisotopes to relieve new skeletal related events

The study met statistical significance for one of its primary objectives: improvement in relative change in serum ALP.

Key results were as follows:

- **Serum ALP:** The relative % change in serum bone-ALP from baseline to 4 weeks after last injection was -66% versus 27% for Ra-223 and Placebo respectively ($p < 0.001$).
- **SRE:** Non-significant ($P = 0.214$) improvement in time to first SRE. Median of 16 weeks vs. 11.0 weeks in Ra-223 compared with Placebo respectively.
- The most commonly reported SRE events were pain severity increase, increase in analgesia and subsequent EBRT.
- 37% vs. 19% confirmed 50% PSA decline for Ra-223 and Placebo respectively ($p = 0.15$).
- Delay in time to PSA progression with a median of 26 vs. 8 weeks for Ra-223 and placebo respectively ($p = 0.04$).
- Trend toward improved survival ($p = 0.095$) with a median of 62 weeks vs. 46 weeks for Ra-223 and Placebo respectively.
- Patient diary data on pain scores and pain recorded during clinic visits (Brief Pain Inventory) showed no significant difference between the groups.

Study BC1-04: Randomized phase 2 repeat dose study ($N = 122$) of three dose levels (25, 50 and 80 kBq/kg) given every 28 days for 3 injections. Confirmed PSA decrease by 50% was the primary endpoint.

- A significant dose-response relationship was seen with confirmed PSA $\geq 50\%$ declines seen in 0 (0%), 2 (5.6%) and 5 (12.8%) patients in the 25-, 50- and 80-kBq/kg per-protocol groups respectively.
- There was no significant difference in Alkaline Phosphatase or SRE results between the 50 kBq/kg and 80 kBq/kg groups but both groups appeared to be superior to the 25 kBq/kg group.
- Pain results were limited by missing data. There was no statistically significant difference in pain response between the arms.

Reviewer Comment: The clinical reviewer did not analyze the primary datasets for trials BC1-02 or BC1-04, however the study reports were reviewed and the efficacy results appear supportive of anti-tumor activity for Ra-223 based on a trend in the delay of the appearance of skeletal related events and a trend toward improved overall survival (BC1-02) as well as dose-dependent

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improvement in PSA response (BC1-04). Both studies were limited by small sample size. Pain was recorded using brief pain index and WHO analgesic scores (0-none, 1-non-opiates, 2-weak opiates, 3-strong opiates) during both studies. The interpretation of pain results and higher PSA responses seen in BC1-02 are complicated by the administration of EBRT at the start of the study on both arms. The pain results seen in these two trials were limited by missing data and small sample sizes (b) (4)

The BC1-04 trial revealed dose dependent improvements in confirmed 50% PSA declines and there did not appear to be an increase in toxicity between the 50 and 80- kBq/kg cohorts. The results from BC1-04 suggest that the optimal dose of Ra-223 may be higher than the 50 kBq/kg used in the pivotal clinical trial.

Clinical Trial BC1-06 "ALSYMPCA":

The key clinical study supporting this application is the BC1-06 "ALSYMPCA" trial: A double-blind, randomized, multiple dose, Phase III, multicenter study of Alpharadin (Ra-223) in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases." While an end of phase 2 meeting offered advice for the design of the trial, there was no special protocol assessment agreement in place. The original protocol was submitted 12/2007 and it was amended 6 times (Table 12).

Table 12: Clinical Trial BC1-06 Protocol Amendments

Date	Amendment	Major Changes
12/14/2007	Original	<ul style="list-style-type: none">• None
5/23/2008	Amend #1	<ul style="list-style-type: none">• Stratification Factors Changed:• ECOG PS 0-1 vs. 2 REMOVED• Current Use of Bisphosphonates Yes/No ADDED• Any Prior Cytotoxic Chemotherapy CHANGED to Any prior use of Docetaxel (Yes/No)
7/9/2008	Amend #2	<ul style="list-style-type: none">• Sample size increased from 450 to 750• Unblinded interim analysis of OS by IDMC ADDED• Exclusion: eligible for 1st dose of docetaxel ADDED (IRB/Ethics)• Change in PSA outcome and reporting per PCWG-2 (2008)
7/10/2009	Amend #3	<ul style="list-style-type: none">• Changes hemoglobin eligibility and cutoff for treatment• Longer follow up collection of survival data: collect for all patients until last patient has been followed for 3 years.• Modified definition of adverse event with possible causal relationship• Change in analysis from Cox to stratified log-rank (per FDA)• Changed timing of sample size re-estimation from 350 to 500-600• Change in definition of safety population to randomized patients receiving at least 1 dose of study drug.• Added sub-group analyses (per FDA)
6/23/2010	Amend #4	<ul style="list-style-type: none">• Sample size ↑ from 700 to 900 and statistical power from 80% to 90%
1/20/2011	Amend #5	<ul style="list-style-type: none">• Five secondary endpoints identified as main secondary endpoints• 3 were already included in the protocol and two were added:• Time to first SRE and Total ALP Normalization were added.
6/24/2011	Amend 6	<ul style="list-style-type: none">• Amendment allows unblinding and crossover• Section 9.2 Disease Events defines the composite endpoint SRE

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Reviewer Comment:

The Jan 2011 Amendment #5 added time to skeletal related events as a key secondary endpoint. While the original protocol had individual elements of the composite SRE definition included as secondary endpoints, the single composite endpoint, "time to SRE", was added quite late in the trial. Review of the timing of the protocol amendment and the primary analysis by the clinical and statistical reviewer notes that these changes were made prior to the primary efficacy analysis and thus can be considered pre-specified.

Note, the SRE endpoint will be referred to as symptomatic skeletal event (SSE) later in the review as the reviewers feel the term SSE is more reflective of this composite endpoint largely triggered by symptoms (see description of Key Secondary Endpoints further in the description of study BC1-06 Study Design below).

Investigators and Study Administrative Structure:

128 centers worldwide randomized at least 1 patient.

The responsibility for the conduct and management of BC1-06 is complicated and is as follows:

1. [REDACTED] ^{(b) (4)} was study coordinating investigator
2. [REDACTED] ^{(u) (4)} - Worked with Algeta during pre-IND phase of development
3. Algeta ASA sponsored the study and submitted the initial IND 67,521
4. Bayer took over sponsorship from Algeta 5/21/2011
5. [REDACTED] ^{(b) (4)} is the CRO for the study.

Timeline of Key Events for BC1-06

2008: Enrollment initiated in Europe

Feb 2011 Enrollment completed (922 patients randomized)

Jun 2011 Pre-Planned Interim Analysis at 50% events

BC1-06 Study Design:

The BC1-06 trial randomized symptomatic castration resistant prostate cancer (CRPC) patients with at least 2 bone metastases and no sign of visceral metastatic disease in a 2:1 fashion to receive 6 monthly injections of Ra-223 + best standard of care (BSoC) or placebo + BSoC. The trial was double-blinded and patients were stratified by alkaline phosphatase, use of bisphosphonates and prior use of docetaxel. The study schema is presented in Figure 4 below.

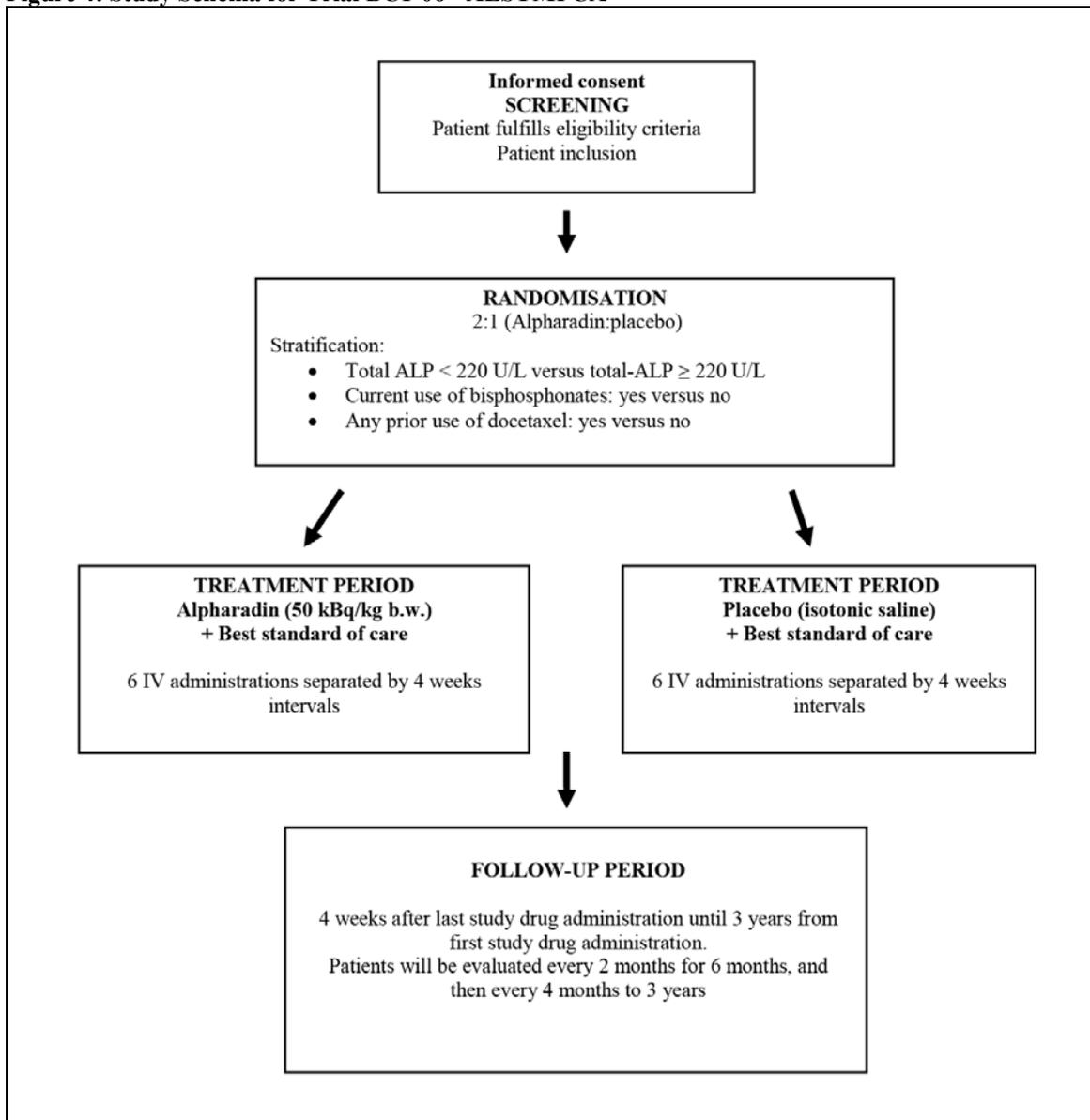
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Figure 4: Study Schema for Trial BC1-06 "ALSYMPCA"



Source: Clinical Study Protocol version 6, 24 June 2011 submitted by Applicant.

Best Standard of Care (BSoC) included routine standard of care at each center:

- local EBRT
- corticosteroids
- antiandrogens
- estrogens
- estramustine
- ketoconazole

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Reviewer Comment: Abiraterone acetate and enzalutamide were not yet approved and thus unavailable during conduct of the trial.

Symptomatic was defined as:

Either regular (not occasional) use of analgesic medication for cancer-related bone pain (\geq level 1; WHO ladder for cancer pain), or treatment with EBRT for bone pain (within the previous 12 weeks before randomization)

WHO analgesic Ladder:

0- none

1- non-opioid

2-opioid for mild to moderate pain

3-opioid for moderate to severe pain

Population: Symptomatic Hormone Refractory (Castration Resistant) Prostate Cancer with Skeletal Metastases

With respect to chemotherapy status, patients may:

- Have received prior docetaxel
- Have been considered not fit to receive docetaxel
- Have not been willing to receive docetaxel
- Have not had docetaxel available for other reasons

Key Inclusion:

- Adenocarcinoma of the prostate
- Progression despite castrate serum testosterone (<50 ng/dL)
- Multiple skeletal metastases (≥ 2 "hot spots") on bone scan with prior 12 weeks
- No radiographic evidence of Visceral Metastases
- No intention to use cytotoxic chemotherapy within next 6 months
- Regular (not occasional) analgesic medication use for cancer related bone pain within prior 12 weeks
- PSA ≥ 5
- Adequate bone marrow function (Hgb ≥ 10 , ANC ≥ 1.5 , Platelet $\geq 100k$)

Key Exclusion:

- Eligible for first course of docetaxel and patient is fit, willing and able (docetaxel available)
- Treatment with cytotoxic chemo within prior 4 weeks or failure to recover from toxicity from prior chemotherapy (baseline neuropathy permitted)
- Prior hemibody external radiotherapy
- Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186 or rhenium-188 within prior 24 weeks
- Blood transfusion or Erythropoietin agent within previous 4 weeks

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- History of visceral metastases or visceral metastases seen on screening abdominal/pelvic CT or chest x-ray within prior 8 weeks.
- Malignant lymphadenopathy exceeding 3 cm in short axis
- Imminent or established spinal cord compression
- Unmanageable fecal incontinence

Reviewer Comment:

The enrolled patient population is notable for requiring patients be symptomatic and for the exclusion of patients with evidence of visceral metastatic disease. The proposed labeled indication of CRPC with bone metastases is more broad than the study population. The inclusion of patients with visceral metastatic disease may be considered a safety issue given the fact that this agent will not treat disease outside of the bone. Delaying systemic treatment for 6 months in the setting of significant lymphadenopathy or visceral metastatic disease may result in progression of the non-bone disease to a point where the window for treatment with subsequent systemic therapy is closed.

Treatment Plan:

- Treatment Arm: Up to 6 doses of Ra-223 at 50 kBq/kg b.w. in 4 week intervals + Best Supportive Care (BSoC).
- Placebo Arm: Up to 6 doses of Isotonic Saline in 4 week intervals + BSoC.

Concomitant Prostate Cancer Therapy:

- Patients must have had orchiectomy or be maintained on LHRH throughout the study
- Bisphosphonates, analgesia, EBRT, steroids, estrogens, estramustine, ketoconazole and anti-androgens were permitted
- Blood transfusions and erythropoietin stimulating agents were permitted
- Cytotoxic agents, systemic radioisotopes, hemibody EBRT or other investigational drugs were prohibited and prompted treatment discontinuation.

Dose Reductions:

- No dose reductions are permitted.

Dose Interruptions:

- Adverse Events: Study drug can be delayed up to 4 weeks
- ≥ 4 week treatment delay for AE leads to treatment discontinuation
- Hematologic Toxicity had to resolve to grade 2 or better prior to administration of next dose
- Non-Hematologic Toxicity had to resolve to grade 2 (GI) grade 3 (other) prior to next dose
- Spinal cord compression: could continue treatment if patient adequately treated and delay < 4 weeks
- Traumatic bone fracture: delay study drug 2-4 weeks from fracture

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Treatment Discontinuation Criteria:

- Unacceptable Toxicity (CTCAE 3-4 ANC or Platelet > 14 days, CTCAE 4 non-hematologic toxicity lasting >7 days despite adequate treatment)
- Initiation of cytotoxic chemotherapy, other systemic radio-isotopes, hemi-body EBRT or other investigational drug

Figure 5: Schedule of Assessments for BC1-06

Timing	Screening Period	Treatment Period ¹							Follow-up period	
	within 2 weeks prior to randomisation	W0	W4	W8	W12	W16	W20	W24	W24-W52 Hospital visit every 2 nd months	W52 – 3 years Hospital visit every 4 months
Alpharadin or placebo		X	X	X	X	X	X	X		
Hospital Visit	X	X	X	X	X	X	X	X	3X	6X
Informed Consent	X									
Eligibility Criteria	X									
PSA	X ²	X	X	X	X	X	X	X	3X	6X
Testosterone level	X									
Haematology ³	X	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X	3X	6X
Clinical chemistry ⁴	X	X	X	X	X	X	X	X	3X	6X
ECG	X		X					X		
Physical Examination ⁶	X	X	X	X	X	X	X	X	3X	6X
Medical History	X									
Bone Tc Scan	X (within 12w)									
Abdomino-pelvic CT and Chest X-ray	X (within 8w)									
Concomitant Medication/Therapy	X	X	X	X	X	X	X	X	Until 12 weeks	
Cancer related treatment only (excluding analgesics)									From 12 weeks	6X
Adverse Events	X	X	X	X	X	X	X	X	Until 12 weeks	
Adverse Drug Reaction only									From 12 weeks	6X
Long Term Toxicity									3X	6X
QoL FACT-P form		X				X		X	M10	
QoL EQ5D form		X				X		X	3X	6X

1. All assessments should be performed **before** study drug administration
2. Has serum PSA progression (two consecutive increases in PSA over a previous reference value, each measurement at least 1 week apart) and PSA value ≥ 5 ng/mL
3. Hematocrit, hemoglobin, platelet counts, red blood cells counts, white blood cell counts, white blood cell differential
4. Sodium, potassium, chloride, calcium, phosphate, magnesium, AST, ALT, LDH, total ALP, γ GT, creatinine, urea, bilirubin (total), albumin, total protein
5. Within 24 hours prior to each study drug administration
6. Abbreviated physical examination with ECOG performance status and assessment of disease related events

Source: Clinical Study Protocol version 6, 24 June 2011 submitted by Applicant.

Reviewer Comment: CBCs were drawn only once every 4 weeks which likely attenuates the reported adverse events associated with bone marrow suppression. Note that there were no scheduled imaging assessments in this study with an overall survival primary endpoint. Clinical progression was considered ECOG deterioration or new skeletal related events. Pain was not specifically identified as a PRO endpoint, however some pain information was obtained as a component of the FACT-P and indirectly via concomitant medications (WHO analgesic scale).

Primary Efficacy Endpoint:

Overall Survival: Time from randomization to death from any cause.

Key Secondary Endpoints:

1. Total-ALP progression
2. Total-ALP response
3. Time to occurrence of first skeletal related event
 - a. Use of external beam radiotherapy to relieve skeletal symptoms
 - b. New symptomatic pathological bone fracture (vertebral or non-vertebral)

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- c. Spinal cord compression
- d. Tumor-related orthopedic surgical intervention.
4. Total-ALP normalization
5. Time to PSA progression

Reviewer Comment: It was noted by the review team that, given there are no scheduled radiographic assessments, skeletal events were most likely to be triggered by symptoms. This is in contrast to prior definitions of SRE composite endpoints for osteoclast-targeted agents which utilized scheduled radiographic assessments and thus likely had more events which were asymptomatic but found on routine radiographic exams. The review team feels the SRE definition in BC1-06 is a more symptom-driven endpoint and more consistent with direct clinical benefit. In order to highlight this difference, the reviewers have renamed the key secondary endpoint time to skeletal related event (SRE) to "time to symptomatic skeletal event (SSE). FDA analyses of this endpoint and the FDA label will use the term "Symptomatic Skeletal Events (SSE)" for this key secondary endpoint.

Disease events that will be used for additional assessments of efficacy include:

- EBRT for skeletal symptoms
- Radio-isotopes for skeletal symptoms
- New symptomatic pathologic bone fractures
- Tumor-related orthopedic intervention
- Spinal cord compression
- Start of other anti-cancer treatments (chemo, hormonal Rx)
- Deterioration of ECOG PS by at least 2 points from baseline

Other Data Collected:

Quality of Life (QoL) assessments were obtained

- Functional Assessment of Cancer Therapy - Prostate (FACT-P) questionnaire
- EuroQoL (EQ-5D) which will also be included in the health economics analysis

Reviewer Comment:

QoL data was obtained relatively infrequently at week 0, W16, W24 and follow-up visit 2 for FACT-P and at all follow up visits for EQ-5D. There was no pre-specified pain endpoint and

(b) (4)

5.3.1 Statistical Analysis Plan:

- All tests are 2-sided
- Superiority for Ra-223 will be based on p value of 0.05
- All primary and secondary efficacy analyses will be performed on the ITT population

Primary Efficacy Analysis:

Intent to Treat Population using stratified log-rank test for the following stratification factors:

- Total-ALP < 220 U/L versus total-ALP ≥ 220 U/L

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- Current use of bisphosphonate: yes versus no
- Any prior use of docetaxel: yes versus no

Sample Size Estimation Assumptions:

- 2-sided Type I error of 5%
- 90% Power
- 50% with prior docetaxel
- 2:1 allocation ratio
- Median Survival in Placebo with no Prior Docetaxel 18 months
- Median Survival in Ra-223 with no Prior Docetaxel 22 months
- Median Survival in Placebo with Prior Docetaxel 12 months
- Median Survival in Ra-223 with Prior Docetaxel 15 months

A total 900 patients required with final analysis conducted after 640 death events.

Overall Survival Censoring:

- Patients who have not died at the time of analysis will be censored on the date they were last known to be alive. The date last known alive will be taken from survival status data obtained prior to the interim and final analyses.
- Patients who withdraw will be followed for survival.
- For withdrawals with no survival data, death will be censored at the time of withdrawal.

Time to Disease Event Censoring:

- Censored on the date that the last efficacy event assessment was performed.

Analysis Population Definitions:

Intent-to-treat (ITT): All randomized patients.

- The ITT population will be the primary population for the analysis of the primary efficacy endpoint and for the analysis of all secondary efficacy and clinical benefit endpoints. Patients will be included in the analyses according to the treatment to which they were randomized.

Safety: All randomized patients who have received at least one study drug administration.

Per-protocol (PP): All patients in the ITT population who received at least 3 treatment cycles, and did not have any major protocol violations or deviations.

Independent Data Monitoring Committee (IDMC) and Interim Analysis of OS

Formal interim analysis at 50% of required deaths (320) was to be conducted by the IDMC using a Lan-DeMets alpha-spending approach with O'Brien-Fleming stopping boundaries requiring two-sided significance level of 0.0031.

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Reviewer Comment:

The statistical review team sent information requests to the Applicant regarding the timing and rationale for amendments to the statistical analysis plan, sample size re-estimation and other specifics related to the statistical methods for this trial. The responses were reviewed and deemed acceptable. Please see the primary statistical review for details.

6 Review of Efficacy

6.1 Indication

The Applicant's proposed indication for NDA 203971 is Ra-223 (radium Ra 223 dichloride) injection for:

"Treatment of castration-resistant prostate cancer patients with bone metastases"

Reviewer Comment: The proposed indication is broad and includes subgroups that were excluded from the primary randomized clinical trial (Asymptomatic patients and those with visceral metastatic disease were excluded).

6.1.1 Methods

The analysis of efficacy focused on the pivotal trial BC1-06 (ALSYMPCA). Two databases were provided with cutoff 10/14/2010 (interim analysis) and 7/15/2011 (updated analysis, prior to cross-over for placebo patients). The key pre-specified analysis is based on the 10/14/2010 datasets. Additional analyses were performed on the 2011 BC1-06 datasets as well as data from three phase 1 and three phase 2 trials as needed to further support the interim analysis findings (Table 10).

The efficacy analyses were performed on the intent to treat population. The statistical analysis plan dated 6/9/2011 defined the ITT population as "all patients randomized into the study and who will be classified according to their assigned treatment group, regardless of the actual treatment received. This population will be used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics."

The FDA clinical review focused on a detailed analysis of the design and conduct of the pivotal clinical trial. The conduct of the pivotal clinical trial was examined including assessment of protocol violations, conflict of interest and results from FDA clinical site visits. Verification of the reliability of the datasets was conducted via random cross validation of CRF and datasets. Recalculation of the primary and secondary efficacy endpoints was performed from the submitted datasets with attention to missing data and other potential confounders. The majority of analyses were performed on the interim analysis dataset with cutoff of 10/14/2010 as this data supports the primary efficacy analysis. Sensitivity analyses were performed as appropriate. Finally, the results of primary and secondary efficacy endpoints as well as quality of life and

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other data were interpreted in the context of the specific disease indication to form an integrated determination of overall clinical efficacy.

6.1.2 Demographics

Geographic Distribution of BC1-06

A total of 809 patients were randomized and a total of 762 (94.2%) received treatment.

Randomization by country was well-balanced between the arms. There were only 10/809 (1.2%) patients from the United States who were included in the primary analysis (interim analysis).

Accrual in both the U.S. and France accelerated following the interim analysis as more sites became activated, however the final study population still consisted of <3% U.S. patients. (Table 13)

Table 13: BC1-06 Randomization by Country

	Ra-223				Placebo			
	2010 Interim		2011 Updated		2010 Interim		2011 Updated	
	N= 541		N=614		N=268		N=307	
United Kingdom	150	27.7%	167	27.2%	76	28.4%	91	29.6%
Norway	81	15.0%	87	14.2%	45	16.8%	51	16.6%
Sweden	51	9.4%	58	9.4%	30	11.2%	32	10.4%
Poland	43	7.9%	43	7.0%	17	6.3%	18	5.9%
Germany	34	6.3%	39	6.4%	15	5.6%	17	5.5%
Czech Republic	29	5.4%	34	5.5%	17	6.3%	18	5.9%
Spain	33	6.1%	34	5.5%	11	4.1%	12	3.9%
Brazil	26	4.8%	28	4.6%	11	4.1%	11	3.6%
Australia	18	3.3%	20	3.3%	7	2.6%	10	3.3%
Hong Kong	14	2.6%	15	2.4%	6	2.2%	6	2.0%
Slovakia	12	2.2%	13	2.1%	8	3.0%	9	2.9%
Canada	14	2.6%	16	2.6%	4	1.5%	4	1.3%
Italy	10	1.8%	13	2.1%	4	1.5%	5	1.6%
Belgium	6	1.1%	6	1.0%	4	1.5%	4	1.3%
United States	7	1.3%	17	2.8%	3	1.1%	6	2.0%
Netherlands	6	1.1%	8	1.3%	2	0.7%	2	0.7%
Israel	2	0.4%	2	0.3%	5	1.9%	6	2.0%
Singapore	2	0.4%	2	0.3%	3	1.1%	3	1.0%
France	3	0.6%	12	2.0%	0	0.0%	2	0.7%

Source: RAW datasets [DM] for data cutoff 10/14/2010 (Interim) and data cutoff 7/15/2011.

Reviewer Comment:

The number of patients enrolled in the U.S. was small. However, given a large majority of patients were enrolled in developed countries in Europe and Scandinavia, it is the reviewer's determination that the results of trial BC1-06 can be reasonably generalized to the U.S. prostate cancer population.

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Patient Characteristics

Baseline patient characteristics were relatively well balanced for height, weight, race, and baseline pain and performance status. Patient age was generally well balanced with the exception of an imbalance in the subgroup of age <55 with 16 patients in the Ra-223 arm compared with 1 in the placebo arm. An FDA analysis removing the age <55 subgroup from the ITT population did not materially affect the OS or SRE primary analysis. The pre-specified stratification factors were well-balanced with approximately 41% of patients reporting current use of bisphosphonates, 58% prior docetaxel and 44% had baseline alkaline phosphatase ≥ 220 U/L.

Table 14: Baseline Patient Characteristics (Interim Analysis)

	Ra-223		Placebo		All	
	N=541		N=268		N=809	
AGE						
Mean	70.2		70.7		70.4	
Median	71		70.5		71	
Range	49-90		44-94		44-94	
<55	16	3.0%	1	0.4%	17	2.1%
<65	139	25.7%	65	24.3%	204	25.2%
65-75	253	46.8%	126	47.0%	379	46.8%
>75	149	27.5%	77	28.7%	226	27.9%
>85	7	1.3%	4	1.5%	11	1.4%
WEIGHT						
Mean	82.9		82.5		82.7	
Median	82		81.9		82.0	
Range	40-139		47-130		40-139	
RACE						
Caucasian	507	93.7%	252	94.0%	759	93.8%
Asian	19	3.5%	12	4.5%	31	3.8%
Black	10	1.8%	3	1.1%	13	1.6%
Other	5	0.9%	0	0.0%	5	0.6%
Hispanic	0	0.0%	1	0.4%	1	0.1%
ECOG Performance Status¹						
0	105	20.7%	57	22.3%	162	21.2%
1	328	64.7%	163	63.7%	491	64.4%
2	70	13.8%	35	13.7%	105	13.8%
3	4	0.8%	1	0.4%	5	0.7%
WHO Ladder for Cancer Pain						
0	12	2.2%	2	0.7%	14	1.7%
1	235	43.4%	124	46.3%	359	44.4%
2	132	24.4%	72	26.9%	204	25.2%
3	162	29.9%	70	26.1%	232	28.7%

¹Based on 763 (507 Ra-223, 256 Placebo) patients with baseline results
Source: Raw dataset [DM], [QSWHO]

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Disease Characteristics at Initial Diagnosis

Prostate cancer characteristics upon initial diagnosis are presented in Table 15 below. There were more cases of metastatic prostate cancer at initial diagnosis in the placebo arm (36% vs. 26%). Also of note, more patients in the placebo arm were recorded as having had a high-grade Gleason score of 8-10 (49% vs. 41%).

Table 15: Disease Characteristics at Diagnosis

	Ra-223		Placebo		All	
	N=541		N=268		N=809	
Gleason						
≤6	90	16.6%	27	10.1%	117	14.5%
7	159	29.4%	76	28.4%	235	29.0%
8-10	223	41.2%	132	49.3%	355	43.9%
Missing	69	12.8%	33	12.3%	102	12.6%
TNM						
T1	29	5.4%	19	7.1%	48	5.9%
T2	75	13.9%	38	14.2%	113	14.0%
T3	201	37.2%	98	36.6%	299	37.0%
T4	29	5.4%	19	7.1%	48	5.9%
N1	45	8.3%	25	9.3%	70	8.7%
M1	139	25.7%	97	36.2%	167	20.6%
TNM Unknown	207	38.3%	94	35.1%	301	37.2%

Source: Raw dataset [DIAG].

Note % calculated based on # of patient on each arm regardless of missing data.

The discrepancy in patients diagnosed with metastatic disease (M1) was reflected by a higher number of patients with M0 disease receiving local therapy with prostatectomy or radiation in the Ra-223 arm (Table 16). Aside from discrepancies in local therapy, prior prostate cancer therapies were well balanced between the arms.

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Table 16: Prior Prostate Cancer Therapies

	Ra-223 N=541		Placebo N=268	
Local Prostate Therapies:				
RADICAL PROSTATECTOMY	103	19.0%	26	9.7%
EXTERNAL RADIOTHERAPY TO THE PROSTATE	191	35.3%	75	28.0%
BRACHYTHERAPY	14	2.6%	8	3.0%
Systemic Prostate Cancer Therapies:				
ORCHIECTOMY BILATERAL	82	15.2%	44	16.4%
EXTERNAL RADIOTHERAPY TO BONE	274	50.6%	129	48.1%
ANTIANDROGEN	461	85.2%	229	85.4%
BISPHOSPHONATES	98	18.1%	47	17.5%
CYTOTOXIC CHEMOTHERAPY	319	59.0%	155	57.8%
EXTERNAL RADIOTHERAPY TO BONE	274	50.6%	129	48.1%
LHRH AGONIST	182	33.6%	81	30.2%
SYSTEMIC RADIOTHERAPY	21	3.9%	8	3.0%
OTHER PREVIOUS TREATMENT	140	25.9%	70	26.1%

Source: Analysis dataset [PRTRTYN] and Raw Dataset [CMPRETRT].

Note % calculated based on # of patient on each arm regardless of missing data.

Prior Docetaxel Use

The prior use of docetaxel was well balanced between the arms at approximately 58% of randomized patients. The extent of docetaxel exposure appeared balanced between the arms (Table 17).

Table 17: BC1-06 Prior Use of Docetaxel

	Ra-223 N=541		Placebo N=268	
Prior Docetaxel	314	58.0%	155	57.8%
Exposure				
<12 Wk	39	7.2%	24	9.0%
>12 Wk	275	50.8%	129	48.1%
<24 Wk	144	26.6%	73	27.2%
>24 Wk	170	31.4%	80	29.9%

Source: Analysis dataset [PRDOCTX] and [PRPT]

Reviewer Comment: Regarding prior LHRH agonist use, an information request was sent to the Applicant who clarified the small number of patients having received prior LHRH agonists in this FDA analysis of prior prostate cancer therapies was due to many patients having their LHRH captured in the concomitant medication CRF form if the LHRH treatment was ongoing. When analyzing this using the concomitant medication dataset of 921 patients in the ITT population at the 7/15/2011 cutoff, 98.9% of patients received either LHRH or Orchiectomy at

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screening. This data is supported by a review of screening laboratory values. Of 787 (97%) available values, 773 were castrate by protocol definition (<1.7 nmol/L) and only 14 (8 Ra-223 and 6 placebo) were 1.7 or higher. Only 2 patients had normal range testosterone recorded; 1 from each arm.

Baseline Disease Characteristics at Screening:

The number of bone metastases at baseline was balanced between arms. Only 3 patients had lymph nodes >3cm and/or visceral metastases as these patients were excluded per eligibility criteria. The time from initial diagnosis of prostate cancer to randomization was shorter in the placebo arm than in the Ra-223 arm (median 51 mo. vs. 59 mo. respectively).

Table 18: Disease Characteristics at Screening for BC1-06 (Interim Analysis)

	Ra-223		Placebo		All	
	N=541		N=268		N=809	
Bone Metastases						
<6	88	16.3%	33	12.3%	121	15.0%
6-20	235	43.5%	129	48.1%	364	45.0%
>20 no Superscan	169	31.3%	80	29.9%	249	30.8%
Superscan	48	8.9%	26	9.7%	74	9.2%
Lymph Nodes >3cm	3	<1%	0	0	3	<1%
Visceral Metastases	2	<1%	0	0	2	<1%
Time from Initial Diagnosis to Randomization						
Median (months)	59		51.1		56.7	
Mean (months)	69.5		61.8		67	
Time from Hormone Refractory to Randomization in Months						
Median (months)	12.4		10.3		12.0	
Mean (months)	17.2		15.9		16.7	

Note: One bone scan finding was missing in the Ra-223 arm. Three patients with lymph nodes >3cm and/or visceral metastases were randomized to the Ra-223 arm. These patients were noted to be protocol deviations and only one was treated on the Ra-223 arm. The patients were included in the ITT primary analysis.

Source: Raw dataset [PEBSCAN], [PECTSCAN] and [DIAG].

Baseline Laboratory Values:

There were several markers of prostate cancer burden that were slightly imbalanced at screening including higher PSA, alkaline phosphatase and lactate dehydrogenase in the placebo arm. There were 5 patients on placebo (1.9%) and 6 patients on Ra-223 (1.1%) with non-castrate levels of baseline testosterone. There are no on-study testosterone laboratory values to review. The remainder of the baseline laboratory values which could be used to assess prostate cancer burden were relatively well balanced.

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Table 19: Baseline Laboratory Values

	Ra-223		Placebo		All	
	N=541		N=268		N=809	
Prostate Specific Antigen (PSA)						
Mean	437		524		467	
Median	159		195		166	
25%-75%	51-450		69-504		55-471	
Alkaline Phosphatase (ALP)						
Mean	369		382		374	
Median	213		224		218	
25%-75%	105-440		126-423		110-437	
<220	304	56.2%	147	54.9%	451	55.7%
≥220	237	43.8%	121	45.1%	358	44.3%
≥1000 ²	30	5.5%	17	6.3%	47	5.8%
Lactate Dehydrogenase (LDH)						
Mean	368		445		411	
Median	317		328		321	
25%75%	219-425		229-478		225-474	
Testosterone (nmol/L) Castrate defined as ≤ 1.7						
Mean	0.6		0.8		0.7	
Median	0.4		0.5		0.5	
25%-75%	0.2-0.7		0.3-0.7		0.2-0.7	
Test > 1.7	6	1.1%	5	1.9%		1.4%
Hemoglobin (Hgb)						
Mean	12.1		12.1		12.1	
Median	12.2		12.1		12.2	
25%-75%	11.0-13.2		11.0-13.0		11.0-13.2	
Hgb<10	41	7.6%	25	9.3%	66	8.2%

Source: Analysis dataset [LAB] cutoff 10/15/2010.

Baseline Disease Characteristics Summary:

The review of disease characteristics both at baseline and at the time of initial prostate cancer diagnosis indicated a slightly higher percentage of patients in the placebo arm with higher Gleason grade and incidence of metastatic disease at diagnosis as well as higher baseline PSA, LDH and alkaline phosphatase at trial entry. Multiple sensitivity analyses adjusting for these

² In order to identify a cohort of patients with severe burden of bone metastases, a threshold of ALP >1000 was chosen by the FDA reviewer. This small group was well balanced between the arms which is consistent with the distribution of # bone metastases data in table 18.

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individual discrepancies (Gleason, M stage, baseline PSA) were performed by the Applicant and the FDA statistical reviewer (see efficacy portion of the review).

In summary, the overall survival results appear robust across multiple sensitivity analyses adjusting for differences in baseline disease characteristics. It is the reviewer's conclusion that there is insufficient evidence to suggest that imbalances in baseline demographics and disease characteristics have materially affected the study results.

6.1.3 Subject Disposition

The ITT population consisted of a total of 809 patients with data cutoff 10/14/2010. Of these patients, 762 (94.2%) received at least 1 injection of study drug. The remainder either withdrew before the 1st injection (14 in Ra-223 arm and 5 in placebo) or had not received their 1st injection at the time of data cutoff due to being randomized on or shortly before the data cutoff date. Figure 6 demonstrates the disposition of subjects at the interim analysis for trial BC1-06.

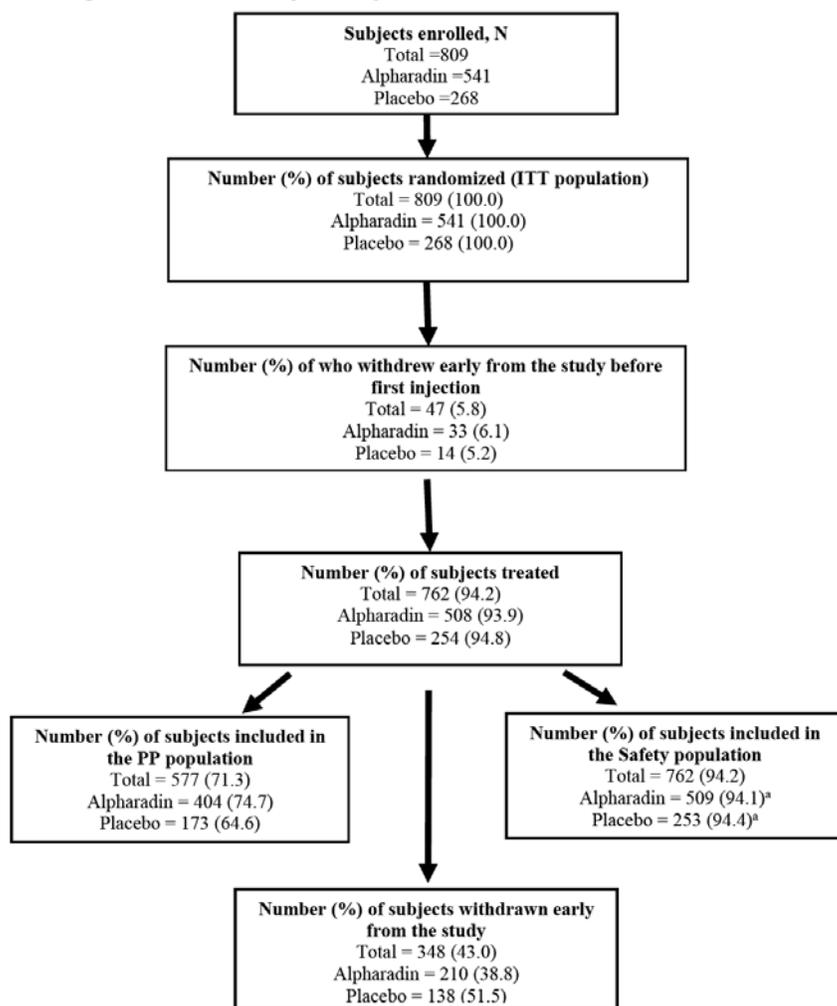
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Figure 6: BC1-06 Study Disposition at Interim Analysis Cutoff (10/14/2010)



Source: Clinical Study Report A58799. Data verified by the FDA clinical reviewer using analysis dataset [DISP]. One subject was randomized to placebo but received Ra-223 accounting for the discrepancy between the number of subjects treated and subjects included in the safety population.

Of the 762 treated subjects, there were 185 patients who were not in the per-protocol population. The most common reason was receiving less than 3 injections (74%). By the data cutoff, half of the Ra-223 patients had completed 6 injections compared with 34% in the placebo arm. More patients in the placebo arm withdrew from the study (52% compared with 39%) and the most common reason for study withdrawal for both arms was death.

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Table 20: BC1-06 Patient Disposition (Interim Analysis)

	Ra-223		Placebo	
	N=541		N=268	
Completed 6 Injections	272	50.3%	95	35.5%
Treatment Ongoing	117	21.6%	54	20.1%
Withdrew from Study	210	38.8%	138	51.5%
AE	23	4.3%	19	7.1%
Patient Request	25	4.6%	14	5.2%
Investigator Request	11	2.0%	5	1.9%
Death	122	22.6%	85	31.7%
Other	4	0.7%	2	0.7%
Disease Progression	25	4.6%	13	4.9%

Source: Analysis dataset [DISP]. 10/14/2010 data cutoff

Concomitant and Subsequent Anticancer Medications or Procedures:

Concomitant therapies documented after randomization that may have an anti-tumor effect were reviewed. Anti-cancer concomitant medications (systemic steroids, ketoconazole, antiandrogens, cytotoxic chemotherapy) were either well balanced or were used slightly more frequently in the placebo arm. Because of the time in which this trial was conducted, there were no patients who reported concomitant abiraterone or enzalutamide. The FDA approved cytotoxic chemotherapies docetaxel (6.1% vs. 7.1%) and mitoxantrone (1.9% vs. 1.5%) were reported to be used equally between the Ra-223 and Placebo arms respectively in the interim analysis dataset.

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Table 21: Concomitant Medications for Prostate Cancer

Category	Alpharadin N=541			Placebo N=268		
	N ^a	n ^b	%	N ^a	n ^b	%
Concomitant medications for prostate cancer ^c	541	506	93.5	268	254	94.8
From randomization to 1 st injection	541	493	91.1	268	248	92.5
From 1 st injection to EOT	508	472	92.9	254	239	94.1
From EOT to 1 year	356	330	92.7	176	166	94.3
From 1 – 2 years	99	92	92.9	39	35	89.7
From 2 – 3 years	2	2	100	1	1	100
Cytotoxic drugs	541	52	9.6	268	29	10.8
From randomization to 1 st injection	541	1	0.2	268	0	-
From 1 st injection to EOT	508	11	2.2	254	8	3.1
From EOT to 1 year	356	46	12.9	176	25	14.2
From 1 – 2 years	99	19	19.2	39	11	28.2
From 2 – 3 years	2	1	50.0	1	0	-
LHRH agonists	541	450	83.2	268	223	83.2
From randomization to 1 st injection	541	441	81.5	268	221	82.5
From 1 st injection to EOT	508	421	82.9	254	208	81.9
From EOT to 1 year	356	290	81.5	176	147	83.5
From 1 – 2 years	99	78	78.8	39	29	74.4
From 2 – 3 years	2	2	100	1	1	100
Antiandrogens	541	138	25.5	268	102	38.1
From randomization to 1 st injection	541	99	18.3	268	80	29.9
From 1 st injection to EOT	508	104	20.5	254	86	33.9
From EOT to 1 year	356	78	21.9	176	52	29.5
From 1 – 2 years	99	24	24.2	39	12	30.8
From 2 – 3 years	2	0	-	1	1	100
Bisphosphonates	541	233	43.1	268	113	42.2
From randomization to 1 st injection	541	198	36.6	268	96	35.8
From 1 st injection to EOT	508	204	40.2	254	102	40.2
From EOT to 1 year	356	149	41.9	176	69	39.2
From 1 – 2 years	99	38	38.4	39	10	25.6
From 2 – 3 years	2	1	50.0	1	0	-
Steroids	541	244	45.1	268	126	47.0
From randomization to 1 st injection	541	190	35.1	268	88	32.8
From 1 st injection to EOT	508	206	40.6	254	105	41.3
From EOT to 1 year	356	151	42.4	176	82	46.6
From 1 – 2 years	99	42	42.4	39	18	46.2
From 2 – 3 years	2	0	-	1	0	-
Other cancer-related medications ^c	541	20	3.7	268	9	3.4
From randomization to 1 st injection	541	13	2.4	268	3	1.1
From 1 st injection to EOT	508	13	2.6	254	5	2.0
From EOT to 1 year	356	11	3.1	176	7	4.0
From 1 – 2 years	99	2	2.0	39	2	5.1
From 2 – 3 years	2	0	-	1	0	-

Source: Applicant study report, interim analysis. This data was verified by the FDA clinical reviewer using the [CONMED] analysis dataset as well as spot-verified using RAW dataset [CMRPT].

N^a # of subjects in time period. N^b # of subjects taking medication in time period.

This analysis excludes analgesic medications.

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"Other" anticancer agents were mainly ketoconazole in 19 patients (3.5%) on Ra-223 and 8 patients (3.0%) on placebo.

Reviewer Comment: There was no significant imbalance in concomitant medications either during or after treatment with Ra-223 or placebo that would materially affect the efficacy results.

6.1.4 Analysis of Primary Endpoint(s)

The key primary endpoint of overall survival met statistical significance at the pre-specified interim analysis based on an O'Brien-Fleming threshold with a p value of 0.00185 and a hazard ratio of 0.695 (95%CI 0.552, 0.875). The median overall survival was 14.0 months for Ra-223 and 11.2 months for placebo resulting in a median absolute benefit of 2.8 months.

Of note, the IDMC minutes dated 3/18/2011 noted that the statistical analysis plan was ambiguous regarding whether the pre-specified O'Brien-Fleming stopping boundary of 0.00153 was based on a one-sided or two-sided p-value. The IDMC concluded that it was one-sided and that the two-sided stopping boundary for the interim analysis based on 313 death events was $P < 0.002701$. The FDA statistical reviewer re-analyzed the Lan Demets alpha-spending approach and confirmed the threshold at $P < 0.0027$.

Table 22: FDA Analysis of BC1-06 Overall Survival Results (Interim Analysis)

	Ra-223 (N=541)	Placebo (N=268)
Subjects randomized	541	268
Death	191 (35.3%)	123 (45.9%)
Censored	350 (64.7%)	145 (54.1%)
Overall survival (months)		
Median (95% CI)	14.0 (12.1, 15.8)	11.2 (9.0, 13.2)
p value ^a	0.00185 (O'Brien-Fleming Threshold of 0.0027)	
Hazard ratio (95% CI) ^b	0.695 (0.552, 0.875)	

^a p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.

^b Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior used of docetaxel. Hazard ratio < 1 favors Ra-223dichloride.

Source: FDA statistical reviewer using [SURV] BC1-06 Interim Analysis 10/14/2010 cutoff

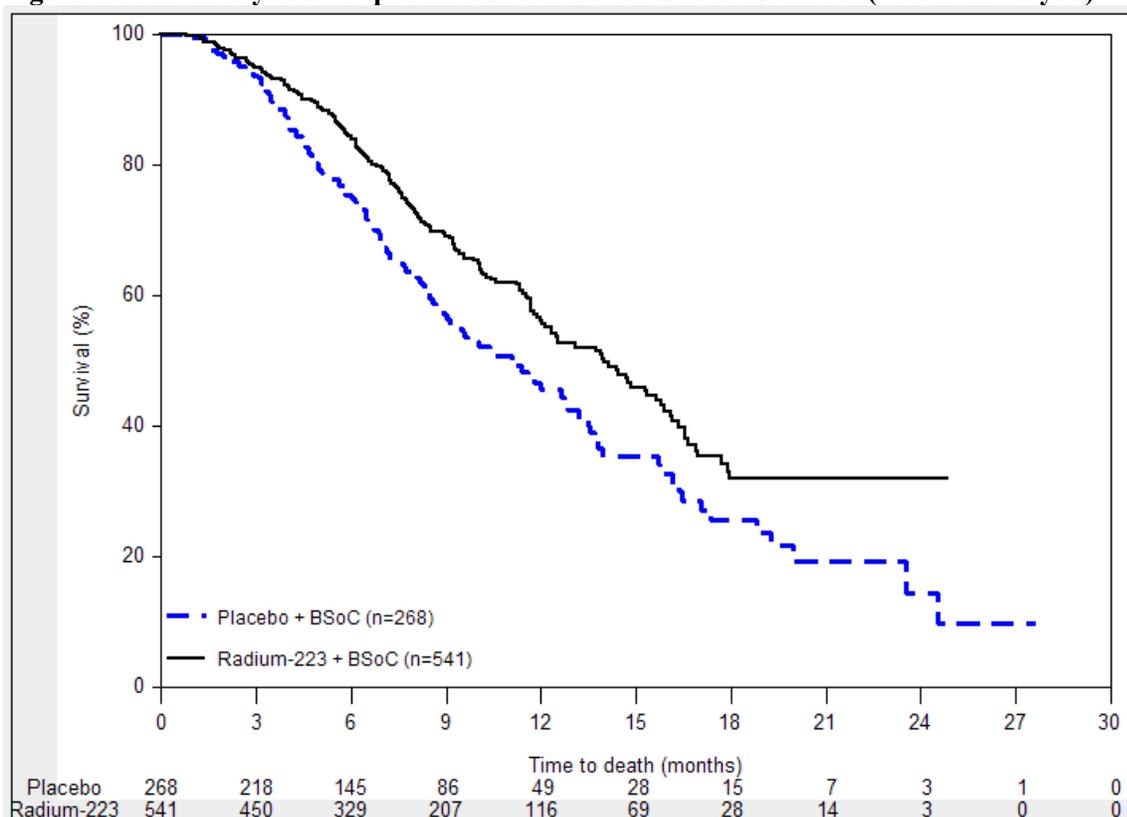
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Figure 7: FDA Analysis of Kaplan-Meier curves for Overall Survival (Interim Analysis)



Note: Cutoff October 14, 2010.

Source: FDA statistical reviewer using [SURV] dataset Interim Analysis.

An updated analysis for overall survival was conducted with a data cutoff of 7/15/2011 after an additional 214 death events were collected. The updated OS analysis revealed a consistent improvement favoring Ra-223.

Table 23: FDA Analysis of BC1-06 Overall Survival Results (Updated Analysis)

	Ra-223 (N=614)	Placebo (N=307)
Subjects randomized	614	307
Death	333 (54.2%)	195 (63.5%)
Censored	281 (45.8%)	112 (36.5%)
Overall survival (months)	14.9	11.3
Median (95% CI)	(13.9, 16.1)	(10.4, 12.8)
p value ^a	0.00007	
Hazard ratio (95% CI) ^b	0.695 (0.581, 0.832)	

^a p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior use of docetaxel.

^b Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior use of docetaxel. Hazard ratio < 1 favors Ra-223dichloride.

Source: FDA statistical reviewer using [SURV] BC1-06 Updated Analysis cut-off date July 15, 2011.

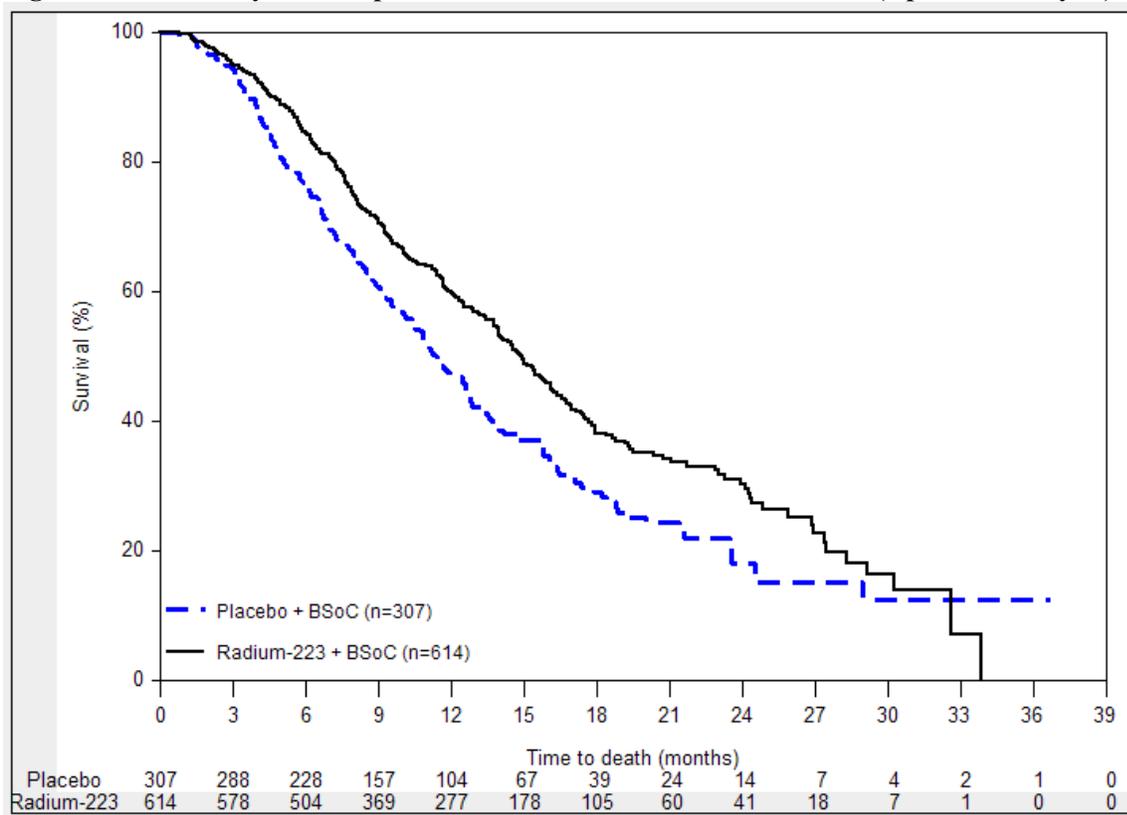
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Figure 8: FDA Analysis of Kaplan-Meier Curves for Overall Survival (Updated Analysis)



Note: Cutoff July 15, 2011.

Source: FDA statistical reviewer using [SURV] dataset Updated Analysis.

Prespecified Subgroup Analysis of OS:

The overall survival results were consistent across multiple pre-specified subgroups as seen by the FDA repeat analysis in Table 24 and Figure 9: Forest Plot of Subgroup Analyses for Overall Survival (Interim Analysis) below.

Table 24: Pre-specified subgroup analysis of OS (ITT population, Interim Analysis)

Variable	Median no. of months (95% CI)		Hazard Ratio ^a (95% CI)	p value ^b
	Ra-223 dichloride	Placebo		
All Patients	N=541 14.0 (12.0, 15.8)	N=268 11.2 (8.9, 13.2)	0.695 (0.552, 0.875)	0.0018
Total-ALP				
<220 U/L	N=305 16.1 (14.5, 18.0)	N=147 13.5 (11.2, 16.4)	0.691 (0.497, 0.962)	0.0278
≥ 220 U/L	N=236 11.3 (9.9, 12.5)	N=121 8.7 (6.9, 10.4)	0.689 (0.504, 0.941)	0.0187
Current bisphosphonates				

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Yes	N=220 15.3 (12.3, NE)	N=111 11.2 (8.3, 16.4)	0.582 (0.397, 0.854)	0.0050
No	N=321 12.5 (11.5, 15.4)	N=157 11.1 (8.5, 13.5)	0.752 (0.567, 0.999)	0.0482
Prior docetaxel				
Yes	N=314 12.5 (11.7, 15.3)	N=156 11.4 (8.8, 13.8)	0.755 (0.565, 1.009)	0.0567
No	N=227 15.8 (13.1, 17.7)	N=112 9.7 (7.2, 12.9)	0.611 (0.423, 0.883)	0.0080
ECOG				
≤ 1	N=467 14.7 (13.1, 16.6)	N=229 12.0 (9.1, 13.7)	0.691 (0.535, 0.892)	0.0043
≥ 2	N=72 10.1 (7.0, 12.3)	N=38 7.9 (5.6, 11.6)	0.731 (0.398, 1.343)	0.3107
EOD				
1 (<6 metastases)	N=88 NE	N=33 NE	0.812 (0.294, 2.241)	0.6869
2 (6-20 metastases)	N=235 12.0 (10.4, 14.9)	N=129 11.4 (8.6, 12.9)	0.723 (0.514, 1.019)	0.0630
3 (>20 lesions but not a Superscan)	N=169 12.3 (10.3, 15.3)	N=80 9.1 (7.0, 11.2)	0.642 (0.434, 0.949)	0.0254
4 (Superscan)	N=48 11.7 (8.0, 16.9)	N=26 11.8 (5.1, 24.5)	0.632 (0.279, 1.429)	0.2665
Opiate use				
Yes	N=294 12.3 (11.3, 14.9)	N=142 8.8 (7.3, 11.4)	0.652 (0.485, 0.875)	0.0042
No	N=247 15.9 (13.1, 18.0)	N=126 13.5 (11.1, 16.4)	0.784 (0.539, 1.142)	0.2043
Ethnicity				
Caucasian	N=507 14.1 (12.0, 15.9)	N=252 10.4 (8.7, 12.8)	0.674 (0.533, 0.853)	0.0009
Non- Caucasian	N=34 12.5 (8.2, NE)	N=16 NE	1.719 (0.347, 8.504)	0.502
Age				
<65	N=139 16.9 (12.5, NE)	N=65 11.2 (6.7, 15.7)	0.485 (0.290, 0.811)	0.0052
65-75	N=252 14.1 (12.0, 16.7)	N=125 12.9 (9.0, 13.9)	0.729 (0.516, 1.030)	0.0718
>75	N=150 10.1 (8.5, 14.0)	N=78 9.1 (7.2, 12.6)	0.824 (0.535, 1.270)	0.3808

^a Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior used of docetaxel. Hazard ratio < 1 favors Ra-223.

^b p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.

Note: Cutoff date October 14, 2010

Source: FDA Statistical Reviewer, see statistical review for details.

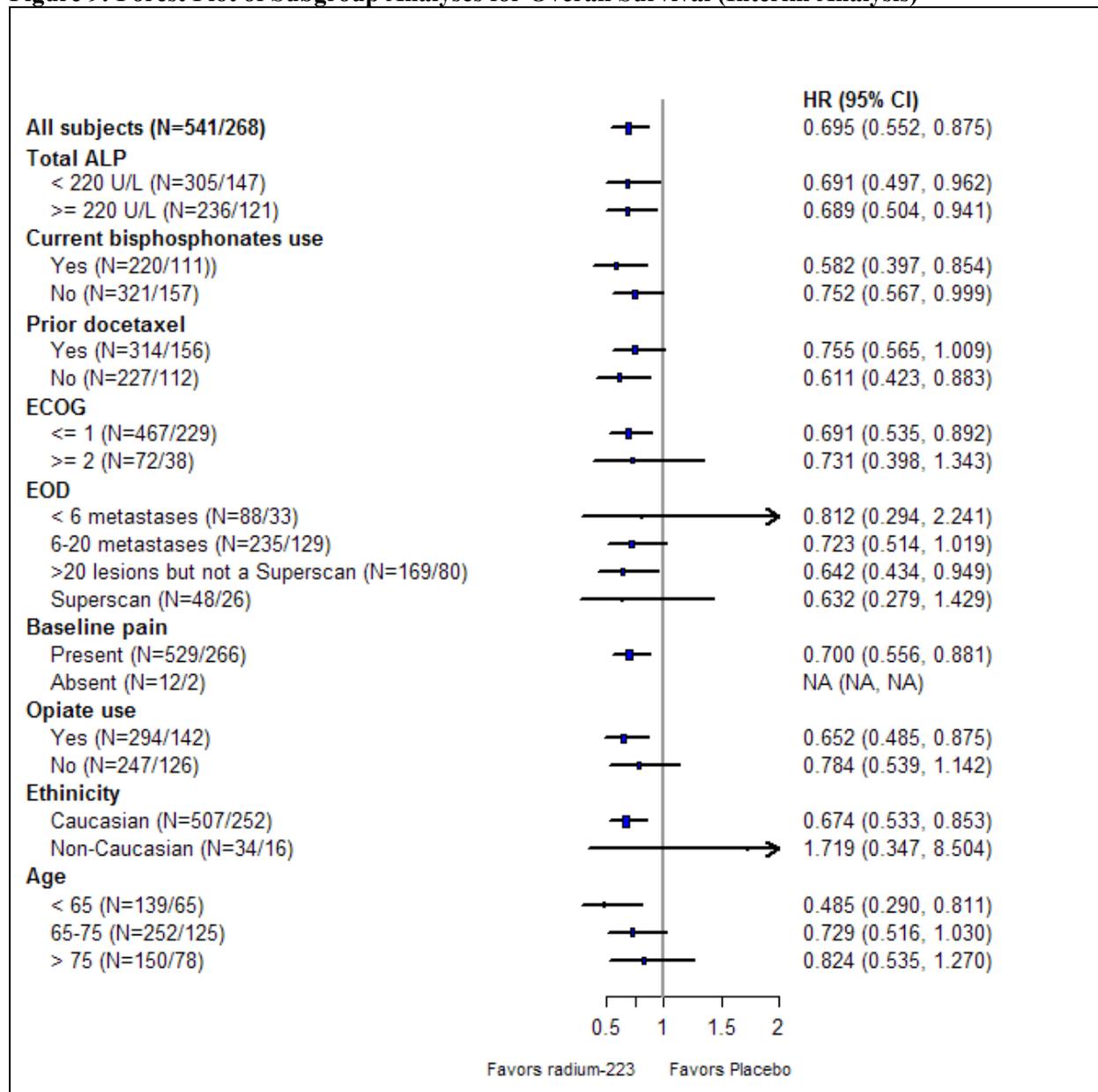
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Figure 9: Forest Plot of Subgroup Analyses for Overall Survival (Interim Analysis)



Source: FDA Statistical Review

Reviewer Comment: The 2.8 month absolute magnitude of overall survival benefit for the Ra-223 group is in line with prior overall survival benefits seen with approved drugs docetaxel and cabazitaxel but with significantly less toxicity. The median overall survival of 14.0 months in the treatment arm (14.9 mo. in the updated analysis) reflects a fairly advanced overall population although there was a mix of both chemotherapy-naive and chemotherapy pretreated patients.

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The degree of benefit differed in some subgroups. The OS effect was more pronounced in patients who had at least 6 or more bone metastases and who were taking opiate pain medication suggesting perhaps an increased benefit with more burden of bone disease. This may be due to the fact that Ra-223 accumulates in areas of bone turnover and that a higher burden of metastases may provide a higher exposure to Ra-223. This finding may be indicative of a suboptimal dosing strategy as has been discussed in the clinical pharmacology section 4.4. Also of note is the slight trend of increasing hazard ratio (less pronounced benefit) with Ra-223 as age increases and in those patients who have received docetaxel chemotherapy. The significance of this result is unclear and it is reassuring that, despite these slight differential findings, all subgroups appeared to have received some benefit from treatment with Ra-223.

Sensitivity Analyses for Overall Survival:

Multiple sensitivity analyses were performed by the statistical reviewer which confirmed the strength of the Overall Survival results:

Table 25: Sensitivity Analyses for Overall Survival in BC1-06 (Updated Analysis)

Sensitivity Analysis Description	HR (95% CI) ^a	p-value
1. Unstratified analysis	0.690 (0.550, 0.865)	0.0013 ^b
2. Stratified analysis based on IVRS randomization stratification factors	0.663 (0.528, 0.834)	0.0004 ^b
3. Stratified analysis adjusted for baseline PSA	0.713 (0.563, 0.903)	0.0049 ^c
4. Stratified analysis adjusted for baseline Gleason score ^d	0.694 (0.551, 0.874)	0.0019 ^c
5. Stratified analysis adjusted for TNM staging ^e	0.689 (0.546, 0.868)	0.0016 ^c
6. Stratified analysis adjusted for time from initiation of hormone therapy to castration resistance ^f	0.667 (0.554, 0.803)	<0.0001 ^c

^a Hazard ratio is from a Cox proportional hazards model. Hazard ratio < 1 favors Ra-223dichloride.

^b p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.

^c p-value is from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.

^d Gleason score is categorized as Missing, <=7 or >7.

^e M stage is categorized as M0, M1, or Unknown (Mx or missing).

^f This analysis used updated analysis data with cut-off date July 15, 2011.

Discrepancy in Baseline Gleason Grade, M-Stage and Screening PSA:

As noted in the demographics section of the FDA review (6.1.2 Demographics), the placebo arm contained a higher percentage of Gleason 8-10 tumors, M1 disease at diagnosis as well as a higher on-study PSA. The FDA statistical reviewer performed an analysis using the Cox model adjusting individually for baseline PSA, Gleason score and M stage and stratifying by total ALP, current use of bisphosphonates and prior use of docetaxel (Table 25). In addition, stratified

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multivariate analysis adjusting for all three variables revealed results were consistent with the primary OS analysis (HR 0.71; 95% CI: 0.557, 0.896).

Discrepancy in Time from Initiation of Hormones to Castration Resistance:

While the approximately 8 month shorter time from diagnosis to randomization seen in the placebo arm (Table 18) may have been due to more placebo patients having been diagnosed with metastatic disease, the time from hormone refractory status to randomization was also shorter in the placebo arm leading to some concern that there may be a more rapidly progressive phenotype on the placebo arm compared to the Ra-223 arm. To further assess the effect of disease pace, the FDA statistical reviewer calculated the time from 1st documented initiation of hormones to castration resistance. This period was also shorter for the placebo arm than for Ra-223 (23 versus 30 months respectively). A sensitivity analysis for overall survival was conducted adjusting for the difference in time from hormone initiation to castration resistance and the results were consistent with the primary analysis (Table 26).

Table 26: Time from Initiation of ADT to Castration Resistance (Updated Analysis)

Variable	Ra-223 (N=614)	Placebo (N=307)	Total (N=921)	
Time to Castration Resistance (Months)				
n	579	291	870	
Mean (SD)	39.0 (33.12)	35.8 (35.45)	37.9 (33.93)	
Median	29.8	23.2	28.0	
Range	0.1 – 227.2	0.1 – 224.5	0.1 – 227.2	
Sensitivity Analysis				
	Ra-223 (N=579)	Placebo (N=291)	Original ITT Population	
			Ra-223 (N=614)	Placebo (N=307)
OS				
Subjects randomized	579	291	614	307
Death	310 (53.5%)	185 (63.6%)	333 (54.2%)	195 (63.5%)
Censored	269 (46.5%)	106 (36.4%)	281 (45.8%)	112 (36.5%)
Overall survival (months)	15.0	11.1	14.9	11.3
Median (95% CI)	(14.0, 16.1)	(9.7, 12.8)	(13.9, 16.1)	(10.4, 12.8)
p value	<0.0001		<0.0001	
Hazard ratio (95% CI)	0.667 (0.554, 0.803) ^a		0.695 (0.581, 0.832)	

^a Hazard ratio is from a stratified Cox proportional hazards model adjusted for time from initiation of hormone therapy to hormone refractory, and stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.

Note: Time to Castration Resistance calculated as 1st recorded LHRH use to Date considered Castration-Resistant
Source: FDA statistical reviewer using updated analysis dataset cutoff July 15, 2011.

This analysis is limited by the fact that some patients initiated hormonal therapy as adjuvant therapy which was likely not equally distributed given the discrepancy in M status at diagnosis. To eliminate the effect of adjuvant LHRH, the Applicant also looked at the time from 1st LHRH

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after a diagnosis of bone metastases to castration and did not find a large difference in that interval between the arms. (13.3 months in Ra-223 compared with 14.2 months for Placebo).

Summary of Overall Survival Results:

The validity of the overall survival data was carefully confirmed through CRF review and source validation by OSI site visits. The OS results were found to be robust when tested using multiple sensitivity analyses including adjusting for baseline demographic discrepancies. It is the clinical reviewer's determination that the overall survival results from BC1-06 are statistically persuasive and clinically meaningful and would support a full approval, particularly in light of the favorable toxicity profile (see FDA review of safety, Section 7.0).

6.1.5 Analysis of Secondary Endpoints(s)

There were five key secondary endpoints:

1. Time to total alkaline phosphatase (ALP) progression
2. Total-ALP response $\geq 30\%$
3. Time to occurrence of first symptomatic skeletal event (SSE)
4. Total-ALP normalization
5. Time to prostate specific antigen (PSA) progression

The above 5 secondary endpoints were pre-specified in the statistical analysis plan and ordered and analyzed by a gate-keeping procedure. All five endpoints met statistical significance providing internal consistency to the overall survival results. The review focused on the most clinically relevant of these endpoints, time to first symptomatic skeletal event (SSE).

Time to Occurrence of first Symptomatic Skeletal Event:

In study BC1-06, a "skeletal related event" was defined as:

- EBRT to relieve skeletal symptoms (bone pain)
- Occurrence of new symptomatic pathologic bone fracture
- Occurrence of spinal cord compression (SCC)
- Tumor-related orthopedic surgical intervention

Reviewer Comment: Notable differences exist between this composite SRE definition and prior FDA approvals based on a delay in SRE. In contrast to past approvals for denosumab and zoledronic acid, there were no pre-specified imaging assessments for this trial. Thus the use of imaging to identify a fracture or cord compression was likely to be triggered by symptoms. This symptom-driven, for-cause identification of events is considered a stronger endpoint. Furthermore, the trial was blinded and the toxicity profile was such that inadvertent unblinding due to toxicity would not have been likely. In order to highlight this difference in endpoint definition, the FDA review team refers to the Applicant's SRE endpoint as "Symptomatic Skeletal Events (SSE)."

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Symptomatic skeletal events (SSE) occurred more frequently in the placebo arm. The time to SSE was significantly delayed in the Ra-223 arm compared with placebo with a hazard ratio of 0.610 (95% CI 0.461, 0.807), $p=0.00046$. (Table 27).

Table 27: BC1-06 Symptomatic Skeletal Events (SSE) Results (Interim Analysis)

	Ra-223 (N=541)	Placebo (N=268)
Interim Analysis		
Subjects randomized	541	268
Experienced	132 (24.4%)	82 (30.6%)
Censored	409 (75.6%)	186 (69.4%)
Time to first SSE (months) ^a Median (95% CI)	13.5 (12.2, 19.6)	8.4 (7.2, NE)
p value ^b	0.00046	
Hazard ratio (95% CI) ^c	0.610 (0.461, 0.807)	
Updated Analysis		
Subjects randomized	614	307
Experienced	202 (32.9%)	116 (37.8%)
Censored	412 (67.1%)	191 (62.2%)
Time to first SSE (months) ^a Median (95% CI)	15.6 (13.5, 18.0)	9.8 (7.3, 23.7)
p value ^b	0.00037	
Hazard ratio (95% CI) ^c	0.658 (0.522, 0.830)	

^a Time to first SRE is calculated as months from date of randomization to date of occurrence of first SRE.

Subjects who died without reporting an SRE were no longer at risk for SRE.

^b p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.

^c Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior used of docetaxel. Hazard ratio < 1 favors Ra-223dichloride.

Note: Cutoff October 14, 2010.

Source: [SURV] analysis dataset. Confirmed by FDA statistical reviewer.

The Kaplan-Meier curves for time to symptomatic skeletal event are provided below in Figure 10 and Figure 11 for both interim- and updated analysis data cutoffs.

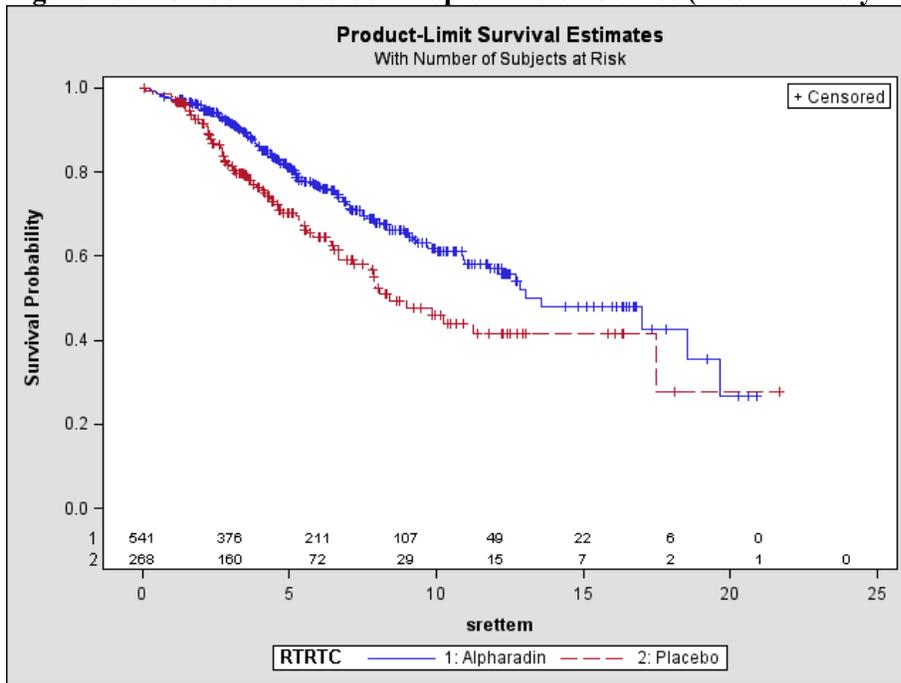
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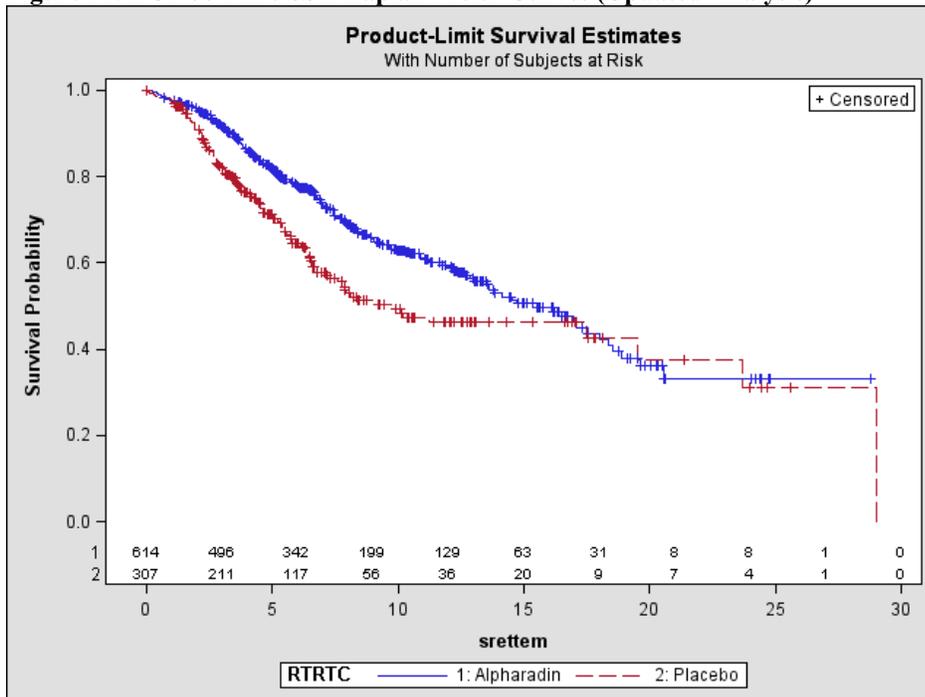
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Figure 10: BC1-06 Time to SSE Kaplan-Meier Curves (Interim Analysis)



Source: Dataset [SURV] cutoff 10/14/2010 confirmed by FDA statistical reviewer.

Figure 11: BC1-06 Time SSE Kaplan-Meier Curves (Updated Analysis)



Source: Dataset [SURV] cutoff 7/15/2011 confirmed by FDA statistical reviewer.

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SSE Discrepancies:

During the reporting phase after unbinding, it was noted by the Applicant that there was an inconsistency between the total # of SSE events and the number of events included in the time to first SSE analysis. It was noted that not all EBRT procedures are conducted for relief of skeletal pain (CNS metastases, bulky lymphadenopathy, etc.) and that some of the discrepancies were due to this problem of EBRT attribution. The same can be said of orthopedic procedures which may not be an SSE if performed for a non-cancer related issue (traumatic fracture from a motor vehicle accident). Furthermore, SSEs could be captured in 3 places in the CRF: efficacy event (EE) page, concomitant procedure page or adverse event page. The key efficacy event page contained a yes/no question for each of the four SSE components. The pre-specified analysis for time to SSE was conducted by utilizing only data recorded on the efficacy event CRF page and thus missed events captured as AEs or as Concomitant Procedures.

A total of 38 unreported SSEs were identified following medical review of the AE and concomitant procedure CRFs. These additional SSEs were added to the existing data from the EE CRF. In the new dataset, 25.4% of Ra-223 patients and 32.1% of placebo patients had experienced an SSE. The post-hoc analysis revealed a delay in time to SSE favoring Ra-223 (HR 0.60; 0.46 - 0.79, p 0.00022). The median time to first SSE was 13.5 months for Ra-223 and 8.1 months for placebo. This analysis was verified by the FDA statistical reviewer.

Reviewer Comment:

A delay in time to SRE has been considered a direct measure of clinical benefit in prostate cancer and has been used as a primary efficacy endpoint for the approval of osteoclast-targeted agents denosumab and zoledronic acid. As such, the significant improvement in time to SSE in this application is an important key secondary endpoint to support the overall survival finding. As was mentioned previously, the SSE data for BC1-06 was updated with an additional 38 SSE events with the subsequent sensitivity analysis continuing to favor Ra-223 with a hazard ratio for time to first SSE of 0.60. The majority of SSE events were EBRT, however the analysis of other important individual SSE events such as time to spinal cord compression and time to pathologic fracture were also in favor of the Ra-223 arm. It is the reviewer's determination that the delay in time to first SSE is statistically persuasive and clinically meaningful in its support for the overall survival findings and should be included in the FDA label. It is also recommended that the endpoint name be changed to time to symptomatic skeletal event [from proposed time to skeletal related event (SRE)] to more accurately reflect the way in which the composite endpoint was collected.

Individual Components of the SSE Composite Endpoint

The majority of events were external beam radiotherapy to painful bone metastases, however events that did not require investigator decision such as spinal cord compression (6.0% vs. 3.3%) and symptomatic pathologic bone fracture (6.7% vs. 3.8%) were more common in the placebo arm compared with Ra-223 respectively. The incidence of individual events was increased

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equally between the arms following the addition of the 38 SSE events in the exploratory sensitivity analysis of the 10/14/2010 data cutoff.

Table 28: Incidence of Individual Symptomatic Skeletal Events (Interim Analysis)

Category of Skeletal Event ¹	Ra-223 N=541		Placebo N=268	
External Beam Radiotherapy				
Primary Interim Analysis	122	23.4%	72	26.9%
Sensitivity Analysis ²	126	24.2%	75	28.0%
Pathologic Fractures				
Primary Interim Analysis	20	3.8%	18	6.7%
Sensitivity Analysis	24	4.6%	19	7.1%
Orthopedic Surgical Intervention				
Primary Interim Analysis	9	1.7%	5	1.9%
Sensitivity Analysis	10	1.9%	5	1.9%
Spinal Cord Compression				
Primary Interim Analysis	17	3.3%	16	6.0%
Sensitivity Analysis	20	3.8%	18	6.7%

Source: Analysis datasets [SURV] and [SURVEE]

Individual skeletal related events and time of events was randomly verified by the FDA clinical reviewer by cross-checking with case report forms.

This table reflects the incidence of a skeletal related event at any time while on study

¹ All skeletal events were defined as related to prostate cancer bone metastases by protocol definition

² Sensitivity analysis dataset includes the 38 additional SSE events found by the Applicant during medical review.

Interval between median SSE and median OS Discrepancy Between the Arms:

A concern regarding the time to SSE endpoint was raised by the statistical team. It was noted that at the time of the interim analysis, the median time to SSE was 13.5 months in Ra-223 group, which was very close to the median OS of 14.0 months (difference = 0.5 months); however, the median time to SSE was 8.4 months and median OS was 11.2 months (difference = 2.8 months) in the placebo group. In the original analyses performed by the Applicant, subjects who had died without experiencing SSE were censored at the last disease assessment date. To assess the contribution of this censoring rule, a post-hoc FDA analyses was conducted which included death date as a SSE event.

Table 29: BC1-06 Time to First SSE including Death as an Event (Interim Analysis)

	Ra-223 (N=541)	Placebo (N=268)
Subjects randomized	541	268
Experienced	262 (48.4%)	160 (59.7%)
Censored	279 (51.6%)	108 (40.3%)
Time to first SSE (months) ^a Median (95% CI)	8.2 (7.5, 9.4)	6.1 (5.1, 7.1)

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p value ^b	<0.0001	
Hazard ratio (95% CI) ^c	0.657 (0.538, 0.803)	
Overall survival (months) Median (95% CI)	14.0 (12.0, 15.8)	11.2 (9.0, 13.2)

^a Time to first SSE is calculated as months from date of randomization to date of occurrence of first SSE.

Subjects who had died without experiencing SSE were defined as SSE events at the date of death.

^b p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.

^c Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior used of docetaxel.

Note: Cut-off date October 14, 2010.

Reviewer Comment: It is the determination of the statistical and clinical reviewer that the discrepancy between the period between median SSE and median OS can be explained by the censoring rules. Taking out the potential informative censoring by including deaths as an event, the time to SSE was still delayed by 2.1 to 2.6 months which is supportive of the overall survival results and can be considered another measure of direct clinical benefit. The fact that this improvement is seen in the setting of 40% of patients receiving concomitant bisphosphonates adds to the strength of the finding.

While there is general agreement that the data supports an improvement in the time to first symptomatic skeletal event, the magnitude of benefit is uncertain and the statistical team does not favor including statistics describing absolute or relative magnitude of benefit in the FDA label. The details of the labeling language for the time to first SSE endpoint were underway at the time of this clinical review.

Secondary Endpoints: Serum Biomarkers:

Alkaline Phosphatase:

Consistent with what was seen in the earlier phase trials, Ra-223 appears to have a strong effect on serum alkaline phosphatase levels which may be a marker for anti-tumor activity in the bone. Trial BC1-06 met all 3 of its pre-specified secondary endpoints relating to changes in alkaline phosphatase.

Alkaline Phosphatase-Related Endpoint Definitions:

Confirmed total-ALP Response is defined as:

- $\geq 30\%$ reduction of the blood level, compared to the baseline value, confirmed by a second total-ALP value approximately 4 or more weeks later.

Total ALP Normalization is defined as:

- Return of total-ALP value to within normal range at 12 weeks in 2 consecutive measurements (at least 2 weeks apart) after start of treatment in patients who have their total-ALP above ULN at baseline.

Total-ALP progression is defined as:

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- In patients with no total-ALP decline from baseline as: $\geq 25\%$ increase from the baseline value, at least 12 weeks from baseline
- In patients with an initial total-ALP decline from baseline as: $\geq 25\%$ increase above the nadir value, which is confirmed by a second value obtained three or more weeks later.

Table 30: BC1-06 Secondary Endpoints Based on Alkaline Phosphatase

	Ra-223 (N=541)	Placebo (N=268)	Hazard Ratio ^c (95% CI)	p value
$\geq 30\%$ Reduction in Serum ALP ^a				
	229/381 (60.10%)	10/160 (6.30%)	N/A	<0.0001 ^b
Total ALP Normalization				
	83/252 (32.9%)	1/107 (0.90%)	N/A	<0.0001 ^b
Time to total ALP progression				
Experienced ALP Progression	79/541 (14.6%)	116/268 (43.3%)		
Median (95% CI)	NE (7.1, NE)	3.7 (3.5, 4.1)	0.162 (0.120, 0.220)	<0.0001

Note: Based on Interim Analysis dataset with Data Cutoff 10/14/2010.

^a Percentage of responders based on number of patients with non-missing values

^b Taken from CMH analysis adjusting for the binary stratification factors: total ALP, current use of bisphosphonates, and prior used of docetaxel

^c Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior use of docetaxel. Hazard ratio < 1 favors Ra-223dichloride.

Prostate Specific Antigen (PSA)

Time to PSA Progression Definition:

Time to PSA Progression is defined as:

- In subjects with no PSA decline from baseline: 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 an initial PSA decline from baseline: 25% increase and an absolute increase of 2 ng/mL above the nadir value, which was confirmed by a second value obtained ≥ 3 weeks later

While the secondary endpoint, time to PSA progression, met statistical significance (Table 31), the magnitude of the result was not as robust as that seen with the alkaline phosphatase findings.

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Table 31: BC1-06 Secondary Efficacy Endpoint Time to PSA Progression

	Ra-223 (N=541)	Placebo (N=268)
Subjects randomized	541	268
Experienced	288 (53.2%)	141 (52.6%)
Censored	253 (46.8%)	127 (47.4%)
Time to PSA progression (months) ^a Median (95% CI)	3.6 (3.5, 3.7)	3.4 (3.3, 3.5)
p value ^b	0.0002	
Hazard ratio (95% CI) ^c	0.671 (0.546, 0.826)	

^a Time to PSA progression is calculated as months from date of randomization to date of PSA progression.

^b p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.

^c Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior used of docetaxel. Hazard ratio < 1 favors Ra-223dichloride.

PSA Response (confirmed 50% PSA decline)

The proportion of patients experiencing a confirmed 50% decline in PSA compared to baseline was 6% in the Ra-223 arm compared with 1% in placebo in trial BC1-06. This PSA response rate is consistent with the confirmed response rate seen in study BC1-04 of 5.6% in the 50 kBq/kg arm. PSA has limitations as an indicator of antitumor activity in prostate cancer; however other cytotoxic agents³ and androgen receptor- directed therapies⁴ in both the chemotherapy-naive and chemotherapy- refractory setting have shown substantially higher PSA declines. A literature search of other approved radioisotopes such as strontium and samarium reveals that low PSA response (defined as PSA decline >50%) may be a class effect for bone-seeking radioisotope monotherapies, and has been reported in the 7%-9% range^{5,6}. Whether this marginal PSA response is due to non-bone foci of prostate cancer being left untreated, incomplete cytotoxicity by radioisotopes, an effect of concomitant therapies diluting the response or other unknown effects is not known. It is notable that in BC1-04, there was a PSA dose response relationship seen with a confirmed PSA response of 0%, 5.6% and 12.8% seen at doses of 25, 50 and 80 kBq/kg respectively. This doubling of PSA response may add additional support to the idea that the optimal dose of Ra-223 has not been reached.

PSA Declines by Extent of Bone Disease

An additional exploratory analysis of PSA response by extent of bone metastases was performed for the Ra-223 arm. Unlike the improvement in the overall survival hazard ratio seen with increasing extent of baseline bone metastases (Table 24), PSA response did not appear to reliably increase with higher burden of bone disease.

³ de Bono J. et al., Lancet (2010); 376: 1147-54. Cabazitaxel PSA Response 39%.

⁴ Ryan et al., NEJM; (2013); 368(2): 138-148. Abiraterone chemo-naive PSA Response 62%.

⁵ Ricci et al., Eur J Nucl Med Mol Imaging (2007) Jul;34(7): 1023-30.

⁶ Sartor et al., Urology (2004); 63: 94-945.

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Table 32: PSA Response in Ra-223 Arm by Extent of Bone Disease

Category	Week 12			End of Treatment		
	N ^a	n ^b	%	N ^a	n ^b	%
≥ 50% reduction in blood level compared to baseline	493	38	7.7	590	54	9.2
EOD =1 <6 metastases	88	8	9.1	98	15	15.3
EOD =2 6-20 metastases	211	17	8.1	253	19	7.5
EOD =3 >20 lesions but not a Superscan	156	9	5.8	186	14	7.5
EOD =4 6-10 superscan	36	4	11.1	51	6	11.8
p-value ^c	0.6423			0.0990		
Confirmed total PSA responses (50%)^d	493	28	5.7	590	33	5.6
EOD =1 <6 metastases	88	8	9.1	98	12	12.2
EOD =2 6-20 metastases	211	12	5.7	253	14	5.5
EOD =3 >20 lesions but not a Superscan	156	6	3.9	186	4	2.2
EOD =4 6-10 superscan	36	2	5.6	51	3	5.9
p-value ^c	0.4105			0.0063		

^a Number of subjects with non-missing values

^b Number of subjects with Response

^c Taken from Chi-square test comparing the proportions between four EOD groups.

^d ≥ 50 % reduction compared to baseline, confirmed by a second PSA value approximately 4 or more weeks later.

Note: Cutoff July 15, 2011.

Source: Datasets [PSAALP, BSCAN] FDA Statistical Reviewer Analysis.

Reviewer Comment: The achievement of an overall survival benefit in the absence of a strong PSA response is unique to this application when compared to prior cytotoxic and androgen receptor based prostate cancer therapies approved with an overall survival benefit. PSA may be a poor surrogate for the prediction of direct measures of clinical benefit both for this application and for prior applications of bone-targeted radioisotopes for the palliation of pain due to bone metastases in prostate cancer. It appears that one can achieve a meaningful reduction of pain (strontium, samarium) and now an improvement in overall survival despite low PSA response results. The lack of effect on disease outside of the bone is likely a significant contributor to this disconnect although there may be other confounding factors.

In conclusion, the FDA review of secondary endpoints confirmed that all 5 secondary endpoints met statistical significance and provides internal consistency to the overall survival results. While time to first SSE was them most relevant endpoint and was felt to show a benefit favoring Ra-223, the magnitude of that benefit is uncertain. The small magnitude of PSA response seen in this application appears to be consistent with PSA data from other radio-isotopes granted approval for pain reduction, and it is the reviewer's determination that the PSA data do not alter the positive risk:benefit assessment of this application based on significant improvements in direct clinical benefit measures of overall survival and delay in symptomatic skeletal events.

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6.1.6 Other Endpoints

Patient Reported Outcomes / Quality of Life Data:

The patient reported outcomes data obtained from both the FACT-P and EQ-5D were presented in the submission as a 119 page report from Oxford Outcomes dated 11/5/2012. The FDA review of the QOL data was based on the submitted report without direct analysis of datasets by the FDA clinical or statistical reviewer. The FDA study endpoints and labeling division (SEALD) was consulted and provided their recommendations.

QOL Collection:

Timing of Assessments:

- FACT-P was obtained at baseline, week 12, week 24 and at the second follow up visit for a total of up to 4 assessments.
- The EQ-5D was obtained at baseline, week 16, week 24 and all follow-up visits for a total of up to 9 post-baseline assessments.

The completion of QOL forms decreased with each subsequent assessment from 94% at baseline to 72-80% at week 16 to 54%-66% at week 24 to 47- 50% for follow up visits.

Table 33: FACT-P Completion Rate BC1-06

FACT-P						
	Observed		Expected		Completion Rate	
	Radium-223	Placebo	Radium-223	Placebo	Radium-223	Placebo
Baseline	574	288	614	307	93.49%	93.81%
Week 16 visit	463	198	576	276	80.38%	71.74%
Week 24 visit	354	131	536	244	66.04%	53.69%
Follow-up 2 visit (Week44)	211	84	418	180	50.48%	46.67%

Source: Quality of Life Analysis final report 11/5/2012 submitted by the Applicant.

Primary Analyses used mixed effect linear regression models to assess average treatment effects on FACT-P total score and EQ-5D utility index score. On treatment analyses as well as an overall analysis including follow up visits were performed.

In addition, HRQoL Response was evaluated and defined as patients with a baseline assessment and at least one on-treatment assessment where an improvement in the respective QOL score was greater than or equal to the upper bound of the minimally important difference recommended by Cella⁷.

⁷ Cella et al., Value Health (2009) 12 (1): 124-9.

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Results:

FACT-P total Score: Overall, quality of life declined in both arms throughout the study. The Ra-223 arm appeared to have a smaller decrement in QOL throughout the trial than did the placebo arm. The difference in mean decrease in QOL between Ra-223 and placebo is shown below.

Table 34: QOL results from BC1-06: Least-square mean scores.

Instrument	Difference in LS-Mean	SE	95% CI	P-Value*
FACT-P Total Score On-Treatment (OT)	3.8	1.4	(1.1 - 6.5)	0.0061
FACT-P Total Score OT + Follow-Up (FU)	3.9	1.3	(1.2 - 6.5)	0.0039
EQ-5D Total Score OT	0.07	0.02	(0.03, 0.11)	0.001
EQ-5D Total Score OT and FU	0.06	0.02	(0.02, 0.10)	0.002

* Mixed-effect linear regression model with covariates including time relative to the baseline visit, treatment, baseline HRQoL score, total ALP, current use of bisphosphonate and any prior use of docetaxel. Least-square mean (LS-Mean) is calculated after adjusting for the other variables in the model.

Source: QOL report for BC1-06 dated 11/5/2012. Primary data was not confirmed by the FDA clinical reviewer.

The improvement in mean difference in total FACT-P score reached statistical significance only at the week 16 follow-up. While still trending toward an improved QOL in the Ra-223 arm compared with placebo, the treatment differences were not significant at the week 24 visit or during follow-up visits. It is also notable that the magnitude of mean improvement in the FACT-P Total Score (around 4 in a scale that ranges from 0 to 156) is less than the 6-10 point difference that is considered a minimally important difference per the Applicant report (Table 1 page 12) which makes the clinical relevance of the difference unclear.

There were significantly more patients on Ra-223 who had an HRQoL response in terms of FACT-P total score (24.6%) when compared to placebo (16.1%) with P=0.02. Significant improvements in HRQoL response were also seen in FACT-P subscales PCS, EWB and FWB favoring Ra-223. In addition, non-significant trends favoring Ra-223 were seen in PWB, prostate cancer pain-related questions subscale and social/family subscale.

Pain:

Despite that fact that 98% of patients were reported to have baseline pain, pain was not a key secondary endpoint of the application and was not measured in a rigorous fashion. However, there are patient reported pain data provided in the FACT-P that can be used to form a FACT-P PCS pain score. The FACT-P PCS pain score for Ra-223 patients was significantly higher (indicating less pain) than placebo at the first on-treatment visit (week 16, P=0.001) but not the second visit (week 24, P=0.077). Within the Ra-223 arm, the mean pain score for Ra-223 patients was significantly higher (improved) than baseline at both on-treatment visits.

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Reviewer Comments: FACT-P and EQ-5D total scores showed a slight improvement for patients receiving Ra-223 when compared to placebo. When evaluated by visit, the statistical significance in the difference between groups decreased over time. Whether this was due to loss of anti-cancer effect of Ra-223 with time or was due to decreased data completion rates is not known, although both are likely contributors. The FDA SEALD review notes that, in prior reviews of the FACT-P and EQ-5D, it was concluded (b) (4)

SEALD also cites limitations specific to the current Ra-223 application including small number of assessments (maximum of 4 for FACT-P), low rate of completion at week 24+ as well as a small observed magnitude of treatment effect. (b) (4)

Based on review of the submitted QOL data and SEALD consultation, it is the clinical reviewer's determination that (b) (4)

. Despite the limitations in choice of instrument, frequency of assessments and completeness of the data, the QOL results are supportive of the overall application in that, on average, the available data appear to trend toward an improvement in the Ra-223 arm and do not show a detriment to quality of life measures or pain in patients treated with Ra-223 when compared to placebo.

Other Evidence of Anti-tumor Activity: Bone Scan Data:

There were no routine follow up bone scans to evaluate in the BC1-06 clinical trial. However, in studies BC1-02, BC1-04 and BC1-08 baseline and routine follow-up scans were performed. The frequency of bone scan assessments for these studies were:

Trial BC1-02: baseline, month 6 and month 12

Trial BC1-04: baseline, month 6 and month 12

Trial BC1-08: baseline and week 12.

An information request was sent to the Applicant inquiring as to whether they had noticed any significant improvement in bone scans on these trials. The sponsor responded noting that bone scans had predominantly been obtained with the purpose of assessing extent of disease and no further assessments were performed or planned. Scans were read onsite with no central read. Each individual baseline and follow scan result was grouped into an extent of disease (EOD) categories:

EOD0: normal or abnormal because of benign bone disease

EOD1: fewer than 6 metastatic sites

EOD2: 6-20 metastatic sites

EOD3: >20 metastatic sites but no superscan

EOD4: superscan

In BC1-02 there may have been some evidence of delay in progression by bone scan in that there were fewer patients in the Ra-223 (Ra-223) group who progressed to EOD3 at month 12 (44%)

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than compared to placebo (86%), however this analysis suffers from limitation in sample size and the primary data was not reviewed the FDA clinical reviewer. See Table 35 below.

Table 35: Bone Scan Extent of Disease by Visit in Trial BC1-02

Visit	Statistic/ Response category	Alpharadin (n=31)	Placebo (n=27)	Total (n=58)
Pre-Study	No. of obs.	31	27	58
	EOD 1 (<6)	11 (35%)	6 (22%)	17 (29%)
	EOD 2 (6-20)	10 (32%)	11 (41%)	21 (36%)
	EOD 3 (>20)	9 (29%)	9 (33%)	18 (31%)
	EOD 4 (superscan)	1 (3%)	1 (4%)	2 (3%)
Month 6	No. of obs.	25	17	42
	EOD 1 (<6)	8 (32%)		8 (19%)
	EOD 2 (6-20)	6 (24%)	5 (29%)	11 (26%)
	EOD 3 (>20)	10 (40%)	11 (65%)	21 (50%)
	EOD 4 (superscan)	1 (4%)	1 (6%)	2 (5%)
Month 12	No. of obs.	16	7	23
	EOD 1 (<6)	2 (13%)		2 (9%)
	EOD 2 (6-20)	6 (38%)	1 (14%)	7 (30%)
	EOD 3 (>20)	7 (44%)	6 (86%)	13 (57%)
	EOD 4 (superscan)	1 (6%)		1 (4%)

Source: Applicant report A58302 page 675. Data not verified by the FDA clinical reviewer.

Reviewer Comment: The assessment of anti-tumor activity for Ra-223 is problematic. Bone scan data is lacking to perform a PFS analysis. PSA response is limited by use of concomitant medications with known anti-cancer activity and continued production of PSA by prostate cancer continuing to grown outside of Ra-223 treated bone lesions. Nonetheless, while of moderate magnitude, PSA and bone scan findings appear to be trending in the direction of antitumor activity and it is the reviewer's determination that the strength of both overall survival and time to SSE results are enough to provide substantial evidence of direct clinical benefit.

6.1.7 Subpopulations

Other than the lowest weight quartile subgroup noted in the clinical pharmacology section, there were no other subpopulations from the clinical trial that were identified as having remarkably inferior or superior safety and/or efficacy results. Results from several subgroups that were analyzed are presented below.

Concurrent Calcium Channel Blocker Use:

While unlikely given the nanogram dose of active drug delivered, there is theoretical concern regarding concomitant calcium channel blockers and interference with Ra-223 transport. Those patients using calcium channel blockers during the active treatment phase of the trial were analyzed and there was no significant detriment to efficacy measured by overall survival or time to skeletal related events for this subgroup (Table 36).

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Table 36: OS and time to SRE in the setting of concomitant Ca Channel Blocker use

	ITT population	Ra-223	Placebo	Hazard ratio	p-value
		N=105	N=59		
OS	Number (%) of patients				
	Death	41 (39%)	29 (49%)		
	Censored	64 (61%)	30 (51%)		
	Overall survival time (months) Median (95% CI)	14.7 (11.7, 16.5)	10.4 (6.5, 13.5)	0.465 (0.279, 0.773)	0.0026
SRE	Number (%) of patients				
	SRE event	24 (23%)	14 (24%)		
	Censored	81 (77%)	45 (76%)		
	Time to SRE (months) Median (95% CI)	18.5 (13.0, NE)	9.0 (6.5, NE)	0.625 (0.308, 1.266)	0.1881

Source: Statistical reviewer analysis of dataset [SURV] cutoff 10/14/2010.

Reviewer Comment:

While theoretically a concern, post-hoc analyses by FDA and the Applicant reveal no data suggestive of a decrease in efficacy or increase in toxicity in patients taking concomitant calcium channel blockers in the BC1-06 clinical trial.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See section 4.4 Clinical Pharmacology regarding inferior efficacy seen in the lowest weight quartile. This effect did not appear to be due to other disease characteristics. A post-marketing commitment to explore higher doses is currently being negotiated.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Ra-223 is given for a maximum of 6 injections. Following cessation of therapy, it is unknown whether antitumor activity in the bone persists. This will be difficult to determine based on the fact that bone scans were not routinely performed in BC1-06. Furthermore, given that Ra-223 does not treat disease outside of the bone, non-bone metastatic disease will eventually require treatment following completion of Ra-223. Further study of Ra-223 given in combination with systemic therapies such as newer generation androgen-receptor based therapies or chemotherapy is warranted.

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6.1.10 Additional Efficacy Issues/Analyses

Stratification:

Stratification assignment was performed using an integrated voice response system (IVRS). FDA analysis of the [SURV] dataset reveals that approximately 10% of patients had a discrepancy between one or more of the IVRS stratification factors and the actual stratification value. (Table 37) No significant imbalance was seen between the arms, study sites or country of enrollment. Re-analysis of OS and time to SRE by the FDA was performed by using the actual stratification values. A sensitivity analysis performed by the FDA statistical reviewer notes that the improvement seen in overall survival and SRE is maintained when using IVRS-derived stratification values.

Table 37: BC1-06 Stratification Discrepancies

	Discrepancies between IVRS and Actual Stratification		
	All Patients N=809	Ra-223 N=541	Placebo N=268
Any Stratification Error	83 (10.3%)	60 (11.1%)	23 (8.6%)
tALP <220 or ≥220	22 (2.7%)	13 (2.4%)	9 (3.4%)
Current Use of Bisphosphonates	57 (7.0%)	44 (8.1%)	13 (4.9%)
Prior Docetaxel	7 (0.9%)	5 (0.9%)	2 (0.7%)

Source: [SURV] Dataset

Reviewer Comment: Discrepancies between IVRS and actual randomization groups showed no sign of bias and does not materially affect the overall survival results.

7 Review of Safety

Safety Summary

In this NDA, the Applicant submitted safety data from 904 patients treated with Ra-223 and 332 patients treated with placebo in the BC1-06 randomized controlled trial or in one of six other Phase 1 or 2 clinical trials. Nearly all (n=894) of these patients had castration-resistant prostate cancer. At the proposed dose of 50 kBq/kg actual body weight (BW), 703 patients were treated with Ra-223. In the BC1-06 trial (a.k.a., ALSYMPCA), patients were scheduled to receive six injections once every 28 days; 600 patients received 50 kBq/kg BW of Ra-223 and 301 patients received placebo. The median number of injections on the Ra-223 arm was six with a median duration of treatment of 20 weeks compared to 5 injections and a median duration of treatment of 18 weeks on the placebo arm. The number of patients and duration of exposure to Ra-223 was adequate for this NDA safety review.

Key findings from the BC1-06 randomized controlled trial:

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- Deaths: Deaths were less common on the Ra-223 arm compared to the placebo arm (55% vs. 63%; respectively) for the original safety analysis (safety cutoff July 15, 2011) and for the 90-Day Safety Update (80% vs. 81%; respectively) (safety cutoff date December 1, 2012).
- Deaths due to Adverse Events (AEs): Deaths due to AEs were less common on the Ra-223 arm compared to the placebo arm (19% vs. 28%; respectively). The most common AEs with an outcome of death were related to progression of disease on both arms (10% vs. 12%; respectively). For Ra-223-treated patients compared to placebo, there was a small increase in deaths related to bone marrow failure (0.3% vs. 0.0%; respectively); and in patients with bone marrow failure, deaths related to vascular hemorrhage (1.2% vs. 0.3%; respectively).
- Nonfatal Serious Adverse Events (SAEs): The overall incidence of nonfatal SAEs was lower on the Ra-223 arm compared to placebo (44% vs. 57%; respectively). There was a small increase in nonfatal SAEs for thrombocytopenia (2.3% vs. 1.0%; respectively), dehydration (2.0 vs. 1.0%; respectively), and renal failure and impairment (1.8% vs. 0.7%; respectively) for Ra-223-treated patients compared to placebo. A majority of the renal failure and impairment SAEs on the Ra-223 arm were due to urinary tract obstruction likely related to prostate cancer; with exclusion of these SAEs a small increase remained (0.8% vs. 0.0%) and these SAEs were likely related to dehydration and negative fluid status.
- Discontinuations due to AEs: Discontinuations due to AEs were less common on the Ra-223 arm compared to placebo (16% vs. 19%; respectively). There was an increase in discontinuations due to bone marrow suppression on the Ra-223 arm compared to placebo (5.3% vs. 2.7%; respectively) and discontinuation due to metastases to non-skeletal sites (1.2% vs. 0.0%); the latter is important in that Ra-223 is not thought to be effective in treating visceral prostate cancer.
- Grade 3 and 4 AEs: Overall there were fewer Grade 3 - 4 AEs on the Ra-223 arm (59%) compared to the placebo arm (65%). The largest increases in Grade 3 - 4 AEs on the Ra-223 arm compared to placebo were thrombocytopenia (6.5% vs. 2.0%; respectively), neutropenia (2.0% vs. 0.3%; respectively), leukopenia (1.7% vs. 0.3%; respectively), and pancytopenia (1.2% vs. 0.0%; respectively).
- Common Adverse Reactions (ARs) and Laboratory Abnormalities: The most common adverse drug reactions (>10%) in patients receiving Ra-223 were nausea, diarrhea, vomiting and, peripheral edema. The most common hematologic laboratory abnormalities (> 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia and neutropenia.
- Bone Marrow Failure and Pancytopenia: In the randomized trial, 2.3% of the patients on the Ra-223 arm experienced bone marrow failure or pancytopenia compared to no patients treated with placebo. A majority of the patients who experienced bone marrow failure required blood transfusions and the bone marrow suppression was ongoing at the time of death. On the Ra-223 arm, 5.3% of the patients permanently discontinued therapy due to

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bone marrow suppression. Nine (1.5%) of the Grade 1-4 AEs were serious (SAEs) and eight (1.3%) were Grade 3 or 4 in severity. Ten (1.7%) of the patients required blood transfusions.

- **Vascular Hemorrhage:** Despite a small increase in deaths due to vascular hemorrhage on the Ra-223 arm, there were no increases in total, minor, or major hemorrhagic SAEs. When comparing the Ra-223 arm to the placebo arm, there was a small increase in Grade 1-4 gastrointestinal hemorrhage (2.0% vs. 1.3%; respectively) and hematoma (0.5% vs. 0.0%; respectively) (MedDRA HLGT terms). Most of these AEs are Grade 1 or 2; there was a small increase in Grade 3 gastrointestinal hemorrhages (0.7% vs. 0.0%, respectfully); only two of these cases were reported with temporally associated thrombocytopenia ARs. Patient #209-003 had Grade 4 thrombocytopenia and a Grade 1 rectal hemorrhage. Patient #111-024 had a Grade 1 thrombocytopenia and subcutaneous hematoma.
- **Blood Transfusions, Erythropoietin, and G-CSF:** Ra-223-treated patients were treated with more of the following compared to patients treated with placebo: blood transfusions (42% vs. 39%; respectively), erythropoietin (3.2% vs. 1.7%; respectively), and G-CSF (1.5% vs. 0%; respectively). A majority of the patients who experienced Grade 3 or 4 thrombocytopenic ARs were managed with transfusions (18 out of 39 patients).
- **Risk of Secondary Malignancies:** Epidemiology studies of short-lived, alpha-emitting, radium-224 have demonstrated an increased risk of bone sarcoma and possible association with other secondary malignancies and hereditary defects. Due to its mechanism of action and nonclinical toxicology data, Ra-223 has the potential to induce secondary malignancies. In the randomized trial, less than 3% of the patients were followed for more than 3 years after initiation of study treatment. The expected latency period for bone sarcomas and other secondary malignancies greatly exceeds the duration of follow up collected in Ra-223 clinical trials. The overall incidence of secondary malignancies in the randomized trial was lower on the Ra-223 arm compared to placebo (0.8% vs. 1.7%; respectively). A majority of the secondary malignancies reported were non-serious non-melanoma skin carcinomas (0.7% vs. 1.0%). The total incidence of solid non-cutaneous malignancies in the Ra-223 database is approximately 0.4%. A Postmarketing Requirement (PMR) for longer term monitoring of a larger patient population treated with Ra-223 is recommended.
- **Subsequent Treatment with Cytotoxic Chemotherapy:** In the randomized clinical trial, 16% of the patients in the Ra-223 group and 18% of the patients in the placebo group received cytotoxic chemotherapy after completion of study treatments. The median time to initiation of chemotherapy (80 days vs. 65 days; respectively) and the duration of the chemotherapy (120 days vs. 113 days; respectively) were comparable for patients treated with Ra-223 and placebo. Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Ra-223 will tolerate subsequent cytotoxic chemotherapy.
- **Bowel Movement Monitoring:** Fecal excretion is the major route of elimination from the body for Ra-223. The rate of elimination from the gastrointestinal tract was influenced by

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the variability in intestinal transit times. Bowel movement frequency should be carefully monitored during treatment with Ra-223.

- Radionuclide Precautions: Patients, providers, and caregivers require precautions to minimize the risk of radioactive contamination and exposure. Given the short path-length of alpha particles, the normal working procedures for radiopharmaceutical handling and universal precautions for healthcare workers (i.e., gloves and barrier gowns) are expected to adequately prevent significant secondary exposure to Ra-223.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Original NDA Submission

The integrated safety summary (ISS) submitted in the original NDA application includes safety data from 1236 patients who received at least one dose of radium-223 dichloride (Ra-223) or placebo in the randomized BC1-06 trial or in one of six other phase 1 or 2 clinical trials (i.e., AT1-BC-1, BC1-02, BC1-03, BC1-04, BC1-05, or BC1-08) (Source: ISS ADSL dataset). The BC1-02 study was a small (n=64), randomized (1:1), placebo-controlled trial. The BC1-03 and BC1-04 studies are both Ra-223 dose response trials. A brief description of the clinical trial designs and the safety cutoff dates for each trial (original NDA submission) are listed in Table 10. In these trials, a total of 904 patients were treated with Ra-223 and 332 patients were treated with placebo. Ra-223 was administered to 894 prostate and 10 breast cancer patients, all with bone metastases. The prostate cancer patients enrolled in these trials had castration-resistant disease (CRPC), or were taking hormone therapy, or had undergone orchiectomy, with the exception of two patients (Patient #3205 and #7317) in the AT1-BC-1 trial. (Source: CSR 15522: Tables 14.2.2.3, 14.2.2.4, 16.1.4, and 16.1.5).

Ninety (90)-Day Safety Update

The Applicant submitted the 90-Day Safety Update (90-Day SU) on March 14, 2013. The safety cutoff date for the 90-Day SU is December 1, 2012. The report includes updated major safety results from the BC1-06 trial, ongoing Ra-223 trials (i.e., BC1-09, BC1-10, 16216, and 15354), and the Ra-223 expanded access program (i.e., 15995). For the BC1-06 trial, a majority of the patients had completed the 12-week follow up visit after discontinuation of study therapies before the original NDA safety cutoff date (July 15, 2011). Therefore, the BC1-06 data in the 90-Day SU is primarily comprised of updated death information with a limited number of post-treatment AEs and SAEs. In the BC1-06 trial, 25 patients originally randomized to the placebo arm were crossed over and treated with Ra-223; 15 crossover patients received six doses of Ra-223 and ten patients received between 1-5 doses. With the exception of the crossover patients, there were no significant changes in Ra-223 exposure.

Overall, the findings in the 90-Day SU are consistent with the original NDA safety findings. When comparing the July 15, 2011 safety findings to the December 1, 2012 safety findings, there

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were no new adverse reactions identified and no updates to any of the major safety findings were required. Consistent with the original NDA findings, OS continued to favor the Ra-223 arm compared to the placebo arm. Based on data derived from the updated [Death] Dataset for the original Safety Analysis Population (SAP), there were a total of 480 deaths (80.0%) on the Ra-223 arm compared to 243 deaths (80.7%) on the placebo arm. There were no new deaths attributed to Ra-223 by the study Investigators. The frequency of deaths that occurred during the treatment period remained unchanged when comparing the Ra-223 and placebo arms (4.3% vs. 7.3%; respectively). A majority of the deaths on both arms were due to prostate cancer occurring during the follow up phase of the trial. When comparing the original and updated safety cutoff dates for the Ra-223 arm of the BC1-06 trial, there were no increases of $\geq 2.0\%$ for any of the following: Grade 1-4 AEs; Grade 3-4 AEs; SAEs; AEs leading to permanent discontinuation; or AEs of interest. There were three new AEs with an outcome of death [Patient #035-037 (malignant disease progression); #152-004 (general physical health deterioration); #178-007 (pulmonary embolism)]. None of the new AEs with an outcome of death occurring while patients were on study therapy or were attributed to Ra-223 by study Investigators. Two new secondary malignancies were reported on each study arm. On the Ra-223 arm, one patient (each) experienced a squamous cell carcinoma and neoplasm skin (unspecified). On the placebo arm, one patient experienced an adenocarcinoma of colon-rectum and one patient a new skin cancer (unspecified). These new cancers were included in the secondary malignancy review in Section 7.3.4. One additional case of multiple myeloma (#2012-095537) was reported in the expanded access program for Ra-223 approximately 16 weeks after initiation of Ra-223 treatment. Knowledge of this case did not change the conclusions in Section 7.3.4 or the overall incidence of secondary malignancies in the Ra-223 safety database.

7.1.2 Categorization of Adverse Events

The Applicant originally coded adverse event (AEs) for these trials using earlier versions of the MedDRA dictionary. This resulted in minor differences in AE terms and frequencies when comparing the pooled databases and the clinical databases for the individual studies. Different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) were also used to grade the severity of AEs. The minor differences in control terminologies did not significantly impact the interpretation of the overall safety results. The MedDRA and CTCAE versions used in the clinical trials in this application are listed in Table 38.

Table 38: Adverse Event Coding and Common Toxicity Criteria Grading

	MedDRA Version	CTCAE version
Clinical Studies		
BC1-06	11.0	3.0
BC1-02	7.0	2.0
BC1-03	9.0	3.0
BC1-04	9.0	3.0
AT1-BC1	4.1	2.0
BC1-05	9.0	3.0
BC1-08	11.1	3.0

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	MedDRA Version	CTCAE version
Pooled Data		
50 kBq/kg	14.1	3.0

Source: Applicant Summary of Clinical Safety

The Applicant defined Treatment Emergent Adverse Events (TEAEs) as events which occur following the first injection of study treatment or that started prior to the first injection and worsened during treatment. In the BC1-06 trial, study Investigators recorded AEs using paper case report forms (CRFs). Investigators were required to report any AEs that occurred after randomization and up to 12 weeks after the last injection of study drugs regardless of attribution to study therapy. Investigators were required to determine if the AE was serious, provide an assessment of the relationship to study drug (i.e., unrelated, possible, or probable), and to follow each AE until resolution or as clinically required. Twelve weeks after the last dose of study therapy (i.e., follow up period), study Investigators reported only AEs considered *related* to the study therapy. Any AEs related to leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer, or other secondary malignancies were reported by Investigators up to 36 months after the first study drug administration. During the follow up period, patients were evaluated once every two months for the first year and then once every four months for up to three years.

On January 28, 2011, in addition to the routine study monitoring activities, the Applicant initiated a “Quality Verification Program” (QVP). Source data verification was conducted for 11% (93/809) of the patients in the ITT population. For the SAP, the QVP determined that 565 out of 5140 (11%) possible treatment-emergent AEs were not reported. Nine out of 790 (1.1%) treatment emergent SAEs were not reported. The incidences of the AEs and SAEs not reported were comparable across treatment arms. All of the AEs and SAEs not reported and found during the QVP were entered into the BC1-06 trial safety databases provided in the original NDA submission. There were no clear patterns for underreporting with regards to treatment arms, countries, geographic region, or Clinical Research Assistant (CRA) assignments. In addition to the QVP program, the Applicant conducted a global re-training of CRAs on key outcomes and expectations with targeted training sessions for individual clinical sites with issues identified in the audits. See Sections 3.1 and 3.2 for more detail on the QVP program.

Reviewer Comments: The quality of the safety data submitted in this application is adequate to conduct the required safety review. Review of the QVP methods used by the Applicant and additional review of CRFs, CRF data clarification forms, and analysis datasets included in the original NDA submission was performed. The AEs/SAEs that were under-reported prior to the QVP do not appear to be systematic, impart bias, or significantly impact the safety findings from the BC1-06 clinical trial. The IDMC also concluded that there were no unexpected AEs identified when reviewing the data not previously reported and the safety profile of Ra-223 remained unchanged before and after the QVP (June 3, 2011).

To verify the accuracy of the AE coding process, verbatim AE terms from randomly selected CRFs were compared to MedDRA Lower Level Terms (LLTs) in the [AESAF] dataset (July 15,

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2011 safety cutoff date). Nearly all of the AE terms reviewed were accurately recorded and coded in the AESAF dataset and no significant discrepancies were identified. For each CRF reviewed, CRA monitoring and use of multiple study Investigator data queries resolved data discrepancies and obtained missing data. The few minor discrepancies that were identified in this comparison were not significant with regards to the overall integrity of the AE database.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from the BC1-06 randomized controlled trial is the primary focus of the FDA safety review and is referred to in this review as the Safety Analysis Population (SAP). A safety cutoff date of July 15, 2011 was used for the major safety analyses. For clinical trials included in the ISS, the Ra-223 doses ranged from 5 kBq/kg actual body weight (BW) to 250 kBq/kg BW with administration of 1 – 6 injections at 3 – 16 week intervals. At the proposed dose of 50 kBq/kg, 703 patients received at least one dose of Ra-223; 600 patients in the BC1-06 trial and 103 patients in the other six phase 1-2 trials (i.e., Phase 1/2 50 kBq/kg BW population). All 703 of the patients treated with doses of 50 kBq/Kg BW of Ra-223 were evaluated in the pooled 50 kBq/kg BW population. In addition, safety data from an additional 201 patients in the ISS who received at least one dose of Ra-223 were reviewed to assess dose response relationships and consistency in key safety findings. These patients received Ra-223 doses of 5 kBq/kg (n= 26), 25 kBq/kg (n= 66), 38 kBq/kg (n= 1), 46kBq/kg (n= 5), 80 kBq/kg (n= 42), 88 kBq/kg (n= 1), 93 kBq/kg (n= 5), 100 kBq/kg (n= 33), 125 kBq/kg (n= 3), 163 kBq/kg (n= 5), 200 kBq/kg (n= 4), 213 kBq/kg (n= 5), and 250 kBq/kg (n=5).

Table 39: Treatment-emergent AEs (TEAEs) for the 50 kBq/kg BW Patient Population

	BC1-06 (50 kBq/kg BW) (N= 600)		BC1-06 (Placebo) (N=301)		Phase 1 / 2 50 kBq/kg BW Population (N= 103)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Nausea	35.5%	1.7%	34.6%	1.7%	33.0%	0.0%
Anemia	31.5%	13.5%	31.2%	13.3%	22.3%^a	8.7%^a
Diarrhea	25.2%	1.5%	15.0%	1.7%	22.3%	0.0%
Vomiting	18.5%	1.7%	13.6%	2.3%	17.5%	1.0%
Edema peripheral	12.8%	1.7%	10.0%	1.3%	3.9%	0.0%
Thrombocytopenia	11.8%	6.5%	5.6%	2.0%	5.8%^b	0.9%^b
Pyrexia	6.3%	0.5%	6.3%	1.0%	2.9%	0.0%
Decreased appetite	5.8%	0.3%	4.3%	0.0%	16.5%	1.9%
Neutropenia	5.2%	2.3%	1.0%	0.7%	2.9%^c	0.0%^c
Hematuria	5.0%	1.2%	5.0%	1.0%	1.0%	0.0%
Arthralgia	4.8%	0.5%	3.7%	0.3%	2.9%	0.0%
Cough	4.8%	0.0%	3.7%	0.0%	1.9%	0.0%
Leukopenia	4.3%	1.7%	0.3%	0.3%	1.0%	0.0%
Headache	4.2%	0.2%	3.0%	0.0%	5.8%	1.0%
Musculoskeletal pain	3.8%	1.2%	3.7%	0.7%	1.9%	0.0%
Dyspepsia	3.5%	0.3%	2.0%	0.0%	4.9%	1.0%
Lower respiratory tract infection	3.3%	1.2%	3.0%	1.0%	1.0%	0.0%

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	BC1-06 (50 kBq/kg BW) (N= 600)		BC1-06 (Placebo) (N=301)		Phase 1 / 2 50 kBq/kg BW Population (N= 103)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Dehydration	3.3%	1.3%	1.3%	0.3%	1.9%	0.0%
Myalgia	3.2%	0.0%	2.7%	0.0%	6.8%	0.0%
Abdominal pain upper	3.0%	0.0%	1.0%	0.0%	0.0%	0.0%

Note: Adverse events with an incidence of $\geq 3\%$ on the Ra-223 arm and occurring at a higher incidence than placebo.

Source: [ISS ADAE] Dataset (July 15, 2011 safety cutoff date)

^a PT terms used were “anemia” or “hemoglobin decreased”.

^b PT terms used were “thrombocytopenia” and “platelets decreased”

^c PT terms used were “thrombocytopenia” and “platelets decreased”

Reviewer Comment: In general, the most common AEs reported in the BC1-06 trial were consistent with the AEs reported in the Phase 1/2 50 kBq/kg BW population when considering the relatively small phase 1/2 population and shorter duration of follow up for patients enrolled in these trials. There was an increase in hematologic toxicity (i.e., anemia, thrombocytopenia, neutropenia, and leukopenia) in the Ra-223 treated patients in the BC1-06 trial compared to the P1/2 50 kBq/kg Ra-223 treated-patients. This may be due to cumulative toxicities since the BC1-06 patients received a median of six injections of Ra-223 compared to the P1/2 trial patients in which a majority of the patients (65%) received ≤ 3 total doses of Ra-223. The increased number of laboratory tests and duration of testing in the BC1-06 arm may have also contributed to the small increase. The differences in the incidences of peripheral edema and decreased appetite between the BC1-06 patients and the Phase 1/2 patients may have been related to differences in the study populations.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Duration

Drug Exposure at Appropriate Dose and Schedule

The proposed Ra-223 dose is 50 kBq/kg BW, 703 patients received at least one dose of Ra-223; 601 patients in the BC1-06 trial; and 103 patients in the other six ISS trials (Source: ISS ADSL dataset). In the BC1-06 trial, 300 patients received matching placebo, and were used for comparison to the Ra-223 analysis population. See Section 7.1.3 for more information.

Demographics of Safety Population

In general, the baseline demographics and baseline disease characteristics for the patients treated with Ra-223 in the BC1-06 trial and the 50 kBq/kg BW pooled safety analysis population were comparable. Table 40 shows the demographics and baseline disease characteristics for these study groups.

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Table 40: Demographics and Disease Characteristics for the Safety Population

	BC1-06 (50 kBq/kg BW) (N= 600)	BC1-06 (Placebo) (N=301)	Pooled 50 kBq/kg BW population (N= 703)
Demographic Characteristics			
Age			
Median (yrs) (range)	71 (49 – 90)	71 (44 – 89)	71 (49 – 90)
Age Group (yrs)			
< 65	153 (25.5%)	71 (23.6%)	184 (26.2%)
65 to 75	278 (46.3%)	142 (47.2%)	327 (46.5%)
> 75	169 (28.1%)	88 (29.2%)	192 (27.3%)
Weight (kg) (range)	82 (40 – 139)	82 (47 – 130)	82 (40 – 139)
Race			
Caucasian	562 (93.7%)	284 (94.4%)	663 (94.3%)
Black	10 (1.7%)	3 (1.0%)	10 (1.4%)
Asian	21 (3.5%)	12 (4.0%)	21 (3.0%)
Other	7 (1.2%)	2 (0.7%)	9 (1.3%)
Geographic Region			
USA and Canada	33 (5.5%)	10 (3.3%)	36 (5.1%)
Europe	523 (87.2%)	265 (88.0%)	623 (88.6%)
Rest of World	44 (7.3%)	26 (8.6%)	44 (6.3%)
Baseline Performance Status			
ECOG Performance Status			
0	162 (27.0%)	77 (25.6%)	193 (27.5%)
1	366 (61.0%)	183 (60.8%)	412 (58.6%)
2	72 (12.0%)	40 (13.3%)	87 (12.4%)
Missing	0 (0.0%)	0 (0.0%)	11 (1.6%)
Baseline Disease Characteristics			
Extent of Disease (# of metastatic sites)			
< 6	99 (16.5%)	37 (12.3%)	127 (18.1%)
6 – 20	256 (42.7%)	145 (48.2%)	287 (40.8%)
> 20 (not superscan)	192 (32.0%)	88 (29.2%)	227 (32.3%)
Superscan ^a	53 (8.8%)	31 (10.3%)	62 (8.8%)
Prior Exposure to Docetaxel			
Yes	347 (57.8%)	169 (56.1%)	369 (52.5%) ^b
No	253 (42.2%)	130 (43.2%)	334 (47.5%) ^b
Missing	0 (0.0%)	2 (0.7%)	0 (0.0%) ^b
External Beam Radiation (any)			
Yes	395 (65.8%)	189 (62.8%)	467 (66.4%) ^c
No	205 (34.2%)	112 (37.2%)	236 (33.6%) ^c

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	BC1-06 (50 kBq/kg BW) (N= 600)	BC1-06 (Placebo) (N=301)	Pooled 50 kBq/kg BW population (N= 703)
External Radiation to the Bone			
Yes	301 (50.2%)	144 (47.8%)	NA
No	299 (49.8%)	157 (52.2%)	NA
Missing	0 (0.0%)	0 (0.0%)	NA
Systemic Radiation^d			
Yes	23 (3.8%)	8 (2.7%)	67 (9.5%) ^b
No	577 (96.2%)	293 (97.3%)	636 (90.5%) ^b
Current use of bisphosphonates			
Yes	372 (62.0%)	181 (60.1%)	372 (52.9%)
No	228 (38.0%)	120 (39.9%)	228 (32.4%)
Missing	0 (0.0%)	0 (0.0%)	103 (14.7%) ^c
Current use of opioid pain medications			
Yes	416 (69.3%)	219 (72.8%)	NA
No	184 (30.7%)	82 (27.2%)	NA
Missing	0 (0.0%)	0 (0.0%)	NA

Source: [ISS-ADSL] Dataset (July 15, 2011 safety cutoff date)

^a Superscan defined as diffuse, intense, skeletal uptake of tracer with absent renal and background activity; intended to signify the presence of extensive bone disease

^b Source 2.7.4 Summary of Clinical Safety, Table 1-13, Subnote g

^c Source 2.7.4 Summary of Clinical Safety, Table 1-13, Subnote h

^d Systemic radiation defined as radiotherapy with strontium-89, samarium-153, rhenium-186 or rhenium-188 for treatment of bony metastases. Patients were excluded from the BC1-06 if they received systemic radiation within one year.

NA= Not available for review

Reviewer Comment: There was a small increase in patients who had received prior systemic radiation in the Phase 1/2 50 kBq/kg Ra-223 trials (9.5%) compared to the BC1-06 trial (3.4%). This is due to BC1-06 study eligibility criteria that excluded patients who had received prior strontium-89, samarium-153, rhenium-186, or rhenium-188 treatment.

Treatment Duration

In the BC1-06 trial, patients were scheduled to receive six injections of 50 kBq/kg BW Ra-223 or placebo once every four weeks (i.e., 20 week duration). Table 41 shows the number of injections and duration of treatment in the BC1-06 trial and for the pooled 50 kBq/kg BW population. Based on data provided in this NDA, no patients have received more than six scheduled injections of Ra-223 at the 50 kBq/kg BW dose or a total cumulative dose of > 300 kBq/kg BW.

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Table 41: Overall Number of Injections and Treatment Duration

	BC1-06 (50 kBq/kg BW) (N= 600)	BC1-06 (Placebo) (N=301)	Pooled 50 kBq/kg BW population (N= 703)
Number of injections			
Median	6	5	6
Mean	5.1	4.5	4.7
(range)	(1-6)	(1-6)	(1-6)
Number (%) of injections completed ^a			
1	18 (3.0%)	21 (7.0%)	44 (6.3%)
2	37 (6.2%)	37 (12.3%)	50 (7.1%)
3	48 (8.0%)	36 (12.0%)	81 (11.5%)
4	60 (10.0%)	34 (11.3%)	89 (12.7%)
5	53 (8.8%)	32 (10.6%)	54 (7.7%)
6	384 (64.0%)	141 (46.8%)	385 (54.8%)
Median duration of treatment (weeks) (range)	20.1 (0.1 – 27.9)	18.1 (0.1 – 27.1)	20.1 (0.1 – 27.9)
Duration of treatment (weeks)			
< 4	23 (3.8%)	28 (9.3%)	49 (7.0%)
4-8	34 (5.7%)	36 (11.9%)	43 (6.1%)
8-12	48 (8.0%)	33 (10.9%)	55 (7.8%)
12-16	55 (9.2%)	32 (10.6%)	114 (16.2%)
16-20	72 (12%)	37 (12.3%)	74 (10.5%)
20-24	347 (57.8%)	131 (43.5%)	347 (49.4%)
> 24	21 (3.5%)	4 (1.3%)	21 (3.0%)
Total Cumulative Activity Injected / BW (kBq/kg) median (range)	292.8 (43.5- 337.3)	NA	NA
Total Cumulative Activity Injected (kBq) median (range)	21,726 (2700- 41,985)	NA	NA

Source: [EX] and [ISS-ADEX] Dataset (July 15, 2011 safety cutoff date)

^a Infusions that were recorded in the dataset as not completely successful (i.e., EXSUCCESS; ETHNYOTH; EXTOTVOL) were not included in the FDA calculations.

A majority (64%) of the patients who received Ra-223 received all six of the scheduled injections and patients on the Ra-223 arm had more injections (median=6) administered than patients on the placebo arm (median=5). The small differences in the number of injections

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administered between the pooled 50 kBq/kg BW population and the 50 kBq/kg patients in the BC1-06 is likely due to different Ra-223 injection schedules in the Phase 1 and 2 trials. The median duration of therapy was 20 weeks for the Ra-223-treated patients compared to 18 weeks for patients treated with placebo. If injections were administered exactly 28 days apart as scheduled, the expected duration of therapy for six injections would be 20 weeks. The difference in duration between the Ra-223 treated patients and placebo is small, and likely primarily due to more rapid progression of skeletal CRPC on the placebo arm. The median total cumulative activity of Ra-223 administered is approximately equal to the scheduled cumulative activity per kg of BW (i.e., 293 kBq/kg vs. 300 kBq/kg).

Reviewer Comment: Overall, toxicities related to Ra-223 do not appear to significantly reduce the duration of therapy when scheduled at doses of 50 kBq/kg BW for six doses administered once every 28 days.

Dose Delays

In the BC1-06 trial, 15.0% of the Ra-223-treated patients experienced dose delays due AEs compared to 17.9% of the patients on the placebo arm. Table 42 lists the dose delays due to AEs experienced by patients in the BC1-06 trial.

Table 42: BC1-06 Dose Delays due to Adverse Events (Updated Analysis)

Dose Delays due to Adverse Events	BC1-06 (50 kBq/kg BW) (N= 600)	BC1-06 (Placebo) (N=301)
Patients with at least 1 AE leading to dose delay	90 (15.0%)	54 (17.9%)
Neutropenia	8 (1.3%)	1 (0.3%)
Thrombocytopenia	8 (1.3%)	2 (0.7%)
Diarrhea	5 (0.8%)	0 (0.0%)
Hematuria	4 (0.7%)	0 (0.0%)
Renal failure and Impairment ^a	4 (0.7%)	0 (0.0%)
Vomiting	4 (0.7%)	1 (0.3%)
Dehydration	3 (0.5%)	0 (0.0%)
Nausea	3 (0.5%)	1 (0.3%)

Based on AEs occurring at an incidence of >0.5% on the Ra-223 arm and more commonly in Ra-223 than Placebo.

Source: [AESAF] Dataset (July 15, 2011 safety cutoff date)

^a MedDRA HLT level term

Reviewer Comment: The dose delays due to AEs are consistent with the ARs reported in the BC1-06 trial.

7.2.2 Explorations for Dose Response

See the Clinical Pharmacology review for more information.

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7.2.3 Special Animal and/or In Vitro Testing

See the Nonclinical Pharmacology/Toxicology review for more information.

7.2.4 Routine Clinical Testing

In the BC1-06 trial, laboratory analyses and abbreviated physical exams were obtained at screening, once every 28 days during the treatment period, once every two months during the follow up period from Weeks 24-52, and then once every 4 months from Week 52 up to 3 years after initial administration of Ra-223 or placebo. Twelve-lead ECGs were performed at screening, Week 4, and Week 24. See Figure 5 for more information.

The BC1-06 trial included a QTc substudy that was submitted in a separate study protocol. See Section 7.4.5 and the FDA QTc Integrated Review Team (IRT) review for more information.

Reviewer Comment: In Phase 1 and 2 trials, the Applicant established that the nadir for hematologic toxicities related to Ra-223 occurred between 10-14 days after administration. As scheduled in the BC1-06 trial, measurement of hematologic laboratory parameters 28 days after drug administration may under report hematologic AEs in terms of incidence and severity. Lack of laboratory data (scheduled and unscheduled) during the timeframe in which the nadir for these hematologic toxicities occur complicates interpretation of hematologic toxicities. Conversely, the hematologic AEs reported for patients treated at 50 kBq/kg in the Phase 1 and 2 trials were reported at a lower incidence and severity than in patients treated in the BC1-06 trial. Future trials of Ra-223 should include hematologic laboratory monitoring more frequently and include more complete unscheduled laboratory values in the datasets to assess the incidence, impact, and severity of these toxicities with more precision.

7.2.5 Metabolic, Clearance, and Interaction Workup

The pharmacokinetics of Ra-223 in blood was linear in terms of dose proportionality and time independence in the dose ranges investigated [46 to 250 kBq (1.24 to 6.76 microcurie) per kg body weight]. After intravenous injection, Ra-223 is rapidly cleared from the blood and is distributed primarily into bone or excreted into the intestine. Fifteen minutes after injection, approximately 20% of the injected radioactivity remained in the blood. After four hours, approximately 4% of the injected radioactivity remained in blood, with a decrease to less than 1% approximately 24 hours after the Ra-223 administration. At ten minutes post injection, radioactivity was detected in bone and the intestine. At 4 hours post-injection, the percentage of the radioactivity present in bone and intestine was approximately 61% and 49%, respectively. No significant uptake was seen in other organs such as heart, liver, kidneys, urinary bladder, and spleen four hours after injection. Ra-223 is an isotope which decays and is not metabolized. The whole body measurements indicated that approximately 63% of the administered radioactivity was excreted from the body within 7 days after injection (after correcting for decay). Fecal excretion is the major route of elimination from the body. At 48 hours after injection, the cumulative fecal excretion was 13% (range 0-34%), and the cumulative urine excretion was 2%

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(range 1- 5%). There was no evidence of hepato-biliary excretion based on imaging data. The rate of elimination of Ra-223 dichloride from the gastrointestinal tract is influenced by the high variability in intestinal transit rates across the population. Hepatic impairment is not expected to affect the pharmacokinetics of Ra-223 dichloride. Since excretion in urine is minimal, and the major route of elimination is via the feces, renal impairment is not expected to affect the pharmacokinetics of Ra-223 dichloride.

See the FDA primary Clinical Pharmacology review for more information.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are currently no therapeutic alpha-emitting radionuclides approved in the United States. As discussed in Section 2 of this review, for Ra-223, the most relevant approved products are bone-targeted, beta-emitting, radioisotopes used for palliation of bone pain from metastatic disease. There are limitations when comparing Ra-223 to these beta emitting radionuclides due to the differences in alpha- vs. beta emission, radioactive decay half-lives, and the primary clearance pathways for these products (renal) compared to Ra-223 (fecal). Strontium-89 [beta emission (max. energy= 1.46 MeV); max. range= 8 mm in tissue; rad. t1/2= 50.5 days] and samarium-153 [beta emission (max. energy= 0.23 MeV); max. range= 3.0 mm in tissue and 1.7 mm in bone; rad. t1/2= 46.3 days] are both rapidly cleared from the blood and have an affinity for bone with concentration in areas of bone turnover. Approximately 2/3 of the unbound strontium-89 is excreted in the urine, with the highest excretion rate in the first two days following injection. The remaining 1/3 of unbound strontium-89 is excreted fecally. Unbound samarium-153 is eliminated in the urine with approximately 35% ($\pm 15\%$) excreted within six hours after intravenous injection.^{8,9}

The most significant toxicity related to strontium-89 and samarium-153 is bone marrow suppression. For strontium-89, the incidence of Grade 3 decreases in hemoglobin, leukocyte, and platelet count increased approximately 4 - 8% compared to placebo. There was a slight increase in the incidence of Grade 4 hemoglobin (2% vs. 1%, respectively) and platelet count decrease (1% vs. 0%, respectively). For samarium-153, the most common ARs were thrombocytopenia (69.3% vs. 8.9%, respectively), leukopenia (59.3% vs. 6.7%, respectively), hemoglobin decreased (40.7% vs. 23.3%, respectively), and infection (17.1% vs. 11.1%, respectively). For strontium-89, the bone marrow toxicities are primarily related to platelet and white blood cell counts, result in an approximate 30% reduction in platelet counts, and usually occur 12 – 16 weeks after administration, with recovery within six months after treatment in the absence of disease progression or additional therapies. For samarium-153, white blood cell and platelet counts decreased to a nadir of approximately 40% to 50% approximately 3 – 5 weeks after administration and returned to the pre-treatment levels in approximately 8 weeks. Other toxicities related to strontium-89 and/or samarium-153 include the potential for fetal harm, risks for nursing and excretion in human milk, “calcium-like flushing sensations” related to rapid

⁸ Metastron® (strontium chloride, sr-89) Prescribing Information. GE Healthcare, Medi-Physics, Inc. Aug 2007

⁹ Quadramet® (samarium sm 153 lexitronam injection, solution) Prescribing Information. EUSA Pharma (USA), Inc. August 2011

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injections (strontium-89 only), urinary catheterization for incontinent patients, precautions for patients with renal dysfunction, and requirements for appropriate radiopharmaceutical and waste handling, administration, and controls. Use in patients with evidence of seriously compromised bone marrow from previous therapy or disease infiltration, or with concomitant chemotherapy or external beam radiotherapy (EBRT) is not recommended.^{9, 10}

There is no significant exposure data available for Ra-223 from other human experience unrelated to this Ra-223 dichloride developmental program. Historical toxicity findings related to radium-224 (t_{1/2}= 3.6 days) are relevant to Ra-223 (t_{1/2}= 11.4 days) because both radium - 223 and -224 are short-lived alpha-emitting radioisotopes.^{10, 11} The shared mechanisms of action are both due to the high linear energy transfer associated with alpha particle emission. Internal exposure from radium-224 is available from use as an injectable therapy to treat ankylosing spondylitis (spinal arthritis) and bone tuberculosis. Based on the radium-224 experience, potentially serious or life-threatening toxicities for Ra-223 include bone marrow failure, bone sarcoma, secondary malignancies, and osteonecrosis. Historical data from radium-224 exposure establishes a clear association with bone sarcoma and bone marrow failure. The bone sarcomas were usually osteosarcomas, with chondrosarcoma and fibrosarcoma rarely reported. These bone sarcomas presented in the radial skeleton, long bones, and in major joints. Based on additional long term epidemiology studies, the incidence of other malignancies, including solid tumors and leukemia, may also be increased with short-lived alpha-emitting radionuclides. In the “Speiss” study, 900 German patients were treated with relatively high doses of radium-224 over approximately 10 weeks [mean skeletal dose= 2.08 Gy (SD=1.5)] between 1945 and 1955. These patients were followed until as recently as December of 2007. Fifty-seven bone sarcomas were reported in 56 patients compared to an estimated expected number of 0.2 for this study. Bone sarcoma incidence peaked approximately eight years (range: 4 - 33 years) after initial radium-224 exposure. These patients were compared to the German Saarland Cancer Registry to calculate Standardized Incidence Ratios (SIRs) for other secondary cancers. Excluding cancers occurring within five years of initial exposure (latency period) and non-melanoma skin cancers, 231 non-skeletal solid tumors were reported compared to 151 expected cases (p= < 0.001). The authors concluded that there were significant increases in secondary cancer of the breast [SIR = 3.3], connective tissue [SIR = 10.5] thyroid [SIR = 7.2], liver [SIR = 4.2], kidney [SIR = 2.6], pancreas [SIR = 2.2], bladder [SIR = 2.0], and female genitalia [SIR = 1.9], with a non-statistical increase in leukemia [SIR=1.8]^{12, 13, 14} A controlled, prospective epidemiologic study compared 1471 patients treated with injections of 1 MBq of radium-224 once a week for 10 weeks (0.56 Gy to marrow-free skeleton of a 70 kg patient) with a control group (n=1324 patients) who did

¹⁰ Rowland, RE. Radium in Humans: A Review of U.S. Studies. Argonne National Laboratory. Argonne, IL. September 1994: 1-117

¹¹ Committee on the Biological Effects of Ionizing Radiation. Health Risks of Radon and Other Internally Deposited Alpha-Emitters (BEIR IV). Washington, DC: The National Academy Press, 1988:176-244

¹² Mays CW., Speiss H., Gerspace, A. Skeletal effects following ²²⁴Ra Injections into humans. Health Physics 1978 (35):83-90

¹³ Chmelevsky, D., Kellerer, AM., Land, CE, Mays CW., Spiess H. Time and dose dependency of bone sarcomas in patients injected with radium-224. Radiat Environ Biophys. 1988(27):103-114.

¹⁴ Nekolla AN., Walsh L, Spiess H. Incidence of malignant diseases in humans injected with radium-224. Rad Res 2010(174):377-386.

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not receive radioactive treatment. The authors of this study reported a statistically significant ($p < 0.001$) increase in the incidence of leukemia (primarily myeloid) in patients treated with lower exposure levels of radium-224.¹⁵ An additional case control study performed by Wick et. al. evaluated lower doses of radium-224 (mean skeletal dose= 0.56 Gy) in ankylosing spondylitis patients and identified 11 bone marrow failures (0.7%; 11/1501) on the radium-224 arm compared to 4 bone marrow in control patients (0.3%; 4/1556).^{8, 16} In the “Speiss” study, tooth breakage was reported in 12% of the pediatric patients and in 2% of the adults treated with radium-224.¹⁷ The mechanism of action for bone necrosis and osteomyelitis related to radium may be related to a disruption of blood flow in Haversian systems due to “mineral plugs” and destruction of small blood vessels in the bone.¹¹ The exposure level required to induce these toxicities or to increase the risk of secondary cancers is controversial and not clearly defined. There appears to be a dose response relationship related to secondary malignancies with an increase in the incidence of secondary cancers at higher doses, but it is unclear if the dose response curve is linear, if linear extrapolation underestimates the risk at low doses, or if there is a specific threshold of exposure in which these risks significantly increase or become impractical in relation to the human lifespan. Although there is a lack of unequivocal evidence, radium is assumed to be carcinogenic even at the lowest dose levels.^{10, 11, 14}

Reviewer Comment: In addition to typical concerns related to cross study comparisons, the ability to compare radium exposure levels across these studies is significantly limited by differences in the dosimetry, dose estimations, and exposure calculations used for the referenced studies.

7.3 Major Safety Results

7.3.1 Deaths

For the BC1-06 trial, the Applicant recorded deaths attributed to AEs in two independent Case Report Forms (CRFs); the Death CRF and the AE CRF. The Applicant used these CRFs to generate the [Death] and the [AESAF] datasets (respectively). The FDA AEs with an outcome of death analyses use the treatment-emergent deaths related to AEs from both sources. Instances in which progression of disease or the development of prostate cancer metastases was recorded as an adverse event are removed from this analysis.

¹⁵ Wick RR., et. al. Increased risk of myeloid leukemia in patients with ankylosing spondylitis following treatment with radium-224. *Rheumatology* 2008(47):855-859.

¹⁶ Wick RR., Chmelevsky D., Gossner W., Radium-224 risk to bone and hematopoietic tissue in ankylosing spondylitis patients. *The Radiobiology of Radium and Thorotrast*. Commission of the European Communities. Radiation Protection Programme. Urban and Schwarzenberg. 1986:38-44

¹⁷ Speiss H. Life-span study of late effects of ²²⁴Ra in children and adults *Health Phys.* 2010(99)(3):266-91.

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Table 43: BC1-06 AEs with an Outcome of Death

	Treatment Period + 30 Days		3-Year Follow Up	
	Alpharadin N = 600	Placebo N = 301	Alpharadin N = 600	Placebo N = 301
All	16 (2.7%)	14 (4.7%)	44 (7.3%)	36 (12.0%)
Blood and Lymphatic Disorders				
Anemia				1
Bone Marrow Failure			1	
Disseminated Intravascular Coagulation		1		
Thrombocytopenia			1	
Cardiac Disorders				
Angina/Myocardial Ischemia			2	
Myocardial Infarction	2	1	4	3
Cardiopulmonary Failure			1	2
Cardiorespiratory Arrest/Cardiac Arrest		1	1	1
Cardiac Failure		2	5	3
Gastrointestinal Disorders				
Intestinal Obstruction	1			
General Disorders				
Death NOS	3		5	4
Gen Physical Health Deterioration	2		3	2
Multi-Organ Failure	1		1	1
Sudden Death	1	1	1	
Hepato-Biliary Disorders				
Hepatic Failure			1	
Infections and Infestations				
Pneumonia ¹	2	1	8	3
Sepsis	1			1
UTI/Urosepsis		1		1
Injury, Poisoning, Procedural Complications				
Extradural Hematoma			1	
Post-procedure Complication				1
Traumatic Cerebral Hemorrhage				1
Metabolism and Nutrition				
Cachexia	1			1
Neoplasm				
Gastric Cancer				1
Nervous System Disorders				
Cerebral/Intracranial Hemorrhage		1	2	
Cerebral Ischemia		1		
CVA/Cerebral Infarction			1	2
Spinal Cord Compression			1	
Psychiatric Disorders				
Confusional State	1			
Renal Disorders				
Renal Failure			1	4
Respiratory Disorders				
Dyspnea	1			3
Pleural Effusion		1		
Pulmonary Edema			1	
Pulmonary Embolism		2	1	1

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Respiratory Arrest/Failure		1	2	
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¹Includes lower respiratory infection and aspiration pneumonia

There were four deaths on Ra-223 arm in which the Applicant and the FDA analyses differ with regard to cause of death.

- Patient #011-006 was a death attributed to thrombocytopenia by the Applicant and by the Investigator on the CRF, but this death was attributed to pneumonia in the case narrative. In the table above this death is reported as thrombocytopenia, but the case is discussed among the lower respiratory infections below.
- Patient #146-004 was a death attributed to multiple organ failure by the Applicant, but the case narrative noted depression of the bone marrow. FDA notes he experienced hemorrhagic complications with high grade thrombocytopenia, platelet transfusions, and bleeding at the time of death. This death is considered in the FDA vascular hemorrhage analyses and in the analyses of bone marrow suppression and multi-organ failure.
- Patient #004-001 was reported as a death due to renal failure by the Applicant. However, the Investigator attributed the death to bleeding and hypovolemia in the setting of Grade 4 pancytopenia. This death is considered in the FDA vascular hemorrhage analyses.
- Patient #037-012 was reported as a death due to a fatal extradural hematoma associated with Grade 3 thrombocytopenia that required multiple whole blood transfusions before the event, so this death is significantly confounded, but the contribution of Ra-223 cannot be ruled out, and this death was considered related to vascular hemorrhage.

The following sections include brief summaries of the AEs of interest with an outcome of death that occurred on the Ra-223 arm of the BC1-06 trial. These summaries include adverse events that occurred during the treatment period + 30 days and adverse events that occurred during the 3 year follow up.

Vascular Hemorrhagic Deaths

Deaths related to hemorrhage or with potential hemorrhagic complications were grouped together as vascular hemorrhagic disorders (MedDRA HLG T term) and compared across the BC1-06 study arms. There was a small increase (1.0% vs. 0.3%) in deaths related to vascular hemorrhage for patients treated with Ra-223 (Patient #002-013, #004-001, #037-012, #170-002, #146-004, #173-008) compared to patients treated with placebo. Investigator attribution for four of these deaths was possible (Patient #002-013; #004-001; #173-008; #146-004). On the Ra-223 arm, all of the patients experiencing vascular hemorrhage-related deaths had thrombocytopenia with platelet nadirs of $< 100 \times 10^9 / L$. Interpretation of the magnitude of the platelet nadirs is complicated by administration of multiple blood transfusions and limited laboratory test results for unscheduled analyses in the Applicant data provided. In addition to other methods to stop the hemorrhagic events, all of these patients required blood transfusions. An additional patient (#034-004) treated with Ra-223 who experienced treatment-emergent Grade 4 thrombocytopenia and hemorrhagic complications approximately 77 days after his last dose of Ra-223 was not included in the FDA fatal vascular hemorrhagic due to significant confounding factors related to the hemorrhagic event. *See the narratives for deaths due to bone marrow suppression for more information on this death.* In the 90-Day safety update, one additional death due to rectal

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hemorrhage occurred in Patient #9-050-018, who had crossed over from the placebo arm to the Ra-223 arm. Thirty-six days after his fifth dose of Ra-223 he developed a new Grade 4 rectal bleeding, thrombocytopenia ($21 \times 10^9/L$), and anemia (Hgb= 9.9 g/dL) AEs. He died three days later (39 days after last Ra-223 dose). The rectal bleeding, thrombocytopenia, and anemia were ongoing at the time of his death. Investigator attribution for the AEs was possibly related to Ra-223 with his death attributed to prostate cancer progression.

Bone Marrow Suppression and Multiple Organ Failure Deaths

Deaths on the Ra-223 arm that were attributed to bone marrow or multiple organ failure are summarized below:

Multi-organ Failure: Patient #146-004 was a 77-year old man with CRPC (TNM unknown; EOD= > 20 lesions; Total Gleason = 9) who received one dose of Ra-223 and experienced Grade 4 thrombocytopenia (platelet level not provided), multiple hemorrhages, and “bone marrow destruction” 11 days after treatment that progressed into fatal multiple organ failure five days later (16 days after treatment). His previous treatments included docetaxel with no prior radiotherapy to the bone or prostate. The docetaxel treatment was discontinued approximately 60 days prior to Ra-223 therapy initiation. After the onset of these events, he received 24 units of red blood cells, 6 units of platelets, fibrinogen, and tranexemic acid for anemia, thrombocytopenia, and bleeding. Approximately two weeks before Ra-223 treatment, his platelet count was $144 \times 10^9/L$ and his hemoglobin was 11.6 g/dL. On Day 0, his pre-treatment platelet count was $75 \times 10^9/L$ and hemoglobin was 11.3 g/dL. At the onset of the hemorrhagic event 11 days later, his platelet count was $49 \times 10^9/L$ and hemoglobin 9.9 g/dL. Throughout the hemorrhagic event, white blood cell and neutrophil counts remained at or near the normal range. The Investigator attributed the death to depression of the bone marrow most likely caused by the previous chemotherapy (docetaxel). Given the temporal association to the nadir of Ra-223, and the known risks of thrombocytopenia, this death is possibly related to Ra-223 because the contribution of Ra-223 cannot be adequately ruled out. However, it is important to note that thrombocytopenia occurred prior to the 1st dose of Ra-223. This death also includes hemorrhagic complications and is considered in the vascular hemorrhagic death analyses.

Bone marrow failure: Patient #034-004 was a 63-year old man with CRPC (TNM unknown; EOD= 6- 20 lesions; Total Gleason = 9) who received two injections of Ra-223. His previous treatments included EBRT to bone (30 Gy), docetaxel, and mitoxantrone. His medical history included cancer of the transverse colon, hereditary nonpolyposis colon cancer, and right hemicolectomy. Approximately 14 days after his second dose of Ra-223, he experienced Grade 4 cerebrovascular ischemia that led to permanent discontinuation of Ra-223. Approximately 28 days after his last dose of Ra-223, his platelet count was $120 \times 10^9/L$ (baseline= $165 \times 10^9/L$) and his hemoglobin was 10.4 g/dL (baseline= 11.1 g/dL). Approximately 69 days after his second and last dose of Ra-223, he experienced Grade 4 bone marrow failure, including Grade 4 anemia (Hgb nadir= 5.6 g/dL) and thrombocytopenia (platelet nadir = $11 \times 10^9/L$). During these

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events, he received transfusions of four units of red blood cells and three units of platelets. White blood cell counts remained within the normal range during these events. The subject died approximately 77 days after his last dose of Ra-223. The Investigator reported that the death was unrelated and due to prostate cancer with skeletal metastases. However, the death was also reported as a Grade 5 bone marrow failure AE with an outcome of death. Approximately 7 – 8 days prior to death and during the bone marrow failure, he experienced an upper gastrointestinal bleed, hematemesis, melena, and platelet levels of 11, 12, 53 (post transfusion), and $27 \times 10^9/L$. Evidence to support a prostate cancer-related death include lack of a strong temporal association with Ra-223, a rapidly rising PSA prior to the death (28 days after discontinuation = 468 ng/mL; 56 days after discontinuation = 971 ng/mL), and significant weight loss that occurred after discontinuation of Ra-223. Due to the most likely cause of death being related to progression of disease and the significant confounding factors for this death, this case was not included in the FDA vascular hemorrhage analyses.

Multiple organ failure: Patient #028-003 was an 83-year old man with CRPC (TNM unknown, EOD= 6-20 lesions; Total Gleason=8; PSA = > 2000 ng/mL). His relevant medical history included ongoing hydronephrosis, edema of the lower limbs, arterial hypertension, COPD, constipation, sleeplessness, groin pain, anorexia, anemia, and worsening bone pain. Approximately 26 days after his second and last injection of Ra-223, he was admitted to the hospital with Grade 2 anemia, Grade 4 decreased general status, Grade 4 pulmonary edema, and Grade 4 renal insufficiency. He was treated with dexamethasone, a red blood cell infusion, bilateral nephrostomy, and other palliative care measures. Platelet counts remained in the reference range and there was no significant neutropenia or signs of infection reported. The Investigator considered the renal insufficiency, pulmonary edema, decreased general status, and multiple organ failure to be unrelated to Ra-223. The Investigator reported that the death was caused by prostate cancer with skeletal and lymph node metastases.

Lower Respiratory Tract and Lung Infection Deaths

When comparing Ra-223-treated patients to patients who received placebo, there was a small increase in deaths due to lower respiratory tract and lung infections (1.7% vs. 1.3%; respectively); but no increase in infection- or sepsis- related deaths overall. If patient 011-006 is included in this group, 11 deaths (1.8%) due to lower respiratory infection occurred in the Ra-223 arm. For the 11 deaths on the Ra-223 arm, the median time from the last dose of Ra-223 was 57 days (range: 20-356 days), with six of these deaths occurring within 60 days after receiving Ra-223 therapy. Ten out of the eleven deaths were reported without neutropenia; Patient #233-005 had Grade 3 neutropenia reported. Investigator attribution was unrelated to Ra-223 for all of the cases except Patient #011-006. All of these patients had received either prior cytotoxic chemotherapy or EBRT to the bone or prostate. Seven of these deaths occurred in patients who had received prior docetaxel treatment. Five patients had received prior EBRT to the bone, two received prior EBRT to the prostate, and three patients received EBRT to both the bone and the prostate; Patient #045-012 had not received prior EBRT therapy. The deaths that occurred with

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neutropenia (Patient #233-005) and were possibly related to Ra-223 per Investigator attribution (Patient #011-006) are summarized below:

Pneumonia: Patient #233-005 was a 78-year old man with CRPC (unknown TNM; EOD= 6-20 lesions; Gleason=7) who received six injections of Ra-223. His previous treatments for prostate cancer included external EBRT to bone (8 Gy) and bicalutamide; no prior cytotoxic chemotherapy was administered. Twenty-one days after his last injection of Ra-223, he was admitted to the hospital with Grade 3 dehydration, Grade 1 thrombocytopenia ($80 \times 10^9/L$), Grade 2 anemia (Hgb= 9.4 g/dL), and Grade 2 neutropenia (ANC= 1100). The patient was treated and discharged but these AEs persisted and progressed. Forty days after the last dose of Ra-223 was administered, the patient was readmitted to the hospital with Grade 3 dehydration, Grade 2 thrombocytopenia ($61 \times 10^9/L$), Grade 3 anemia (Hgb= 7.2 g/dL), and Grade 3 neutropenia (ANC= 670). He was treated with intravenous antibiotics and died the same day. His chest X-ray on admission was consistent with bronchopneumonia; an autopsy was not performed. The Investigator attribution for this death was to prostate cancer due to skeletal metastases that was unrelated to study therapy. The patient's PSA supports this conclusion, with a baseline value of 78 ng/mL that increased to 790 ng/mL at the time of his last injection of Ra-223, and then to 860 ng/mL three weeks before his death.

Pneumonia: Patient #011-006 was a 68-year old man with CRPC (T3, N1, M1; EOD= 6-20 lesions; Total Gleason=7) who received six injections of Ra-223. His previous treatments consisted of orchiectomy, EBRT to the bone (30 Gy), and cyproterone. No clinically relevant neutrophil count reductions occurred while he was receiving Ra-223 treatment. His baseline (week 0) platelet count and hemoglobin were $199 \times 10^9/L$ and 11.1 g/dL; respectively. His Week 4, 8, 12, 16, and 20 platelet counts were 205, 180, 153, 117, and $113 \times 10^9/L$; respectively. Platelet counts drawn 56 and 112 days after completion of Ra-223 therapy were 74 and $80 \times 10^9/L$; respectively. He received additional EBRT to the bone (20Gy) approximately 120 days after his last dose of Ra-223. Approximately 180 days after his last dose, he received three red blood cell transfusions (2 units each). Approximately 225 days after his last dose of Ra-223, his platelet count was $33 \times 10^9/L$. Approximately 255 days after his sixth injection his platelet count was $15 \times 10^9/L$. The subject's status worsened and he died 256 days after his last dose of Ra-223. The Investigator reported that the death was not caused by prostate cancer and possibly related to Ra-223 "due to the profound and long-standing thrombocytopenia". The Applicant confirmed the death was due to pneumonia and that no hemorrhage had occurred. Disease progression with bone marrow infiltration is a potential confounding factor due to an increase in PSA prior to the death. PSA was 35 ng/mL at baseline, 35 ng/mL at Week 24, and 54 ng/mL 90 days after discontinuation of Ra-223. Approximately 30 days prior to his death, his PSA had risen to 149 ng/mL.

Non-Hemorrhagic Gastrointestinal Disorder Deaths

There was only one AE with an outcome of death (Patient #035-027) for the gastrointestinal system-organ class. Patient #035-027 was a 68-year old man treated with two doses of Ra-223

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who experienced abdominal distention and fatal bowel obstruction approximately 25 days after his last dose of Ra-223. His medical history was significant for CRPC (Total Gleason = 9; T3 disease) with skeletal metastases (>20 lesions), sigmoid diverticular disease, non-insulin dependent diabetes, previous myocardial infarction, and COPD. He had no history of prior therapy with a radical prostatectomy, radiotherapy, or brachytherapy. He was taking opioid pain medications at the time of this event. He also experienced nonserious Grade 2 constipation and decreased appetite prior to his death. His last bowel movement was reportedly 10 days before the onset of the bowel distention event. He died at home and no autopsy was performed. This death is possibly related to Ra-223, but is significantly confounded by the use of concomitant opioid medication, decreased appetite/poor oral intake, and a medical history that includes diverticulitis and diabetes. Disease progression is also a potential confounding factor due to his intact prostate and locally advanced disease at baseline.

General Physical Health Deterioration Deaths:

Deaths related to general physical health were reviewed to evaluate if any of these deaths were likely related to Ra-223. All of these deaths were most likely due to progression of disease, disease-related comorbidities, or comorbid patient conditions. Four of the five deaths (Patient #017-017; #017-030; #028-002; #173-009) on the Ra-223 arm included rapidly rising PSA levels and/or signs of clinical disease progression such as worsening bone pain or pathologic fracture. The remaining death (Patient #078-003) was a 74-year old man with CRPC (T2b, EOD= > 20 lesions; Total Gleason= 9) who died approximately 65 days after his sixth injection of Ra-223 “due to continued worsening of general conditions”. No relevant laboratory tests or treatment information was provided approximate to his death. The Investigator reported that the death was unrelated and due to prostate cancer.

Reviewer Comment: Despite potential confounding factors, the contribution or additive effect of the Ra-223 to the bone marrow failure/suppression and hemorrhagic death are biologically and clinically possible given the bone marrow suppression adverse reactions associated with Ra-223. It is difficult to interpret if bone marrow suppression and/or failures are due to disease progression with bone marrow infiltration or due to Ra-223 induced toxicity. These interpretations are limited to clinical factors that would suggest disease progression such as increasing pain, changes in laboratory parameters, reductions in performance status, increases in PSA, or temporal presentation of other likely disease-related events (e.g., pathologic fractures). Treatment emergent bone scans and autopsies were also not available for review.

Deaths Within 30 days of Drug Initiation and Drug Discontinuation

All deaths (including disease progression) occurring within 30 days after initiation of study therapy were more common in placebo-treated patients compared to Ra-223-treated patients [1.7% (5/301) vs. 0.8% (5/600), respectively]. On the Ra-223 arm, Investigators attributed four out of five of the deaths to prostate cancer. The one death (#133-012) not attributed to prostate cancer occurred within one day of the first dose of Ra-223 after the patient left the clinical center. The cause of this death was reported by the patient’s wife and attributed to dyspnea. The Investigator attributed the most likely (probable) cause of the fatal dyspnea to be due to a “pulmonary embolism due to a coagulation disturbance secondary to prostate cancer”. Platelet

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counts were in the reference range at the time his death; pre-treatment D-dimer was > 12 X ULN (6408 µg/L) (e.g., possible DIC unrelated to Ra-223). Investigator attribution was “unrelated” to study therapy for four out of five of these deaths. The 2nd death (Patient #146-004) not attributed to prostate cancer and possibly related to study therapy was due to bone marrow failure and is discussed above.

Deaths due to adverse events occurring within 30 days of treatment discontinuation were more common for placebo-treated patients compared to Ra-223 treated patients [4.7% (14/301) vs. 2.7% 16/600), respectively]. The most common non-prostate cancer-related deaths that occurred within 30 days of treatment discontinuation were related to cardiac disorders. Consistent with these findings, there were more cardiac deaths on the placebo arm (1.3%; 4/301) compared to the Ra-223 arm (0.3%; 2/600). Note that there was also one death attributed to bowel obstruction (Patient #035-027). Investigators attributed two deaths that occurred within 30 days of treatment discontinuation as possibly related to study therapy (Patient #035-027 and #146-004) for more information related to these deaths.

7.3.2 Nonfatal Serious Adverse Events

In the BC1-06 trial, 546 nonfatal SAEs were reported in 266 patients (44.3%) on the Ra-223 arm and 328 nonfatal SAEs were reported in 170 patients (56.4%) on the placebo arm. The nonfatal SAEs occurring in > 1% of the patients on the Ra-223 arm of the trial and that were more common compared to placebo are listed in Table 44.

Table 44: Nonfatal SAEs in the BC1-06 Trial

Nonfatal Serious Adverse Events (SAEs)	BC1-06 (50 kBq/kg BW) (N= 600)	BC1-06 (Placebo) (N=301)
Patients with at least 1 nonfatal SAE	266 (44.3%)	170 (56.5%)
Malignant neoplasm progression	31 (5.2%)	14 (4.7%)
<i>Thrombocytopenia</i>	<i>14 (2.3%)</i>	<i>3 (1.0%)</i>
<i>Dehydration</i>	<i>12 (2.0%)</i>	<i>3 (1.0%)</i>
<i>Renal failure and impairment</i>^a	<i>11 (1.8%)</i>	<i>2 (0.7%)</i>
Infection (unspecified)	10 (1.7%)	3 (1.0%)
Hydronephrosis	8 (1.3%)	2 (0.7%)
Lower respiratory tract infection	7 (1.2%)	2 (0.7%)

Note: AEs were selected which occurred > 1% on the Ra-223 arm and > placebo

Source: [AESAF] Dataset (July 15, 2011 safety cutoff date);

^a MedDRA HLT term

Overall, nonfatal serious adverse events (SAEs) reported in the BC1-06 trial occurred more frequently in the placebo arm when compared to the Ra-223 arm. The most common SAEs reported were malignant neoplasm progression, which occurred in approximately 5% of the patients on both study arms. Consistent with other safety findings, there were small increases in thrombocytopenia and dehydration SAEs on the Ra-223 arm compared to the placebo arm. The gastrointestinal and hemorrhagic SAEs reported in the BC1-06 trial were comparable across

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treatment arms (this analysis is limited to SAEs, please see Vascular Hemorrhage below). Including the SAE for rectal hemorrhage (Patient #9050-018) in the 90-Day safety report, gastrointestinal hemorrhage SAEs occurred at an incidence of 0.8% on the Ra-223 arm and 0.7% on the placebo arm; gastrointestinal ulceration and perforation SAEs occurred at an incidence of 0.5% on the Ra-223 arm compared to 0.7% on the placebo arm. There were no increases in any, minor (e.g., epistaxis, hematemesis, hematuria), or major [e.g., cerebral hemorrhage, cerebrovascular accident (hemorrhagic), urinary tract/bladder/prostatic hemorrhage, or gastrointestinal hemorrhage] hemorrhagic SAEs on the Ra-223 arm compared to the placebo arm in the BC1-06 trial.

Since the primary excretion pathway for Ra-223 is fecal with minimal renal excretion, and the dosimetry for Ra-223 predicts low renal organ radiation exposure, direct nephrotoxicity associated with Ra-223 is not expected. On the Ra-223 arm, the increase in renal failure and impairment is primarily driven by urinary tract obstruction that is likely disease-related (i.e., Patient #006-001; #028-003; #037-007; #042-030; #043-012; #041-010). These SAEs were treated with nephrostomy or catheterization procedures, with five out of six resolving, and three patients receiving additional Ra-223 without recurrence of the renal SAEs (i.e., negative rechallenge). The two cases reported on the placebo arm (Patient#017-028; #133-029) were also likely related to obstructive or pelvic metastases. Similarly, the hydronephrosis SAEs were all due to urinary obstruction and confounded by disease progression; none were attributed to Ra-223 by the study investigators. All eight hydronephrosis SAEs reported on the Ra-223 arm were treated with a nephrostomy and/or urinary catheterization procedure performed to restore urinary function (e.g., positive dechallenge). Seven out of eight of the hydronephrosis SAEs resolved after the procedures with four patients being retreated with Ra-223 without recurrence of the hydronephrosis SAE (i.e., positive rechallenge).

Since Ra-223 is related to increases in gastrointestinal adverse reactions such as diarrhea, nausea, vomiting, and dehydration that may affect fluid status; the contribution of Ra-223 is possible for the remaining five non-obstructive renal insufficiency or failure SAEs (Patient #'s: #039-027; #070-003; #071-006; #154-004; #204-001) (0.8% vs. 0% on placebo). These five renal SAEs do not appear to be related to urinary obstruction. Two SAEs ruled out obstruction diagnostically (#071-006; #204-001); one SAE was attributed to “exsiccosis” (#154-004); one SAE was attributed to heart failure in the presence of anorexia and nausea suggestive of hypovolemia (#070-003); and one SAE included no evidence of urinary obstruction (#036-027). All five of the patients experienced at least one of the following AEs: dehydration, anorexia, nausea, vomiting, or diarrhea ARs temporally with these SAEs. One SAE (#204-001) was considered “possibly related” to Ra-223 by the Investigator. The median onset of these renal SAEs was 20 days (range: 17-24 days) after the last dose of Ra-223. Three cases were treated with intravenous fluids, with two cases also reporting diuretic treatment; the other two cases did not report specific treatments administered for the SAEs. Four of the five cases resolved after treatment. In addition to advanced age [median=74 years (range= 62 – 76 years)], all of the patients had at least one risk factor for renal insufficiency (three patients had hypertension) or were taking concomitant NSAID therapies for pain (4 patients).

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Reviewer Comment: Despite small increases in infections (unspecified) and lower respiratory tract infections, there does not appear to be a significant increase in overall infection SAEs on the Ra-223 arm compared to the placebo arm. Total infection SAEs (SOC term) were more common in patients on the placebo arm (12.6%; 38/301) compared to the Ra-223 arm (10.2%; 61/600). The “infection” (PT term) SAEs consist primarily of infections of unknown origin, pathogen, and/or cause. The increase in lower respiratory tract infection SAEs does not occur with a corresponding increase in pneumonia SAEs. When combined with pneumonia (HLT level term), there were more lower respiratory tract and lung infections on the placebo arm compared to the Ra-223 arm (4.3% vs. 3.7%; respectively). Additionally, there was no increase in other serious infections for patients treated with Ra-223 compared to placebo (e.g., sepsis, urinary tract infection, pyelonephritis, upper respiratory tract infection, bone and joint infections). Monitoring fluid status during treatment with Ra-223 appears to be of particular importance for patients who experience Ra-223-induced gastrointestinal toxicities and this recommendation should be included in the prescribing information.

7.3.3 Dropouts and/or Discontinuations

In the BC1-06 trial, there were more discontinuations due to adverse events (AEs) on the placebo arm (18.9%; 57/301) compared to the Ra-223 arm (15.5%; 93/600). If the AEs likely related to progression of disease such as malignant neoplasm progression and metastases to the CNS, liver, and lung are removed; the increase on the placebo arm is maintained compared to the Ra-223 arm (16.7% vs. 13.1%; respectively). The treatment discontinuations due to AEs are listed below in Table 45.

Table 45: Treatment Discontinuations due to Adverse Events

Treatment Discontinuation due to Adverse Events		BC1-06 Ra-223 (N= 600)	BC1-06 Placebo (N=301)
Patients with at least 1 AE leading to treatment discontinuation ^a		93 (15.5%)	57 (18.9%)
Patients with at least 1 AE leading to treatment discontinuation not due to malignant neoplasm progression or metastases ^b		79 (13.2%)	50 (16.6%)
<i>Blood and lymphatic system disorders</i>	<i>Any</i>	32 (5.3%)	8 (2.7%)
	Anemia	14 (2.3%)	3 (1.0%)
	Thrombocytopenia	10 (1.7%)	4 (1.3%)
	Neutropenia	3 (0.5%)	1 (0.3%)
	Leukopenia	2 (0.3%)	0 (0.0%)
	Lymphadenopathy	2 (0.3%)	0 (0.0%)
	Pancytopenia	1 (0.2%)	0 (0.0%)
<i>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</i>	<i>Any</i>	25 (4.2%)	9 (3.0%)
	Malignant neoplasm progression	18 (3.0%)	9 (3.0%)
	<i>Metastases to specified sites</i> ^c	7 (1.2%)	0 (0.0%)

Note: AEs were selected which occurred $\geq 0.5\%$ on the Ra-223 arm and $>$ placebo; or AEs of interest

Source: [AESAF] Dataset (Safety data cutoff: July 15, 2011)

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- a Some patients had multiple AEs reported that lead to permanent discontinuation.
- b Excludes malignant neoplasm progression and metastases to specified sites.
- c HLT term

There was an increase in permanent discontinuation due to bone marrow suppression on the radium arm compared to the placebo arm (5.3% vs. 2.7%). There were more AEs that led to permanent treatment discontinuation due to progression of disease on the Ra-223 arm. This was driven by a small increase in discontinuation due to metastases to non-skeletal sites (i.e., CNS (n=2), liver (n=3), and lungs (n=2) on the Ra-223 arm.

Reviewer Comment: The small increase in progression of metastatic disease at non-skeletal sites on the radium arm is likely related to the inability of Ra-223 to treat visceral metastases due to rapid distribution to the bone and the short travel length of alpha-emission.

7.3.4 Significant Adverse Events

Grade 3 and 4 AEs

Overall there were fewer Grade 3-4 AEs in patients on the Ra-223 arm (59%) compared to the placebo arm (65%). When comparing Ra-223-treated patients to placebo, the largest increases in Grade 3-4 AEs were related to thrombocytopenia (6.5% vs. 2.0%; respectively), neutropenia (2.0% vs. 0.3%; respectively), leukopenia (1.7% vs. 0.3%; respectively), and pancytopenia (1.2% vs. 0.0%; respectively). There were no other increases of > 1 % for any Grade 3-4 ARs in the BC1-06 trial.

Bone Marrow Suppression, Pancytopenia, and Blood Transfusions

Pancytopenia (N=12), bone marrow failure (1), and aplastic anemia (1) were reported on the Ra-223 arm. There were no reports of these events on the placebo arm. One patient (034-004) died due to bone marrow failure 76 days after his 2nd injection of Ra-223. Nine of the Grade 1-4 AE were serious (SAEs) and eight were Grade 3 or 4 in severity. The median onset for these AEs was 28 days (range= 1-70 days) after the last injection of Ra-223. A majority (n=8 patients) of the events occurred after the patient had received his sixth scheduled injection of Ra-223.

Investigator attribution to Ra-223 was probable for five patients, possible for five patients, and not related for three patients. Patients experiencing these events had a median age of 66 years (Range: 57-78 years). All but one patient (#139-009) had prior docetaxel (n=11); EBRT to the bone (n= 6) or prostate (n=2); or systemic radiation (n=1; Sm-153). Three of the patients who received docetaxel were also previously treated with mitoxantrone. No patients were retreated with Ra-223 after these AEs occurred. For the nonfatal AEs, ten of the patients required blood transfusions, with two patients receiving platelets, and two receiving whole blood transfusions. A majority of the AEs (n=8) were reported as ongoing or not recovered at the time of death. Five patients recovered from the AEs after blood transfusions; two patients recovered without blood transfusions. For the patients experiencing these AEs, the median baseline platelet count was $219 \times 10^9 / L$ (range: $115 - 498 \times 10^9 / L$) and median baseline hemoglobin was 12.0 g/dL (range: 9.1 - 15.0). Based on the last platelet level available for these patients, four patients had platelet recovery to $\geq 100 \times 10^9 / L$, two patients to $\geq 75 \times 10^9 / L$, one patients to $\geq 50 \times 10^9 / L$ (Grade 2 or less), and six patients did not achieve post-radium doses of $\geq 50 \times 10^9 / L$ (i.e., no

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resolution to Grade 2 or less). Patient #139-009 experienced Grade 3 pancytopenia (probably related per Investigator) after receiving the sixth injection of Ra-223 that recovered. A diagnosis of aplastic anemia was provided for only one patient (#149-009). Patient #149-009 had received multiple prior cytotoxic and radiation therapies [i.e., docetaxel, EBRT to bone (30 Gy and 10 Gy), and Samarium-153]. His baseline platelet count was $252 \times 10^9 / L$ with a hemoglobin of 10.8 g/dL. He recovered with sequelae (e.g., Grade 3 platelet counts and Grade 2 hemoglobin with transfusions) and was alive at the safety study cutoff date approximately one year after discontinuation of Ra-223.

Platelet value analyses are complicated by the blood transfusions administered and incomplete reporting of unscheduled laboratory values. In the randomized controlled trial, blood transfusion and erythropoietin were used to manage myelosuppression, and G-CSF was used to manage persistent or febrile neutropenia. For both study arms, 41% of the patients required blood transfusions. Ra-223-treated patients were treated with more of the following compared to patients treated with placebo: blood transfusions (42% vs. 39%; respectively), erythropoietin (3.2% vs. 1.7%; respectively), and G-CSF / PEG-G-CSF (1.5% vs. 0%; respectively). Monitor patient blood counts values, identify negative trends, and initiate supportive care measures to manage bone marrow suppression when clinically indicated.

Reviewer Comment: Most of the patients enrolled in the BC1-06 trial have prostate cancer-related anemia that requires close monitoring of blood cell counts. It appears that a majority of the patients who experienced Grade 3 or 4 grade thrombocytopenia ARs were monitored closely and managed with whole blood or platelet transfusions (18 out of 39 patients).

Vascular Hemorrhage

In patients with bone marrow suppression, there was a small increase (1.2% vs. 0.3%) in deaths related to vascular hemorrhage for patients treated with Ra-223 compared to patients treated with placebo. See Section 7.3.1.2 for more information. Increases in total, minor, or major hemorrhagic SAEs were not observed on the Ra-223 arm compared to the placebo arm in the BC1-06 trial. See Section 7.3.2 for more information. When comparing the Ra-223 arm to the placebo arm, there was a small increase in Grade 1-4 hemorrhage, bleeding, and hematoma AEs (reported without trauma) (3.8% vs. 3.0%; respectively). This difference appears to be driven primarily by small increases in Grade 1-3 gastrointestinal hemorrhage (2.0% vs. 1.3%; respectively) and hematoma (0.5% vs. 0.0%; respectively) (MedDRA HLGTT terms). Most of these AEs are Grade 1 or 2; there was a small increase in Grade 3 gastrointestinal hemorrhages (0.7% vs. 0.0%, respectfully). Including the SAE for rectal hemorrhage (Patient #9050-018) in the 90-Day safety report, the rate of gastrointestinal hemorrhage is 2.1% vs. 1.3% (respectively).

Reviewer Comment: There was a small increase in Grade 1-3 gastrointestinal hemorrhage and in fatal vascular hemorrhages, and information related to these hemorrhagic effects will be recommended for inclusion in the prescribing information. The slight increase in gastrointestinal bleeding on the Ra-223 arm is consistent with the small increases in Grade 3-4 thrombocytopenia and pancytopenia. A majority of these cases are Grade 1 or 2. An increase in

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gastrointestinal hemorrhage is mechanistically plausible given the fecal elimination pathway for Ra-223 and thrombocytopenia.

Long term bone marrow suppression and subsequent chemotherapy

Follow up visit #1 was scheduled for 90 days after the last dose of Ra-223 or placebo. Table 46 lists the incidence of hematologic toxicity for all patients who had continued bone marrow suppression at the F/U #1 visit.

Table 46: BC1-06 Incidence of Hematologic Toxicity at Follow Up Visit #1

	Ra-223				Placebo			
	N= 342				N= 136			
	G 1-4	%	G 3-4	%	G 1-4	%	G 3-4	%
Anemia ^a	305	89.2	19	5.6	106	77.9	4	2.9
	N= 335				N=124			
	G 1-4	%	G 3-4	%	G 1-4	%	G 3-4	%
Neutropenia ^b	12	3.6	4	1.2	1	0.8	0	0.0
	N=342				N=136			
	G 1-4	%	G 3-4	%	G 1-4	%	G 3-4	%
Thrombocytopenia ^c	81	23.7	17	5.0	25	18.4	3	2.2

Source: [LAB2] Dataset (Safety data cutoff July 15, 2011)

^a Lower limit of normal defined as 13.0 g/dL

^b Lower limit of normal defined as $1.50 \times 10^9/L$

^c Lower limit of normal defined as $150 \times 10^9/L$

When comparing the patients treated with Ra-223 to placebo, there was a small increase in hematologic toxicity (i.e., anemia, neutropenia, and thrombocytopenia) at Follow-Up Visit #1. For two out of four of the patients (#006-015; #066-001) who had Grade 3-4 neutropenia on the Ra-223 arm, subsequent cytotoxic chemotherapy was initiated after completion of Ra-223 therapy and prior to Follow Up Visit #1. With the exception of Patients #006-015 and #066-001, none of these other patients went on to receive additional cytotoxic chemotherapy. On the Ra-223 arm, all of the patients who experienced Grade 3 or 4 neutropenia or thrombocytopenia had received cytotoxic chemotherapy before enrolling in the BC1-06 trial, with the exception of one patient (#074-002), who had been treated with previous EBRT to the bone.

Reviewer Comment: Interpretation of small changes in the hematologic laboratory toxicities at follow-up #1 are complicated by subsequent chemotherapy and the fact that ~40% of the patients on this trial received blood transfusions. After Follow-Up Visit #1, < 50% of the patients on each arm have laboratory values available for analysis.

Hematologic laboratory abnormalities were reviewed for patients in the BC1-06 trial who did not receive subsequent chemotherapy after completion of study therapy (n=754). Table 47 lists the percentage of these patients by CTCAE grade for hemoglobin, neutrophil count, and platelet counts by follow up visit.

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Table 47: Post-treatment Hematology Laboratory Values for Patients Without Subsequent Cytotoxic Therapy

Follow Up Visit #	Ra-223						Placebo					
	# of patients	CTCAE Grade					# of patients	CTCAE Grade				
		0 ≥LLN	1 <LLN- 10.0 g/dL	2 <10.0- 8.0 g/dL	3 <8.0- 6.5 g/dL	4 <6.5 g/dL		0 Norm. Ref. Range	1 <LLN - 10.0 g/dL	2 <10.0- 8.0 g/dL	3 <8.0- 6.5 g/dL	4 <6. 5 g/dL
Hemoglobin (Low)												
		%	%	%	%	%		%	%	%	%	%
1	269	9	63	23	4	1	93	18	54	26	2	0
2	193	6	60	29	4	2	68	21	57	16	6	0
3	153	7	67	22	5	0	48	21	56	21	0	2
4	75	9	56	25	9	0	22	18	64	18	0	0
5	33	9	58	27	6	0	10	30	50	20	0	0
6	16	0	69	31	0	0	4	0	75	25	0	0
Neutrophil Count (Low)												
Follow Up Visit #	# of patients	0 ≥LLN	1 <LLN- 1.5 x10 ⁹	2 <1.5 - 1.0 x10 ⁹	3 <1.0 - 0.5 x10 ⁹	4 <0.5 x10 ⁹ -	# of patients	0 ≥LLN	1 <LLN -1.5 x10 ⁹	2 <1.5 - 1.0 x10 ⁹	3 <1.0- 0.5 x10 ⁹	4 <0. 5 x10 ⁹
		%	%	%	%	%		%	%	%	%	%
1	268	95	1	3	1	0	93	97	2	1	0	0
2	193	96	2	1	1	0	68	94	3	3	0	0
3	153	94	5	1	1	0	48	100	0	0	0	0
4	75	97	3	0	0	0	22	100	0	0	0	0
5	33	97	3	0	0	0	10	100	0	0	0	0
6	16	94	6	0	0	0	4	100	0	0	0	0
Platelet Count (Low)												
Follow Up Visit #	# of patients	0 ≥LLN	1 <LLN- 75 x10 ⁹	2 <75 - 50 x10 ⁹	3 <50 - 25 x10 ⁹	4 <25 x10 ⁹ -	# of patients	0 ≥LLN	1 <LLN -75 x10 ⁹	2 <75 - 50 x10 ⁹	3 <50 - 25 x10 ⁹	4 <2 5 x10 ⁹
		%	%	%	%	%		%	%	%	%	%
1	269	77	13	4	4	2	93	82	13	2	2	1
2	193	80	16	2	2	2	68	85	10	0	4	0
3	153	75	15	6	4	0	48	81	15	0	4	0
4	75	84	8	4	1	3	22	82	14	5	0	0
5	33	76	15	3	6	0	10	80	20	0	0	0
6	16	63	19	13	0	6	4	75	0	0	25	0

Source: [LB2] Dataset (Safety cutoff date July 15, 2011)

After completing treatment in the BC1-06 trial, a small percentage of patients on both arms received subsequent cytotoxic chemotherapies; 15.5% (93/600) of the patients on the Ra-223 arm and 17.9% (54/301) of the patients on the placebo arm. The most common cytotoxic chemotherapy administered was docetaxel, with 66 patients (11.0%) on the Ra-223 arm and 39 patients (13.0%) on the placebo arm. Subsequent chemotherapy was started a median of 80 days (range: 1- 667 days) after the last dose of Ra-223 compared to a median of 64.5 days (range: 2 -

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448 days) after the last dose of placebo. The median duration of the chemotherapy was 120 days on the Ra-223 arm compared to 113 days on the placebo arm. For the patients that received subsequent cytotoxic chemotherapy after completion of the BC1-06 trial, 63 out of 93 (67.7%) of the patients on the Ra-223 arm and 32 out of 54 (59.3%) of the patients on the placebo arm, had received prior docetaxel.

Reviewer Comment: Based on very limited data, it appears that a majority of the patients treated with Ra-223 could be eligible for chemotherapy based on the hematologic laboratory values measured. Subsequent chemotherapy was initiated in a small percentage of patients who received prior Ra-223 therapy. No conclusions can be made with regards to how patients will tolerate chemotherapy after Ra-223 based on the data provided. The Applicant provided limited laboratory results from the scheduled Month 6, 8, and 12 follow up visits to evaluate how patients tolerated subsequent chemotherapy. The relevance of this data is extremely limited due to infrequent monitoring and an unknown or random relationship with the timing of the chemotherapy administration. The laboratory parameters that were collected also included a significant number of missing chemotherapy patients at each time point collected (~ 40% at Month 6, ~25% at Month 8 and ~50% at Month 12). In addition, AEs not attributed to the study therapies (i.e., Ra-223 or placebo) were not recorded during the follow up phase of the trial; no relevant AE safety data that relates to how chemotherapy was tolerated exists during this period.

Risk of Bone Sarcomas and other Secondary Malignancies

Treatment with Ra-223 results in independent radiation exposure and increased cumulative radiation exposure for patients who have received other radiation-based therapies to prostate cancer. Based primarily on long term epidemiology studies of non-cancer patients exposed to other radium-224, and the nonclinical data for Ra-223; Ra-223 is assumed to be carcinogenic even at relatively low dose levels. The Ra-223 exposure levels required to significantly increase the risk of secondary cancers have not been established. In non-cancer patient populations, radiation exposure with short-lived, alpha-emitting, radium-224 resulted in a significant increased risk of bone sarcoma. Long term epidemiologic data also suggests an increased risk of secondary solid tumors and leukemia. For radium-224, bone sarcoma incidence peaked approximately 8 years after the initial exposure and these cancers were reported approximately 4 - 33 years after initial exposure. Nearly all of the non-skeletal solid and soft tissue tumors related to radium-224 occurred at least five years after radium-224 exposure. See Section 7.2.6 for more information on alpha-emitting radionuclide class-related toxicities and secondary malignancies.

Based on long term epidemiology studies, the latency period for secondary malignancies potentially related to Ra-223 will exceed the life expectancy of nearly all of the patients enrolled in the BC1-06 trial. During the BC1-06 trial, patients were evaluated at 8, 10, 12, 16, 20, 24, 28, 32 and 36 months after the initial dose of study therapy if alive and not lost to follow up. The CRFs included a specific evaluation for acute myelogenous leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer, or primary cancer in other organs. Physical examinations and blood samples were also included in these follow up visits. Approximately 80% of the patients in the BC1-06 trial experienced death as of January 31, 2013. Of the 22

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patients who reached three years of follow-up, 10 patients have been re-consented to permit continuation of follow up, six patients died shortly after the 3 year follow-up visit, and six patients have not been re-consented. The other Ra-223 trials included in the ISS had limited follow up for long term toxicities for relatively short periods of time (e.g., up to two years). Table 48 was provided by the Applicant in response to an FDA information request to update and describe the duration of follow up for the patients in the BC1-06 trial.

Table 48: BC1-06 Follow Up for Long Term Toxicities and Secondary Malignancy

	July 15, 2011 cutoff	As of January 31, 2013
Follow-up 1 (8 months)	522 (56.7%)	567 (61.6%)
Follow-up 2 (10 months)	396 (43.0%)	472 (51.3%)
Follow-up 3 (12 months)	310 (33.7%)	406 (44.1%)
Follow-up 4 (16 months)	171 (18.6%)	290 (31.5%)
Follow-up 5 (20 months)	85 (9.2%)	214 (23.2%)
Follow-up 6 (24 months)	42 (4.6%)	138 (14.9%)
Follow-up 7 (28 months)	15 (1.6%)	84 (9.1%)
Follow-up 8 (32 months)	6 (0.7%)	51 (5.5%)
Follow-up 9 (36 months)	0	22 (2.4%)

Source: Applicant submission. Primary data unavailable for FDA verification.

Despite the lack of long term follow up sufficient to adequately evaluate an association between Ra-223 and bone sarcomas and other secondary cancers, FDA reviewed the available data for secondary cancers that were observed in the Ra-223 trials. Table 49 lists the secondary malignancies that occurred in the BC1-06 trial and in other Ra-223 trials reported as of December 1, 2012 (90-Day SU cutoff date).

Table 49: Secondary Malignancies in the Ra-223 Clinical Trial Database

Study #	Study Arm	Pat. #	Patient Age (years)	Secondary Malignancy	Approximate Onset Time after Initial Exposure	Prior Radiation and/or Cytotoxic Chemotherapies	Relevant Medical History	Outcome	FDA Comments
BC1-06	Ra-223	#244-001	80	Bladder	30 weeks	Docetaxel	None	No action taken, ongoing at death (unknown cause ~ 8 months after last Ra-223 dose)	Grade 2
BC1-06	Ra-223	#205-005	83	Squamous cell carcinoma (Right wrist)	20 weeks	Docetaxel	Melanoma (5 years prior)	Resected, resolved	Grade 3; presented with Grade 2 keratosis

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Study #	Study Arm	Pat. #	Patient Age (years)	Secondary Malignancy	Approximate Onset Time after Initial Exposure	Prior Radiation and/or Cytotoxic Chemotherapies	Relevant Medical History	Outcome	FDA Comments
BC1-06	Ra-223	#241-001	77	Non-melanoma skin	20 weeks	None	None	No action taken, ongoing at death (mCRPC)	Grade 1
BC1-06	Ra-223	#254-003	72	Non-melanoma skin neoplasm (abnormal growth, face)	< 12 weeks after 1 st injection (unspecified onset date)	EBRT to bone and prostate; brachytherapy	Sipuleucel - T	Resected, recovered	Grade 1
BC1-06	Ra-223 (crossover)	#9050-012	80	Squamous cell carcinoma of skin	31 weeks	Brachytherapy	Malignant melanoma; Superficial bladder cancer	Resected; Outcome not reported	Grade 2
BC1-04	Ra-223	#208	65	Squamous cell carcinoma (penis)	4 weeks	Samarium-153; EBRT to bone	None	Death due to Squamous Cell Carcinoma of unknown primary	Graded as severe (No CTCAE grade); unknown primary-probably lung per Investigator; unlikely related per Investigator
BC1-02	Ra-223	#005-506	81	Rectal Cancer	25 weeks	EBRT bone	Rectal bleeding (ongoing); no lesion on proctoscopy	Not reported, Died of mCRPC 62 weeks after 1 st injection of Ra-223	Four injections x 50 KBq/kg + 8 Gy EBRT to bone; EBRT to bone after Ra-223
BC1-02	Ra-223	#007-703	71	Bladder Cancer superficial papillary transitional cell carcinoma	48 weeks	EBRT bone	None	Not reported, alive 13 months after onset of cancer	Four injections x 50 KBq/kg + 8 Gy EBRT to bone
BC1-02	Ra-223	#001-105	81	Pancreatic Cancer	76 weeks	EBRT bone	None	Fatal (4 weeks after diagnosis)	Four injections x 50 KBq/kg + 8 Gy EBRT to bone; mitoxantrone administered after Ra-223
BC1-06	Placebo	#004-008	74	Squamous cell carcinoma (skin)	20 weeks	EBRT to bone docetaxel	None	Resolved	Grade 3 on left hand
BC1-06	Placebo	#006-048	69	Neoplasm (left buttock)	16 weeks	EBRT to bone and prostate; docetaxel	None	Not recovered, no changes expected	Grade 2, nonserious "Not a benign skin

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Study #	Study Arm	Pat. #	Patient Age (years)	Secondary Malignancy	Approximate Onset Time after Initial Exposure	Prior Radiation and/or Cytotoxic Chemotherapies	Relevant Medical History	Outcome	FDA Comments
									neoplasm ⁷⁷ per Investigator
BC1-06	Placebo	#050-001	80	Gastric Cancer	27 weeks	EBRT to bone;	None	Fatal	Grade 4
BC1-06	Placebo	#006-044	82	Rectal cancer (adenocarcinoma)	27 weeks	EBRT to bone (2 X 30 Gy) and prostate	None	Resected; outcome not reported	None
BC1-06	Placebo	#181-038	79	Skin Cancer	120 weeks	EBRT to bone and prostate	None	Resected; outcome not reported	None

Source: Applicant submission and 90-Day Safety Update (December 1, 2012 safety cutoff date)

For the BC1-06 trial, the overall incidence of malignant secondary cancers was low with a slightly lower incidence on the Ra-223 arm compared to placebo (0.8% vs. 1.7%). A majority of the secondary malignancies reported were non-serious non-melanoma or cutaneous squamous cell carcinomas (0.7% vs. 1.0%); these were also more common on the placebo arm. On the Ra-223 arm, only one other solid malignancy (0.2%) was reported on the Ra-223 arm; a Grade 2 bladder cancer. Two solid tumor malignancies (0.7%) were reported on the placebo arm; one was a fatal gastric cancer, and the other a rectal adenocarcinoma that was resectable. In the ISS for Ra-223, there was one additional bladder cancer (superficial), one (each) rectal cancer, one fatal pancreatic cancer, and fatal squamous cell malignancy of unknown primary. The patient with squamous cell carcinoma of unknown primary in the lung was the same patient who was later found to have squamous cell carcinoma of the penis. Metastatic squamous cell carcinoma of the penis is an uncommon cancer and reports will be followed closely for other patients with this malignancy. The total incidence of solid non-cutaneous malignancies in the Ra-223 ISS database is approximately 0.4%. No cases of bone sarcoma have been reported in any clinical trial with Ra-223 as of December 1, 2012. The Applicant considers none of the cases of secondary malignancies to be attributable to Ra-223 based on biodistribution and the typical latency period required for radiation-induced malignancies.

Reviewer Comment: There was no increase or clear association between any secondary malignancies for Ra-223 when delivered at the 50 kBq/kg dose once every 28 days for a duration of six administrations. Given the latency period for solid tumors related to radium exposure, these cancers are probably not related to Ra-223 exposure, but the contribution of Ra-223 can not be completely ruled out. The risk of secondary malignancy is likely greatest for bone sarcoma; none were reported in the Ra-223 integrated safety database (n=904 patients). However, given the short duration of follow up for nearly all of these patients in the Ra-223 database, and the relatively long latency period for bone sarcomas and other secondary malignancies to present, it is also unlikely that there would be any cases or data to support a clear association with Ra-223 at this point. Collection of this type of data would require a significant duration of follow up in a patient population with a longer life expectancy. Given the overall survival and the delay in the time to SRE benefits for Ra-223, submission of this data prior to approval would not be required. For the proposed patient population, this concern is of

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limited relevance given the severity of the advanced prostate cancer and short life expectancy for most of these patients. However, as Ra-223 continues development in earlier in the prostate cancer disease course, and due to potential off label use in patients with longer life expectancies, long term follow up for bone sarcomas and other secondary cancers is germane and important to characterize to enable appropriate risk evaluation and communication to patients evaluating treatment options. Additional post-approval collection of secondary cancer information in patients treated with radum-223, with longer term follow up, is recommended. See Section 1.4 for more information.

Non-pathologic Fractures and other Bone Disorders

The number of patients who experienced fractures (pathologic and non-pathologic) on the Ra-223 and placebo arms was similar (6.7% vs. 6.6%; respectively). A majority of the fractures on both arms were pathologic. There were fewer pathologic fractures on the Ra-223 arm compared to placebo (3.8% vs. 5.3%; respectively). Table 50 lists the incidence and type of fractures patients experienced in the BC1-06 trial (AESAF; July 15, 2012 safety cutoff date). On the Ra-223 arm, Investigator attributions for all seven of the non-pathologic AEs not associated with trauma, spinal cord compression, or vertebral fractures was unrelated. There was a low incidence of other treatment-emergent bone disorders. The other bone disorders reported on the BC1-06 trial were comparable across study arms. Osteoporosis was reported in two patients on the Ra-223 arm and one patient on the placebo arm (both = 0.3%) and osteomalacia was reported in one patient on the Ra-223 arm and described as “oncogenic” (Patient #203-004).

Table 50: BC1-06 Total Fractures From Adverse Event Data

	Ra-223		Placebo	
	N	%	N	%
Total fractures	40	6.7	20	6.6
Pathologic	23	3.8	16 ^a	5.3
Non-pathologic	18 ^b	3.0	5 ^c	1.7
Traumatic	6	1.0	2	0.7
Spinal cord compression / Vertebral fracture	5	0.8	0	0.0
Lower limb	4	0.7	0	0.0
Upper limb	2	0.3	1	0.3
Rib	1	0.2	0	0.0
Tooth	0	0.0	1	0.3

Source: [AESAF] Dataset (July 15, 2011 safety cutoff date)

^a Patient #006-045 experienced a femoral neck fracture that was coded as non-pathologic by the Applicant, but the verbatim AE term states this is a pathologic fracture; FDA analysis considered this a pathologic fracture.

^b Patient #033-023 experienced both a pathologic (femur) and non-pathologic fracture (broken arm, traumatic).

^c Patient #020-010 experienced both a pathologic rib fracture and non-pathologic vertebral fracture.

Reviewer Comment: Overall, the incidence of each type of fracture was comparable across the study arms. The small increase in non-pathologic fractures on the Ra-223 arm is primarily driven by spinal cord compression and vertebral fractures that are probably disease related. After removing fractures related to trauma and spinal cord compression, there was a slight increase in non-pathologic fractures in Ra-223 treated patients compared to placebo (1.2% vs.

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0.7%; respectively). Given the Investigator attribution (unrelated) for all of these AEs, presence of skeletal disease for all of the patients enrolled in the BC1-06 trial, and multiple other potential confounding factors, the significance of this slight increase is unclear. An association with Ra-223 is also not supported by a cumulative dose or late effect since a majority of the non-pathologic events presented early in the treatment phase [Ra-223: median= 105 days (range 12-220 days); placebo= 223 days (1 event onset missing)].

Osteonecrosis

In the BC1-06 trial, osteonecrosis AEs were not common (< 1.0%) and occurred in only five patients; four on the Ra-223 arm (0.7%) and one on the placebo arm (0.3%). All received zoledronic acid. The osteonecrosis AEs reported on the Ra-223 arm were all related to osteonecrosis of the jaw (ONJ), and included one case (each) of “osteonecrosis jaw”, “mandibular necrosis”, “mandibular osteonecrosis”, and “osteolysis mandible”. Table 51 lists the patients who experienced ONJ in the BC1-06 trial.

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Table 51: BC1-06 Osteonecrosis of the Jaw (ONJ) Adverse Event Cases

Pat. #	Age (yr)	Study Treatment / Dates	Date of ONJ	Treatment Dates / Bisphosphonate	Serious (yes or no) / Grade	Prior Therapies	Outcome / Treatment	Investigator Attribution / Notes
#033-027	58	Ra-223 / 3 Aug 2010 – 21 Dec 2010 (6 injections)	10 Nov 2010	Apr 2009 – Mar 2010 / Zolendronate	No / Grade 2	Docetaxel, EBRT to bone (8 Gy x 2)	Not recovered, no changes expected	Possibly related / Grade 1 gum infection Aug 2010 / Rechallenged without progression
#071-004	65	Ra-223 / 14 Dec 2009- 13 Jan 2010 (2 injections)	10 Feb 2009	Apr 2006 – 14 Dec 2009 / Zolendronate	No / Grade 3	Docetaxel, vinorelbine, mitoxantrone, EBRT to bone (30 Gy)	Yes / teeth extraction (Oct 2010)	Unrelated / Permanently discontinued Ra-223
#071-010	74	Ra-223 / 29 Oct 2010 – 26 Nov 2010 (2 injections)	22 Dec 2010	5 Feb 2010 – 20 Aug 2010 / Zolendronate	No / Grade 2	Docetaxel, EBRT to bone (30 Gy)	Not recovered, no changes expected	Unrelated / Permanently discontinued Ra-223 / Prior history of tooth extraction (unk. date)
#149-002	68	Ra-223 / 13 Nov 2009- 10 Mar 2010 (6 injections)	14 Dec 2009	Unk. 2002 – 16 Feb 2010 / Zolendronate	No / Grade 1	Docetaxel, EBRT to prostate, EBRT to bone (50.4 Gy and 24 Gy)	Not recovered, no changes expected	Unrelated / Rechallenged without progression
#151-002	69	Placebo / 14 Jan 2010- 6 May 2010 (5 injections)	25 Jun 2010	May 2005- May 2010 / Zolendronate	Yes / Grade 3	Docetaxel, EBRT to bone (30 Gy)	Recovered with sequelae	Unrelated/ Past history of ONJ

Source: Applicant submission.

Reviewer Comment: No other cases of osteonecrosis were reported on the Ra-223 arm of the trial. All five of the patients who experienced ONJ had recent exposure to zolendronate, a bisphosphonate bone resorption inhibitor associated with ONJ. All five cases included patients treated with EBRT to the bone (and docetaxel). All of the cases on the Ra-223 arm were non-serious. Investigator attribution for four of the five cases was unrelated; with one case possibly related to study therapy on the radium arm (#003-027). This case was confounded by a gum infection prior to the onset of ONJ, and a rechallenge with Ra-223 did not result in progression. On the Ra-223 arm, one additional case also included a prior tooth extraction (#071-010) and

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one case included a rechallenge without progression of ONJ (#149-002). The ONJ case on the placebo arm was confounded by previous medical history of this AE.

The FDA reviewer also reviewed the AEs for pain reported in the jaw and oral pain for potential ONJ AEs. These AEs were also uncommon and balanced across study arms (0.7% on both arms). All four of the PIJ AEs on the Ra-223 arm were nonserious and Grade 1 or 2.

Severe Gastrointestinal AEs (Perforation, Ulcers, Ileus, Necrosis, Colitis)

With the exception of gastrointestinal hemorrhage (see above), there were no significant increases of > 2.0% for Grade 1 - 4 AEs or > 0.5% for Grade 3-4 AEs for severe gastrointestinal AEs. The incidence of constipation was lower on the Ra-223 arm compared to placebo for Grade 1- 4 (18.0% vs. 21.3%; respectively) and Grade 3 - 4 (1.0% vs. 1.3%; respectively) AEs. The incidence of Grade 1-4 gastrointestinal stenosis and obstruction was 0.7% on the radium arm compared to 0.3% on the placebo arm (Grade 3-4: 0.5% vs. 0.3%). Gastrointestinal ulceration was not common and occurred at a lower incidence in Ra-223 treated patients (0.2% vs. 0.3%); intestinal perforations occurred at 0.2% vs. 0.7% (respectfully). On the Ra-223 arm, there was one case of duodenitis (erosive) (Patient 021-002) and colitis (Patient #054-001) compared to no cases on the placebo arm. In the 90-Day Safety Update, one patient (#027-002) on the Ra-223 arm experienced severe bowel necrosis. He was a 69-year old man with recurrent constipation and a history of external beam radiation to the sacrum who developed fatal multi-organ failure due to necrosis of the large intestine. Histology did not detect tumor infiltration and described the necrosis as “severe ischemic damaged terminal ileum/mucosa of the colon”. Investigator attribution to Ra-223 was possible. The Applicant did not attribute this AE to Ra-223 based on the onset time for the AE. This single case of gastrointestinal necrosis occurred 18 months after discontinuation of Ra-223 and lacks a clear temporal association to the drug.

Reviewer Comment: The single cases of severe gastrointestinal toxicities reported on the BC1-06 trial are not adequate to establish clear associations with Ra-223. FDA will continue to monitor for safety signals for these biologically plausible AEs given the fecal elimination of Ra-223.

AEs for Patients who Experience Constipation:

The incidence of constipation was lower on the Ra-223 arm compared to placebo for Grade 1- 4 (18.0% vs. 21.3%; respectively) and Grade 3 - 4 (1.0% vs. 1.3%; respectively) AEs. An information request was sent to the Applicant on January 8, 2013 requesting evaluation of whether patients experiencing constipation experienced higher incidence rates of TEAEs. The Applicant responded on January 25, 2013 (eCTD #0009). The frequency of Grade 1-4 AEs for patients with and without constipation were calculated and compared across the BC1-06 study arms. There was an increase in most of the AEs reported in patients with constipation compared to patients without constipation for *both* study arms. For the G1-4 ARs related to Ra-223, there were no increases of more than 3% for any specific AR. On the Ra-223 arm, there was an increase in total Grade 3-4 AEs for patients with constipation (75%) compared to patients without constipation (58%). However, this difference appears to be primarily due to conditions possibly related to (or confounded by) disease progression (i.e., bone pain, spinal cord

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compression, malignant neoplasm progression, musculoskeletal pain, and hydronephrosis). Based on this exploratory post hoc analysis, no additional ARs or significant increases in the risk of AEs were detected in patients who experienced constipation while being treated with Ra-223.

Reviewer Comment: Recommendations to carefully monitor and manage bowel movement frequency in all patients treated with Ra-223 will be included in the prescribing information to limit the exposure to alpha radiation in the lower gastrointestinal tract.

Eye Disorders

Eye disorders were less common in Ra-223 treated patients compared to patients who received placebo (5.6% vs. 3.8%; respectively). Grade 3 and 4 AEs were not common and were comparable across the study arms (0.8% vs. 0.7%; respectively). No Grade 4 eye disorders occurred on the Ra-223 arm. There were no significant increases (> 0.5%) in any of the eye disorder AEs on the Ra-223 arm of the trial compared to placebo.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In order to increase the likelihood that the reported adverse event was drug related, the common adverse reactions table (Table 52) was based on adverse events which occurred at an incidence of > 4% in the Ra-223 arm and at a > 2% absolute increase in incidence over the placebo arm, or were adverse events of interest based on mechanism of action.

Table 52: BC1-06 Common Adverse Reactions (Safety Analysis Population)

	Ra-223 (N= 600)				Placebo (N=301)			
	G 1-4	%	G 3-4	%	G 1-4	%	G 3-4	%
Anemia ^a	555	92.5	33	5.5	264	87.7	17	6
Nausea	213	35.5	10	1.7	104	34.6	5	1.7
Diarrhea	151	25.2	9	1.5	45	15.0	5	1.7
Vomiting	111	18.5	10	1.7	41	13.6	7	2.3
Edema peripheral	77	12.8	10	1.7	30	10.0	4	1.3
Thrombocytopenia	71	11.8	39	6.5	17	5.6	6	2.0
Neutropenia ^a	105	17.5	12	2.0	14	5.0	1	0.3
Leukopenia	26	4.3	10	1.7	1	0.3	1	0.3
Dehydration	20	3.3	8	1.3	4	1.3	1	0.3
Renal failure and impairment ^b	17	2.8	8	1.3	3	1.0	3	1.0
Pancytopenia ^c	14	2.3	9	1.5	0	0.0	0	0.0
Injection site reactions ^d	7	1.2	0	0.0	0	0.0	0.	0.0

Note: Adverse events occurring > 4% incidence and > 2% increase vs. placebo; or AR of interest

Source: [AESAF] Dataset (Safety data cutoff: July 15, 2011)

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^a Based on laboratory data [LAB2] Dataset (safety data cutoff July 15, 2011)

^b MedDRA HLT term

^c Includes pancytopenia, bone marrow failure, and aplastic anemia.

^d Includes injection site pain, rash, reaction, swelling, and erythema.

7.4.2 Laboratory Findings

Hematology

Table 53 lists the treatment-emergent laboratory abnormalities reported in the BC1-06 trial.

Table 53: BC1-06 Treatment-emergent Hematology Laboratory Abnormalities

	Ra-223 N = 600				Placebo N = 301			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	N	%	N	%	N	%	N	%
Anemia (Hgb)	555	92.5	33	5.5	264	87.7	17	5.6
Lymphocytopenia	429	71.5	121	20.2	161	53.4	20	6.6
Leukopenia (WBC)	211	35.2	19	3.2	31	10.3	1	0.3
Thrombocytopenia	184	30.7	16	2.7	65	21.6	6	0.7
Neutropenia (ANC)	105	17.5	12	2.0	14	4.7	1	0.3

Source: [LAB2] Dataset (July 15, 2011 safety cutoff date)

There were consistent increases in Grade 1-4 laboratory abnormalities on the Ra-223 arm compared to placebo for all of the measured values. There were small increases in the Grade 3-4 laboratory abnormalities for all of the measured values, with the exception of anemia.

Laboratories were obtained at baseline and prior to each 4-week cycle. In the phase 1 study, AT1-BC-1, after administration of a single dose of Ra-223 neutrophil and platelet count nadirs occurred after 2 to 3 weeks with recovery occurring 4 to 6 weeks later. As an adverse reaction, Grade 3-4 thrombocytopenia was reported in 7% of patients on Ra-223 and in 2% of placebo.

Among patients who received Ra-223, the laboratory abnormality grade 3-4 thrombocytopenia occurred in 1% of docetaxel-naïve patients and in 4% of patients who had received prior docetaxel. Grade 3-4 neutropenia occurred in 1% of docetaxel-naïve patients and in 3% of patients who have received prior docetaxel.

Reviewer Comment: The higher incidence of Grade 3-4 thrombocytopenia in the AE dataset compared to the laboratory dataset may be related to the lack of some unscheduled laboratory values in the laboratory datasets. That is, the laboratory NADIRs occurred 2-3 weeks after administration, and recovery occurred prior to the next scheduled laboratory analysis.

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Treatment-emergent NADIRs

In the BC1-06 trial, baseline values for hemoglobin (12.2 g/dL), neutrophils ($4.5 \times 10^9/L$), platelets ($242 \times 10^9/L$), and lymphocytes ($1.37 \times 10^9/L$) were nearly equal for both treatment arms. FDA analyzed the treatment-emergent NADIR values for these hematology laboratory values up to 30 days (+7 per study protocol) after the last dose of treatment. Table 54 lists the laboratory values and onset times for these hematologic laboratory tests.

Table 54: BC1-06 Treatment-emergent Hematologic NADIR Values and Timing

	Ra-223	Placebo
Hemoglobin (g/dL)		
	N=586	N= 288
Median	10.7	10.9
Min	4.2	6.4
Max	15.2	15.1
NADIR time to onset (Days after first dose)		
Median	116	85
Min	21	25
Max	205	191
Neutrophil Count ($\times 10^9/L$)		
	N=584	N=287
Median	2.63	3.60
Min	0.34	0.61
Max	12.9	12.4
NADIR time to onset (Days after first dose)		
Median	85	57
Min	17	25
Max	205	183
Platelet Count ($\times 10^9/L$)		
	N=586	N=289
Median	178	199
Min	13	20
Max	487	532
NADIR time to onset (Days after first dose)		
Median	112	59
Min	13	25
Max	205	204
Lymphocytes ($\times 10^9/L$)		
	N= 585	N= 286
Median	0.74	1.10
Min	0.14	0.00
Max	3.03	3.70
NADIR time to onset (Days after first dose)		
Median	113	71
Min	17	25
Max	223	197

Source: [LAB2] Dataset (July 15, 2011 safety cutoff date)

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When comparing the Ra-223 and placebo median NADIR values, hemoglobin (Hgb) was comparable across study arms (10.7 vs. 10.9 g/dL; respectively) and occurred later on the Ra-223 arm (116 days vs. 85 days; respectively). For the neutrophil, platelet, and lymphocyte counts, there were modest decreases in median NADIR values, with occurrence later in the treatment period for the Ra-223-treated patients.

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Table 55 below lists the treatment-emergent chemistry laboratory abnormalities and severity (grade) between the treatment arms.

Table 55: BC1-06 Treatment-emergent Chemistry Laboratory Abnormalities

	Ra-223 N = 600				Placebo N = 301			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	N	%	N	%	N	%	N	%
AKP (%)	340	56.7	51	0.5	246	81.7	84	27.9
Hypocalcemia ^a	221	36.8	6	1.0	114	37.9	3	1.0
AST (%)	185	30.8	10	1.7	130	43.2	8	2.7
Hyponatremia	129	21.5	13	2.2	72	23.9	9	3.0
Creatinine (%)	110	18.3	1	0.2	64	21.3	0	0.0
Hypophosphatemia	102	17.0	31	5.2	43	14.3	12	4.0
ALT (%)	92	15.3	6	1.0	42	14.0	3	1.0
Hypokalemia	83	13.8	4	0.7	25	8.3	2	0.7
Hyperkalemia	77	12.8	1	0.2	51	16.9	1	0.3
Hypermagnesemia	74	12.3	1	0.2	57	18.9	2	0.7
Hypomagnesemia	71	11.8	0	0.0	19	6.3	0	0.0
Hypercalcemia	47	7.8	1	0.2	26	8.6	0	0.0
Hypernatremia	40	6.7	0	0.0	15	5.0	0	0.0
Bilirubin (%)	18	3.0	1	0.2	15	5.0	0	0.0
Hyperphosphatemia	0	0.0	0	0.0	0	0.0	0	0.0

Source: [LAB2] Dataset (July 15, 2011 safety cutoff date)

^a Corrected calcium = 0.02 (40-pt alb) + calcium

Overall, abnormal laboratory values were more common on the placebo trial for the measured parameters in most cases. Consistent with previous trials for Ra-223, the incidence of elevated alkaline phosphatase (ALK) was lower on the Ra-223 arm (57%) compared to the placebo arm (82%). The abnormal laboratory values with an increase in incidence of > 5% on the Ra-223 arm compared to the placebo arm (i.e., hypokalemia, hypomagnesemia) did not have significant increases (> 1%) in Grade 3-4 laboratory abnormalities.

7.4.3 Physical Exam, ECOG, Patient Weight

In the BC1-06 trial, an abbreviated physical exam was performed at screening and each study visit (Weeks 0, 4, 5, 12, 16, 20, and 24; then every second month up to Week 52; then every

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fourth month up to 3 years after initiation of study therapies. The abbreviated physical examination included assessments of ECOG performance status (PS) and general body systems (i.e., Appearance, Lungs, Cardiovascular, Abdomen, and Other Physical Findings). The Applicant did not record or provide blood pressure or heart rate data. If there were changes in the general systems, Investigators were instructed to report the appropriate AEs or update the patient medical history (if applicable). Patient body weight was recorded at each visit in which study therapies were administered.

Table 56 lists the ECOG performance status of patients for the first 10 study visits and rounded to nearest whole number percentage (%). A majority of the patients on both arms maintained an ECOG status of 0 or 1 throughout the BC1-06 trial. The incidence of patients with ECOG 2 or higher are comparable through the first 10 study visits.

Table 56: BC1-06 ECOG Performance Status Shift Table

Visit	Ra-223							Placebo						
	# of patients	ECOG PS						# of patients	ECOG PS					
		0 %	1 %	2 %	3 %	4 %	5 %		0 %	1 %	2 %	3 %	4 %	5 %
1	600	27	61	12	0	0	0	300	26	61	13	0	0	0
2	597	23	63	14	1	0	0	300	24	63	13	0	0	0
3	579	24	59	16	2	0	0	284	18	63	15	3	0	0
4	544	24	58	17	1	0	0	243	20	57	19	4	0	0
5	493	25	54	19	2	0	0	210	18	60	16	6	0	0
6	440	22	57	18	3	0	0	173	16	58	21	6	0	0
7	387	22	52	24	2	0	0	146	16	55	20	9	0	0
8	461	18	46	24	9	3	0	217	11	41	27	15	6	0
9	350	17	43	30	9	1	0	138	13	46	30	9	1	0
10	264	13	49	29	7	2	0	107	14	50	30	3	3	0

Source: [ECOG] Dataset (July 15, 2011 safety data cutoff)

Table 57 lists the changes in patient body weight for the second through the seventh study visits listed by visit sequence number and rounded to nearest whole number percentage (%).

Table 57: BC1-06 Patient Body Weight Shift Table

Visit	Ra-223						Placebo					
	# of patients	Patient Weight Loss					# of patients	Patient Weight Loss				
		> 5% %	>10% %	> 15% %	>20% %	>25% %		> 5% %	>10% %	>15% %	>20% %	> 25% %
2	600	4	8	1	0	0	298	6	1	0	0	0
3	582	12	2	0	0	0	279	16	3	0	0	0
4	545	19	4	1	0	0	243	25	9	2	0	0
5	497	24	7	1	0	0	206	30	9	2	0	0
6	437	27	10	1	0	0	173	32	13	2	0	0
7	388	30	10	2	0	0	144	35	11	5	1	0

Source: [VS] Dataset (July 15, 2011 safety data cutoff)

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A majority of the patients on both arms did not experience weight loss of > 10% from baseline while on study therapies. The incidences of patients with weight loss of > 10% while on study therapies were comparable and slightly higher on the placebo arm compared to the Ra-223 arm for all visits and % weight loss categories.

7.4.4 Electrocardiograms (ECGs)

The FDA Interdisciplinary Review Team for QT Studies (QT-IRT) was consulted to evaluate the QTc prolongation potential of Ra-223 dichloride (Ra-223). The results summarized are based on the FDA QT-IRT consultative review. *See the FDA QT-IRT review and Clinical Pharmacology review for more information.*

In the BC1-06 trial, the Applicant conducted a study to evaluate QTc interval prolongation in a subgroup of the patient population. All 12-lead ECGs were collected in triplicate and were measured at ≥ -1 hour, -45 minutes, -30 minutes, $+\leq 1$ minute, +30 minutes, and +1, +2, +3, and +4 - 6 hours after injection. An additional ECG was collected at the 4-week and 24-week follow up visit after discontinuation of study therapies. A copy of all ECG measurements was sent electronically to the core ECG laboratory for interpretation. Analysis of the ECGs was performed by a Board-Certified independent cardiologist in a blinded manner. A total of 29 patients were included in the substudy, with 21 receiving Ra-223 and eight receiving placebo. Two patients #017026 (placebo) and #017030 (Ra-223) had a history of cardiac arrhythmia. Four patients, #001039 (Ra-223), #017026 (placebo), #148019 (Ra-223) and #148021 (placebo) had been treated with concomitant medication that could prolong the QT interval and/or induce Torsade de Pointes (TdP).

There were no clinically relevant morphological changes in the ECGs and no adverse events as per ICH E14 guidance were reported (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) in this substudy. The FDA IRT reviewer determined that the mixed model of the pooled post-dose data for Δ QTcF, heart rate (HR), PR analyses, and QRS analyses was the better correction method for the study data provided. The largest upper bound of the 2-sided 90% CI for the mean difference between Ra-223 and placebo for QTcF was 8.3 msec. No patient's QTcF was above 480 msec in the Ra-223 treatment group. In all patients the change from baseline was below 30 msec. The largest upper limit of the 90% CI for the HR mean difference between Ra-223 and placebo is 4.6 beats per minute (bpm) with only one patient experiencing a HR greater than 100 bpm. The largest upper limit of the 90% CI for the PR mean difference between Ra-223 and placebo is 14.5 msec. There are 4 (20.0%) patients in the Ra-223 group and 3 (37.5%) patients in the placebo group who experienced a PR greater than 200 msec. No post-baseline PR intervals were > 10% from baseline values. The largest upper limit of the 90% CI for the QRS mean difference between Ra-223 and placebo is 4.3 msec. There are 3 (14.2%) patients in the Ra-223 group and 1 (12.5%) patient in the placebo group who experienced QRS interval greater than 110 msec.

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Based on study design limitations for the QT substudy, the QT-IRT concluded that the QT substudy was inconclusive with regards to adequately characterizing Ra-223's ability to prolong the QT interval. The QT-IRT did not consider this a pre-approval issue because there were no AEs of concern in the clinical program and the substudy did not include any large effects on the QTc interval. The primary issues in the QT substudy were related to the trial design; only collecting ECGs up to 4-6 hours post-dose (inadequate to cover the potential delayed effects over 24 hours); and the lack of collection of time-matched PK samples (negates the ability to conduct exposure-response analyses).

The potential risk of Ra-223 causing delayed effects on the QTc interval of treated patients 4-6 hours post-dose appears to be very limited when considering the lack of cardiac safety signals, clinical pharmacokinetics for elimination, the absorbed radiation dose to the heart, and the relatively small dose of Ra-223 compared to calcium concentrations in the blood (e.g., potential electrolyte shifts). Evaluation of the clinical pharmacology and radiation dosimetry for Ra-223 shows that there is rapid clearance of Ra-223 from the blood and limited distribution of the Ra-223 to the heart. Fifteen minutes post injection, about 20% of the injected radioactivity remained in blood. At 4 hours, about 4% of the injected radioactivity remained in blood. The radiation exposure to the heart wall was estimated to be only 0.0063 Gy. The amount of Ra-223 in each 1000 kBq vial is 0.53 ng Ra-223 and is not clinically relevant in relation to calcium levels in the blood.

Reviewer Comment: In an internal meeting, the FDA review team for Ra-223 determined that a PMR to repeat the QTc interval substudy for Ra-223 would not be required. This was based on the considerations discussed above and the relatively low risk of Ra-223 causing delayed QT prolongation greater than 4-6 hours after administration. The review team agreed to describe the FDA QT-IRT reviewer's conclusions in the prescribing information with a description of the limitations of the BC1-06 QTc substudy.

7.4.6 Immunogenicity

Not Applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

During the early phase clinical trials for Ra-223 dichloride, the maximum tolerated dose (MTD) was not established. There is no clear dose dependency for AEs for the dose levels evaluated in these clinical trials.

See the Clinical Pharmacology review for detailed information on dose response.

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7.5.2 Time Dependency for Adverse Events

There is concern regarding delayed toxicity including bone marrow suppression and secondary malignancies. See Section 7.3.4 for detailed information. There were no other time dependent concerns for AEs.

7.5.3 Drug-Demographic Interactions

No overall differences in safety were observed with regards to age or other demographic factors. In the BC1-06 trial, the median age of patients was 71 years (range: 44-90 years) on both arms. Of the 600 patients treated with Ra-223 dichloride in the phase 3 study, 153 patients (26%) were < 65 years of age, 278 patients (46%) were 65-75 years of age, and 169 patients (28%) were > 75 years of age. For these three age categories, the Grade 1-4 adverse events reported in > 5% of the patients on the Ra-223 arm were all comparable with no differences across any of the three arms of > 10%. Nearly all of the AEs reported failed to show consistent increases in incidence with increases in age across the three age categories. For two of the three AEs that did show a consistent increase with age (i.e., anorexia and pathologic fracture), the differences across the three age categories were all < 5%. Asthenia increased from 3.3% to 4.3% to 10.7% across the age categories respectively, but remained comparable to the incidence of asthenia reported in placebo patients > 75 years of age (8.0%).

7.5.5 Drug-Drug Interactions

No formal clinical drug interaction studies were performed by the Applicant. Subgroup analyses indicated that the concurrent use of bisphosphonates or calcium channel blockers did not affect the safety and efficacy of Ra-223 in the randomized clinical trial.

See the Clinical Pharmacology Review for more information.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Animal studies have not been conducted to evaluate the carcinogenic potential of Ra-223. However, in repeat-dose toxicity studies in rats, osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses 7 to 12 months after the start of treatment. The presence of other neoplastic changes, including lymphoma and mammary gland carcinoma, was also reported in 12- to 15-month repeat-dose toxicity studies in rats.

See the Nonclinical Pharmacology and Toxicology review for detailed information.

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7.6.2 Human Reproduction and Pregnancy Data

Genetic toxicology studies have not been conducted with Ra-223. However, the mechanism of action involves induction of double-strand DNA breaks, which is a known effect of radiation. Animal studies have not been conducted to evaluate the effects of Ra-223 on male or female fertility or reproductive function. Ra-223 may impair fertility and reproductive function in humans based on its mechanism of action. The prescribing information will include information related to precautions for patients of reproductive potential to use condoms during treatment and for a minimum of 6 months following completion of Ra-223 treatment. Although the proposed indication in this application is a disease only found in men, it is possible that women with bone-related metastases from other tumors could receive Ra-223 “off-label”; therefore Ra-223 is contraindicated in women.

See the Nonclinical Pharmacology and Toxicology review for detailed information.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

As currently dispensed, the risk for overdose with Ra-223 is low. In the worst case scenario, if a patient was inadvertently injected with the entire vial of Ra-223 they would receive a dose of approximately 13,800 kBq of Ra-223. This would equate to a dose of approximately 200 kBq/kg for a 70kg man. Single doses of Ra-223 have been administered up to 250 kBq/kg of Ra-223 in the phase 1 clinical trial program with limited acute toxicity reported.

While there is no specific clinical experience with overdose of Ra-223, single dose animal toxicology studies were conducted with intravenous Ra 223 dichloride administration up to approximate human equivalent doses of 500 kBq/kg in rats and 250 kBq/kg in dogs. The findings in these studies appear to be consistent with findings in the repeat-dose toxicology studies in rats and dogs at lower Ra-223 dichloride doses and adverse events in humans, but with greater incidence and severity. There were dose-dependent increases in myelotoxicity marked by decreases in red blood cells, hematocrit, hemoglobin, white blood cells, platelets and granulocytes, decreases in cellularity of the bone marrow, and increased splenic extramedullary hematopoiesis. There were also dose-dependent decreases in body weights. In rats, there were additional findings including depletion of osteoclasts and osteoblasts and disruption of the physis/growth plate in the femur and of the bone socket of growing teeth. The single-dose study in dogs included retinal detachment at the highest dose, but this was likely a species specific finding. These findings are in addition to the neoplastic changes in rats. Many of the rats administered higher doses of Ra-223 dichloride died within 1 year of receiving a single dose, likely due to neoplastic changes including osteosarcomas and related metastases.

Based on the mechanism of action, known clinical toxicity at the approved dose and existing animal data on higher doses, if accidental overdose occurs, patients should be monitored closely

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for severe hematologic toxicity with periodic complete blood counts (CBC). In the event of severe myelosuppression, the use of growth factors should be considered. To decrease gastrointestinal exposure, constipation should be prevented. Patients who have experienced an overdose should also be followed carefully for development of secondary malignancies.

7.7 Additional Submissions / Safety Issues

Bowel Movement Frequency Monitoring

According to the Applicant's proposed labeling, fecal excretion is the major route of elimination from the body for Ra-223 with up to 5% eliminated through the kidneys. The whole body measurements of Ra-223 approximately seven days after injection indicate that a median of 76% of administered activity was excreted from the body. The secretion/excretion of radium from blood into the small intestine is believed to occur primarily through the small intestine wall via transport mechanisms for other divalent cations (e.g., Ca^{2+} , Mg^{2+} and Ba^{2+}). Based on the calculated absorbed doses to the gastrointestinal tract, the intestines also appear to be the dominant excretory organ. The rate of elimination from the gastrointestinal tract was influenced by the variability in intestinal transit times across the population. Based on these considerations; patients, providers, and caregivers should carefully monitor bowel movement frequency after administration of Ra-223

Radiation protection

The administration of Ra-223 is associated with potential risks for medical staff, care givers and members of the patient's family from radiation or contamination from spills of body fluids such as feces or urine. Therefore, radiation protection precautions must be taken in accordance with national and local regulations. Following the normal working procedures for the handling of radiopharmaceuticals and use of universal precautions for patient care is expected to be sufficient given the physical properties of Ra-223. Due to the fecal elimination pathway of Ra-223, patients should use a toilet and the toilet should be flushed several times after each use whenever possible. Clothing soiled with Ra-223 or patient fecal matter or urine should be washed promptly and separately from other clothing. In the event of spillage of Ra-223, the local radiation protection advisor should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area.

Ra-223 is primarily an alpha emitter, with a 95.3% fraction of energy emitted as alpha-particles. The fraction emitted as beta-particles is 3.6%, and the fraction emitted as gamma-radiation is 1.1%. The external radiation exposure associated with handling of patient doses is considerably lower than other therapeutic radiopharmaceuticals as the administered radioactivity will usually be below 8,000 KBq (216 microcurie). In keeping with the **As Low As Reasonably Achievable (ALARA)** principle, for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or

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administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

The gamma radiation associated with the decay of Ra-223 and its daughters allows for the radioactivity measurement of Ra-223 and the detection of contamination with standard instruments.

See the FDA primary CMC review for detailed information related to safe handling, radiation protection, instructions for preparation, and dose calibration.

8 Postmarket Experience

Not Applicable.

9 Appendices

9.1 Literature Review/References

Please see footnotes at bottom of specific page where reference is cited.

9.2 Labeling Recommendations

See final FDA label.

9.3 Advisory Committee Meeting

An advisory committee meeting was considered unnecessary for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PAUL G KLUETZ
04/10/2013

VIRGINIA E MAHER
04/11/2013

PAUL G KLUETZ on behalf of WILLIAM F PIERCE
04/11/2013

CLINICAL FILING CHECKLIST FOR NDA 203971

NDA/BLA Number: 203971

**Applicant: Bayer
Pharmaceuticals**

Stamp Date: 12/14/2012

Drug Name: XOFIGO®

NDA/BLA Type: NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		Efficacy data relies on a single phase 3 study. A pooled analysis for efficacy was not performed. This was agreed to by FDA documented in pre-NDA meeting minutes. Separate efficacy datasets for phase 2 trials were included.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: ATI-BC1, BC1-03, BC1-04, BC1-08	X			

Clinical Filing Checklist: NDA 203971, Radium-223 Dichloride, (XOFIGO®)

CLINICAL FILING CHECKLIST FOR NDA 203971

	Content Parameter	Yes	No	NA	Comment
	Study Title: See Application Sample Size: N=31, 100, 122 and 10. Arms: See Application Location in submission: Module 5.3.3.1 and 5.3.3.2				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: BC1-06: Phase 3 placebo controlled international multicenter. Indication: CRPC with symptomatic metastases Additional Studies: BC1-02 Randomized placebo-controlled phase 2 trial showed trend in SRE delay and improved survival. BC1-03 Multi-dose uncontrolled phase 2 trial showed dose-related effect on pain. BC1-04 Multi-dose uncontrolled showed dose-related effect on PSA.	X			There is a single large placebo controlled randomized clinical trial (BC1-06) to support the NDA. There is an additional randomized placebo controlled phase 2 trial and other supportive studies included in the application.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Pivotal Trial endpoints of Overall Survival and Time to SRE have been used in prior prostate cancer approvals.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			5.2 Statement of Compliance with 21 CFR 312.120. Also found in section 4.2.5 of the Clinical Overview. See Review Issues Below.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			This information is located in the Summary of Clinical Safety (2.7.4). This includes a total of 12 clinical trials administering at least one dose of Ra-223 dichloride to a total of

Clinical Filing Checklist: NDA 203971, Radium-223 Dichloride, (XOFIGO®)

CLINICAL FILING CHECKLIST FOR NDA 203971

	Content Parameter	Yes	No	NA	Comment
					904 patients. Seven of these trials are completed with CSRs in this submission to support this NDA. The five ongoing trials have SAE information listed in Module 5.3.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			In the End-of-Phase 2 meeting (IND 67,521), FDA informed the sponsor that the safety database from the Phase 1/2 studies and study BC1-06 would “probably be adequate”.
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			The MedDRA and CTCAE coding dictionaries were provided. The AE and AESAF datasets include the MedDRA terms and the verbatim reported terms (AETERM) for each AE reported.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			The Applicant analyzed AML, MDS, aplastic anemia, osteosarcoma, and other new cancers in the Summary of Clinical Safety (Module 2.7.4, Section 4.1.7). The latency period can be prolonged for radiation-induced malignancies. The current data is sufficient for an

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 203971

	Content Parameter	Yes	No	NA	Comment
					affirmative filing decision. Additional requirements to monitor long term toxicities will be a review issue.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Listed in Clinical Study Report A58800 Section 15, links to narratives, narratives link to CRFs.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			Clinical Overview Section 5.7.7
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			5.2 Statement of Compliance with 21 CFR 312.120. Also found in section 4.2.5 of the Clinical Overview. See Review Issues Below.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			

Clinical Filing Checklist: NDA 203971, Radium-223 Dichloride, (XOFIGO®)

CLINICAL FILING CHECKLIST FOR NDA 203971

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			5.2 Statement of Compliance with 21 CFR 312.120

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None. Information Requests will be sent to the applicant throughout the review as necessary.

Reviewing Medical Officer: Paul G. Kluetz, M.D. Date

Reviewing Medical Officer: William Pierce, Pharm. D. Date

Clinical Team Leader: V. Ellen Maher, M.D. Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PAUL G KLUETZ
02/13/2013

VIRGINIA E MAHER
02/14/2013

WILLIAM F PIERCE
02/14/2013