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RESEARCH**

APPLICATION NUMBER:

203971Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 29, 2013
From	V. Ellen Maher
Subject	Radium-223
NDA/BLA # Supplement#	203971/S0
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
Date of Submission	December 14, 2012
PDUFA Goal Date	August 14, 2013
Proprietary Name / Established (USAN) names	Xofigo/radium Ra 223
Dosage forms / Strength	Single-use vial containing 6000 kBq/6 mL (0.162 mCi/6 mL)
Proposed Indication(s)	The treatment of castration-resistant prostate cancer patients with bone metastases
Recommended:	Approval

1. Introduction

On December 14, 2012, Bayer Pharmaceuticals submitted a New Drug Application for radium-223 for the following indication.

- Xofigo is a therapeutic alpha particle-emitting pharmaceutical for the treatment of castration-resistant prostate cancer patients with bone metastases.

2. Background

Radium-223 is a radioactive divalent cation that releases alpha particles during its decay to lead-207. It accumulates in areas of high bone turnover where it can replace calcium in its complex with hydroxyapatite. Alpha particles have a high energy transfer and cause DNA double strand breaks. Despite the high energy transfer, alpha particles have only a short path-length, < 100 microns. This is approximately 10 cell diameters. It is thought that this short path length will minimize damage to surrounding normal tissue such as the bone marrow. While radium-223 is primarily an alpha emitter (95.3%), it also emits a small amount of beta (3.6%) and gamma (1.1%) radiation.

The place of radium-223 in the treatment of prostate cancer is still being developed. The Phase 3 trial in this application was conducted primarily in Europe between June 2008 and February 2011. As a result, approximately half the patients entering this trial had received docetaxel (approved in the EU in 2005), but none had received cabazitaxel or abiraterone (approved in the EU in 2011). It is unclear whether patients who have received radium-223 will tolerate cabazitaxel and limited information is available on the use of cytotoxic chemotherapy after radium-223. Further, while radium-223 targets only the bone, newer agents like abiraterone and enzalutamide target both visceral and bone metastases making the placement of radium-

223 uncertain in the treatment of prostate cancer. The table below provides information on the agents approved for the treatment of metastatic prostate cancer.

Table 1: Prostate Cancer Therapies			
Agent	Comparator	Endpoint	Hazard Ratio p-value
Mitoxantrone + Prednisone	Prednisone	2-point decrease 29% vs. 12% ¹ Duration of decrease 7.6 vs. 2.1 mos	p = 0.011
Docetaxel + Prednisone	Mitoxantrone + Prednisone	Median Overall Survival 18.9 vs. 16.5 mos	HR = 0.76 p = 0.0094
Sipuleucel-T	PBMC ²	Median Overall Survival 25.8 vs. 21.7 mos	HR = 0.59 p = 0.01
Cabazitaxel + Prednisone	Mitoxantrone + Prednisone	Median Overall Survival 15.1 vs. 12.7 mos	HR = 0.70 p < 0.0001
Abiraterone + Prednisone	Prednisone	Median Overall Survival 15.8 vs. 11.2 mos	HR = 0.74 p < 0.0001
Enzalutamide	Placebo	Median Overall Survival 18.4 vs. 13.6 mos	HR = 0.63 p < 0.0001

¹2 point decrease in pain intensity with stable analgesic use ²Peripheral blood mononuclear cells

In addition to these agents, 4 products have been approved as bone-targeting therapy. These are shown in the table below. Note that while radium-223 is a bone-targeting agent that it has also shown an improvement in overall survival in patients with prostate cancer.

Table 2: Bone-Targeting Therapies			
Agent	Comparator	Endpoint	Hazard Ratio p-value
Zoledronic acid	Placebo	Median time to first SRE ¹ Not reached vs. 321 d	HR = 0.67 p = 0.011
		Proportion with a SRE 33% vs. 44%	p = 0.02
Denosumab	Zoledronic acid	Median time to first SRE 20.7 vs. 17.1 mos	HR = 0.82 p = 0.008
Strontium chloride	Placebo	Reduction in pain score and Stable analgesic use over 6-9 mos	
Samarium-153	Placebo	Reduction in pain score over 4 weeks ²	

¹Skeletal-related event ²A 0-10 visual analog scale was used

3. CMC/Device

Radium-223 dichloride is generated from (b) (4)
 (b) (4).
 Radionuclide purity and residual solvents are controlled. Compendial excipients are added and the drug product is packaged as 6 mL of radium-223 dichloride at 1000 kBq/mL in a glass vial with a (b) (4) rubber stopper. Three production lots have been manufactured and the shelf-life is 28 days.

4. Nonclinical Pharmacology/Toxicology

Radium-223 emits alpha particles causing double strand DNA breaks. Given its mechanism of action, it is thought to be carcinogenic, genotoxic, and teratogenic. Formal studies were not required. Radium-223 is calcium-mimetic and it lodges in the bone. In repeat dose toxicology studies, radium-223 affected growing areas of the bone and teeth and caused bone marrow suppression. In animals, osteosarcoma, breast cancer, and lymphoma were seen 6 months after initial administration.

5. Clinical Pharmacology/Biopharmaceutics

Radium-223 is administered as 50 kBq/kg intravenously over approximately 1 minute. It is rapidly cleared from the blood with 20% of the administered dose remaining in the blood at 15 minutes. It is distributed to the bone and intestine. It is secreted into the feces like other divalent cations. At 7 days, ~ 63% of the administered dose has been excreted in the feces. However, fecal excretion does vary markedly with intestinal transit time. The half-life of radium-223 is 11.4 days and dosing must be corrected for product decay. In the body, radium-223 decays into lead-207, a stable isotope. The amount of lead retained by the body is 3.2 ng per 6 mL vial of radium-223.

There is no entero-hepatic circulation and little urinary excretion. Dose adjustment is not needed for mild hepatic impairment or for mild/moderate renal impairment. Use of calcium channel blockers or bisphosphonates did not affect the safety or the efficacy profile of radium-223. No large changes in mean QTc intervals (i.e., > 20 ms) were detected at up to 4 hours post-injection at the proposed dose.

In exploratory analyses, the clinical pharmacology group found an improvement in overall survival with increasing body weight quartile and increasing dose. During drug development, the radium-223 dose was not extensively explored. Dose will be further explored as a post-marketing commitment.

6. Clinical Microbiology

The intravenous product is sterile. Please see the microbiology review.

7. Clinical/Statistical- Efficacy

The Applicant provided the following studies in support of this submission.

1. BC1-06: A double-blind, randomized, multiple dose, Phase III, multicenter study of alpharadin in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases
2. Three Phase 2 Studies: BC1-02, BC1-03, BC1-04
3. Three Phase 1 Studies: AT1-BC1, BC1-05, BC1-08
4. Expanded Access Trial

Phase 3 Study Design

The Phase 3 study randomized patients with metastatic castration-resistant prostate cancer 2:1 to radium-223 or placebo.

Eligibility Criteria

1. Metastatic castration-resistant prostate cancer defined by 2 consecutive rises in PSA and testosterone ≤ 50 ng/dL
 - a. Patients with visceral disease or lymph nodes > 3 cm in short axis were excluded.
 - b. Patients were required to have at least 2 skeletal metastases.
 - c. PSA ≥ 5 ng/mL
2. Prior docetaxel was permitted, but not required.
3. Regular use of analgesic medications (including acetaminophen) for bone pain or treatment with XRT for bone pain within the 12 weeks prior to randomization was required.

Stratification Factors: Alkaline phosphatase (<220 U/L, ≥ 220 U/L), Current use of bisphosphonates (Y/N), Prior use of docetaxel (Y/N)

Treatment

1. Radium-223 50 kBq/kg IV bolus over 1 minute q 4 weeks x 6
2. Placebo (normal saline) IV bolus over 1 minute q 4 weeks x 6
 - Unblinded personnel at the study site prepared the study drug and affixed a blinded patient label to the syringe.
 - Patients on both arms received best supportive care defined as XRT, steroids, estrogens, anti-androgens, estramustine, or ketoconazole.
 - Patients with cord compression or pathologic fracture could undergo XRT and/or surgery and were not required to discontinue study drug. Patients who required cytotoxic chemotherapy discontinued study drug.
 - There were no dose reductions, but treatment could be delayed up to 4 weeks. Patients with grade 3-4 ANC for > 14 days (G-CSF use was suggested) or grade 4 non-hematologic toxicity for > 7 days discontinued study drug.

Safety Monitoring

- Patient visits and laboratories (including PSA) were done monthly during the treatment period then every 2 mos to 1 year and then every 4 mos for 3 yrs.
- Bone scans, abdomino-pelvic CT, and chest X-ray were done at baseline only.
- All adverse events were reported during the treatment period and for 12 weeks after the last dose. After that, only AEs thought to be related to study drug were reported. Information was obtained concerning a new diagnosis of AML, MDS, aplastic anemia, and solid tumors.

Statistical Plan

The primary endpoint was overall survival (OS) defined as the time from randomization until death. This analysis was conducted in the intent-to-treat population. Patients alive at the time of the analysis or lost to follow up were censored at the last date they were known to be alive.

The OS analysis used a stratified (randomization strata) logrank test. The final analysis was to be conducted after 640 events. An interim analysis was to be performed when ~ 50% deaths had occurred. The total alpha for the analysis of OS was 0.05 (2-sided). A Lan-DeMets alpha spending approach was applied with O'Brien-Fleming stopping boundaries at the interim analysis.

Secondary endpoints included time to alkaline phosphatase (ALP) progression, ALP response, time to occurrence of a symptomatic skeletal event (SSE), ALP normalization, and time to PSA progression. These were tested in order using an alpha of 0.05. All time to event analyses censored patients who were lost to follow up or without an event at their last efficacy assessment. Alkaline phosphatase progression, response, or normalization are not established biomarkers for prostate cancer. Time to occurrence of a SSE was defined as the time from randomization until 1 of these events occurred: 1) XRT to relieve skeletal symptoms, 2) new symptomatic pathologic fracture, 3) tumor-related orthopedic intervention, and 4) cord compression. Time to PSA progression was defined as the time from randomization until PSA progression (per Prostate Cancer Working Group 2).

There were substantial changes in the protocol and statistical plan during the study.

1. Amendments 1, 2, and 3: Changed the stratification factors to those cited above and, as a result, increased the sample size to 750. Added a re-estimation of sample size (beyond 750 patients) and an interim analysis at ~ 50% of events. Changed the follow up period to 3 years after entry of the last patient.
2. Amendment 4-June 23, 2010: Increased the sample size to achieve 90% power in the primary analysis. This was the last amendment and SAP prior to the data cutoff for the interim analysis (October 14, 2010). Results of the interim analysis were not presented to the Independent Data Monitoring Committee until June 3, 2011.
3. Amendment 5-January 20, 2011: Provided for hierarchical testing of the secondary endpoints. Added time to SSE and ALP normalization to the secondary endpoints.
4. The last patient was enrolled February 2, 2011 and Amendment 6 (June 24, 2011) allowed for crossover of patients receiving placebo to radium-223.

Patient Disposition

At the time of the interim analysis (October 14, 2010), 809 patients from 128 sites had been randomized. This included 10 patients from the US. In the table below, patients who withdrew prior to treatment are considered separately from those who withdrew after treatment. This table, therefore, differs slightly from that in the primary clinical review.

The percentage of patients who withdrew from treatment was increased in placebo arm (27% vs. 44%). This imbalance occurred in most of the categories of events leading to withdrawal. The largest number of patients, 60 radium-223 and 47 placebo, withdrew due to an adverse event. In the adverse events dataset, using the October 14, 2010 data cutoff, 72 patients in the radium-223 arm and 54 patients in the placebo arm permanently discontinued study drug due to an adverse event. Most of the patients who discontinued due to Patient and Investigator

Decision or Other did so because of disease progression (often clinical progression) or the need for cytotoxic chemotherapy. Finally, it is concerning that the percentage of deaths on the placebo arm is ~ twice that of the radium-223 arm. Most of these deaths were due to progressive disease while approximately 1/3 on each arm were due to an adverse events. In the adverse event dataset, 10% of radium-223 and 17% of placebo-treated patients died due to an adverse event.

Table 3: Patient Disposition		
	Radium-223	Placebo
Randomized	541	268
Withdrew Prior to Treatment	14	5
Not Yet Treated	19	9
Treated	508	254
Ongoing (%)	98	45
Completed	262 (48)	90 (34)
Withdrew from Treatment	148 (27)	119 (44)
Death	23 (4)	23 (9)
Patient/Investigator Decision	47 (9)	38 (14)
Adverse Event	60 (11)	47 (18)
Other ¹	18 (3)	11 (4)

¹Primarily progressive disease or start of cytotoxic chemotherapy

Data Cutoff 10-14-2010

Baseline Patient and Disease Characteristics

Patients in both arms were well-balanced by age. The majority of patients (94%) were Caucasian. The table below provides additional information on performance status and baseline disease characteristics. There is some imbalance in the median PSA and Gleason score. However, the number of bone metastases is well-balanced and demonstrates that most patients had extensive disease. This is supported by information concerning the WHO pain ladder. Here, ~ half the patients required opiates (WHO pain ladder ≥ 2). Finally, the table notes that approximately half the patients received prior cytotoxic chemotherapy. This included > 12 weeks of docetaxel in 51% of radium-223 and 48% of placebo-treated patients.

Patients with visceral metastases or lymph nodes > 3 cm in short axis were excluded from study entry. However, 3 patients on the radium-223 arm did not meet this requirement.

Table 4: Patient Demographics and Baseline Characteristics		
	Radium-223 N = 541	Placebo N = 268
Performance Status		
0-1	86%	86%
2	14%	14%
3	0.8%	0.4%
Median Time from Diagnosis to Randomization ¹ (range)	4.8 yrs (0.6-25.7)	4.2 yrs (0.09-28.5)
Median PSA (25%-75%)	159 ng/mL (51-450)	195 ng/mL (69-504)
Number of Bone Metastases		
< 6	16%	12%
6-20	44%	48%
> 20	31%	30%
Superscan	9%	10%
Prior Prostate Cancer Therapy		
LHRH Agonist/Antagonist	82%	83%
Orchiectomy	15%	16%
XRT to Bone	51%	48%
Cytotoxic Chemotherapy	59%	58%
Antiandrogen	85%	85%
Gleason Score²		
≤ 6	17%	10%
7	29%	28%
8-10	41%	49%
WHO Ladder for Cancer Pain		
0	2%	0.7%
1	43%	46%
2	24%	27%
3	30%	26%

¹Missing: 60 radium-223, 33 placebo ²Missing: 69 radium-223, 33 placebo

Primary Analysis

The table below provides the results of the interim analysis of overall survival that resulted in study discontinuation and the crossover of placebo patients to radium-223. The threshold for study discontinuation was a 2-sided p value = 0.00272. An updated analysis (7-15-2011) prior to crossover with 921 patients and 57% of events found a HR of 0.70. At the time of the updated analysis, the HR for the 43 patients from North America was 0.45.

Table 5: Primary Analysis		
	Radium-223 N = 541	Placebo N = 268
Events	35%	46%
Censored	65%	54%
Median OS (95% CI)	14.0 mos (12.1, 15.8)	11.2 mos (9.0, 13.2)
Hazard Ratio	0.70 (0.55, 0.88)	
p-value (2-sided)	0.00185	

Data Cutoff 10-14-10

The use of best supportive care (although unlikely to affect OS) was examined and found to be similar between arms. Note that this table is based on the number of patients treated at the time of the interim analysis.

Table 6: Use of Best Supportive Care		
	Radium-223 N = 508	Placebo N = 254
Antiandrogens	20%	34%
Bisphosphonates	40%	40%
Steroids	41%	41%
Ketoconazole	4%	3%

Data Cutoff 10-14-10

Since imbalances in Gleason score and PSA, as well as, the presence of metastatic disease at diagnosis were noted between arms, the primary analysis was examined using a Cox model adjusting for these factors. In this analysis, the HR was 0.71. Finally, discrepancies between the stratification factors (e.g., ALP level) entered at randomization and those on the monitored case report forms (CRF) were found in 60 patients on the radium-223 and 23 patients on the placebo arm. The results of the stratified logrank test used in the primary analysis were similar when stratification factors from randomization or from the CRFs were used.

Secondary Endpoints

Analysis of the time to the first symptomatic skeletal event shown in the table below differs from the pre-specified analysis in the statistical plan. The pre-specified analysis did not account for informative censoring due to patient deaths prior to the development of a skeletal event. In this analysis, patient deaths are included as events. The most prominent component of this endpoint is the number of patients who required radiation therapy to the bone. Note that this endpoint differs from skeletal-related events in that routine X-rays were not performed.

Table 7: Time to the First Symptomatic Skeletal Event		
	Radium-223 N = 541 (%)	Placebo N = 268 (%)
Event	262 (48)	160 (60)
Median Time to Event (95% CI)	8.2 mos (7.5, 9.4)	6.1 mos (5.1, 7.1)
Hazard Ratio (95% CI)	0.66 (0.54, 0.80)	
p-value	< 0.0001	

Data Cutoff 10-14-10

An additional secondary endpoint was the time to PSA progression. The median time to PSA progression was 3.6 and 3.4 months in the radium-223 and placebo arms, respectively. An exploratory analysis found that 6% of radium-223 and 1% of placebo-treated patients had a confirmed $\geq 50\%$ decrease in PSA.

Supportive Studies

Six small supportive studies using a variety of doses and schedules were submitted by the Applicant. This includes the 3 Phase 2 studies described below.

- BC1-02: This study randomized 64 patients with castration-resistant prostate cancer and bone metastases to radium-223 50 kBq/kg q 4 weeks x 4 or placebo. All patients had received radiation therapy in the 7 days prior to entry. For both arms, the median field size of the irradiated regions was 202 cm² (range 29-450 cm²) and the median dose was 16 Gy (range 8-30 Gy). The primary endpoints were time to a composite endpoint and change in alkaline phosphatase. The composite endpoint was complex and included an increase in pain and analgesic use as well as the need for radiation therapy or surgical intervention for bone disease. The median time to this composite endpoint was 15.0 weeks in the radium-223 and 13.6 weeks in the placebo arm. The median change in bone-ALP 4 weeks after the last dose was -66% in the radium-223 and +9% in the placebo arm. At 24 months, the hazard ratio for OS was 0.48 in favor of radium-223.
- BC1-03: This study randomized 100 patients with castration-resistant prostate cancer, bone metastases, and a pain score ≥ 2 on the Brief Pain Inventory to 5, 25, 50, or 100 kBq/kg of radium-223 x 1 dose. The primary endpoint was a pain index that included both bone pain and analgesic use. Scores were assessed at multiple time points and were not adjusted for multiplicity. In the per protocol population (patients with a pain index ≥ 2 at baseline), a test for trends found a decrease in the pain index with increasing dose at week 2. This analysis was not significant in the ITT population.
- BC1-04: This study randomized 122 patients with metastatic castration-resistant prostate cancer to 25, 50, or 80 kBq/kg q 6 wks x 3. The primary endpoint was the percentage of patients with a confirmed $\geq 50\%$ decrease in PSA. This was 0 in the 25, 2/36 (5.6%) in the 50 and 5/39 (12.8%) in the 80 kBq/kg groups.

8. Safety

Exposure

Using a data cutoff of July 15, 2011, 600 patients on the Phase 3 trial received 50 kBq/kg radium-223 and 301 patients received placebo. Dose reductions were not permitted and dose delays were seen in a small percentage of patients on the Phase 3 study. In addition to the 600 patients in the Phase 3 trial, an additional 103 patients from the Phase 1-2 trials received 50 kBq/kg radium-223. Information on the adverse event profile of radium-223 in these additional 103 patients is included in the primary clinical review.

Table 8: Patient Exposure on the Phase 3 Trial		
	Radium-223 N = 600	Placebo N = 301
Median Duration of Exposure (range)	20 weeks (0.1-28)	18 weeks (0.1-27)
Percentage Completing 6 Injections	64%	47%
Median Cumulative Activity (range)	21,726 kBq (2,700-41,985)	NA
Dose Delay due to Adverse Event	15%	18%

Data Cutoff July 15, 2011

Overall, 904 patients received radium-223 at doses ranging from 46-250 kBq as a single injection and from 80 kBq/kg every 6 weeks x 3 to 50 kBq/kg every 4 weeks x 6 doses as repeat injections. The highest cumulative dose of radium-223 was 41,985 kBq. The Safety Update (data cutoff December 1, 2012) included 25 patients who crossed over from placebo to radium-223 on the Phase 3 trial and line listings of safety reports in ongoing studies.

Deaths

The table below provides information on the deaths that occurred within 30 days of the last dose of study drug. This includes 1 patient whose death could be attributed to hematologic toxicity. This patient had a platelet count of $75 \times 10^9/L$ on the day of dosing. He subsequently developed grade 4 thrombocytopenia, hemorrhage, and multi-organ failure.

Table 9: Deaths Due to an Adverse Event Within 30 Days of Study Drug		
	Radium-223 N = 600	Placebo N = 301
All	16 (3%)	14 (5%)
Death (no additional information)	3	0
General Physical Health Deterioration	2	0
Myocardial Infarction	2	1
Pneumonia	2	1
Cachexia	1	0
Confusional State	1	0
Dyspnea	1	0
Intestinal Obstruction	1	0
Multi-organ Failure	1	0
Sepsis	1	1
Sudden Death	1	1
Cardiac Failure	0	2
Cardiorespiratory Arrest/Cardiac Arrest	0	1
Cerebral/Intracranial Hemorrhage	0	1
Cerebral Ischemia	0	1
Disseminated Intravascular Coagulation	0	1
Pleural Effusion	0	1
Pulmonary Embolism	0	2
Respiratory Arrest/Failure	0	1

Data Cutoff July 15, 2011

Deaths during the 3 year follow up occurred in 7% of patients in the radium-223 and 12% of patients in the placebo arm. This includes 3 deaths associated with hematologic toxicity in patients who received radium-223.

- This patient developed thrombocytopenia and GI hemorrhage 69 days after his 2nd injection. He was initially treated with supportive care (transfusion), but was then discharged and died 8 days later.
- A 2nd patient died due to pneumonia with grade 4 thrombocytopenia. The Applicant did not report his neutrophil count and neutropenia was not reported as an adverse event.
- A 3rd patient died with grade 3 neutropenia and pneumonia.

There were 3 additional deaths associated with, but not clearly due to hematologic toxicity. One patient died due to a subdural hematoma after a fall with a platelet count of $60 \times 10^9/L$. A 2nd patient died with brain metastases, intracranial hemorrhage, and a platelet count of $62 \times 10^9/L$. A 3th death occurred in a patient with grade 4 pancytopenia (WBC unknown, platelets $14 \times 10^9/L$), hematuria, dyspnea, edema, and renal failure.

In the Safety Update there was 1 additional death in a patient who crossed over to radium-223. This patient died due to rectal hemorrhage with thrombocytopenia.

Discontinuations

Permanent discontinuation of study drug due to an adverse event occurred in 16% and 19% of patients on the radium-223 and placebo arms, respectively. Causes of discontinuation in > 1% of patients on the radium-223 arm (and greater than placebo) included disease progression, anemia, thrombocytopenia (1.7%), and the development of metastases.

Grade 1-4 Adverse Events

The table below provides information on grade 1-4 adverse events that occurred in at least 5% of patients and occurred more commonly in the radium-223 arm than placebo. Interestingly, during the treatment period, bone pain (including bone pain, back pain, neck pain, pain, and extremity pain) was reported in 52% of radium-223 and in 63% of placebo-treated patients.

Table 10: Grade 1-4 Adverse Events in > 5% of patients				
	Radium-223 N = 600		Placebo N = 301	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Any	93%	59%	96%	65%
Nausea	36%	2%	35%	2%
Diarrhea	25%	2%	15%	2%
Vomiting	19%	2%	14%	2%
Peripheral Edema	13%	2%	10%	1%
Thrombocytopenia	12%	7%	6%	2%
Neutropenia	5%	2%	1%	0.7%

Data Cutoff July 15, 2011

As noted during the discussion of patient exposure, 1 patient received a cumulative dose of 41,985 kBq of radium-223. Examining the adverse event profile of the 9 patients who received a total dose > 35,000 kBq, it is concerning that 2/9 patients reported no adverse events. Importantly, their study sites were audited by the Applicant and they did not uncover significant findings. In the other 7 patients, adverse events \geq grade 3 included the development of liver metastases (resulting in death), bone pain, and dyspnea.

Laboratories

The table below provides information on the hematology laboratories obtained during the treatment period. In weekly testing during the Phase 1 program, laboratory nadirs were found to occur 2-3 weeks after dosing. In the Phase 3 trial, laboratories were obtained every 4 weeks. It is likely that this schedule minimized the number of patients with high grade hematologic toxicity. Here, the number of patients with grade 3-4 hematologic toxicity (except lymphocytopenia) in the radium-223 arm is small. The incidence of grade 3-4 hematologic toxicity with radium-223 was not increased in patients who had received prior cytotoxic chemotherapy; 2% grade 3-4 neutropenia and 4% grade 3-4 thrombocytopenia.

Table 11: Hematology Laboratories				
	Radium-223 N = 600		Placebo N = 301	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Hemoglobin	93%	6%	88%	6%
Lymphocytes	72%	20%	53%	7%
WBC	35%	3%	10%	0.3%
Platelets	31%	3%	22%	0.7%
Neutrophils	18%	2%	5%	0.3%

Data Cutoff July 15, 2011

The monthly laboratories were also examined for evidence of cumulative toxicity. Laboratory values did decrease with an increase in the number of doses with a median neutrophil nadir at day 85 and a median platelet nadir at day 112. Note that in many of these patients the nadir value remained within normal limits.

Fourteen patients on the radium-223 arm received cytotoxic drugs before the end of treatment visit (last dose + 4 weeks). Among these, the following adverse events were reported: febrile neutropenia (1), neutropenia (2), and thrombocytopenia (1).

Hematologic toxicity was also examined by reviewing the follow up laboratories in patients who did not receive cytotoxic therapy after discontinuation/completion of radium-223. This may provide some clues to the presence of late toxicity with radium-223. Here, there does appear to be a small increase in hematologic toxicity with radium-223.

Table 12: Hematology Laboratory Values at Follow Up Visit #1 in Patients Who Did Not Receive Subsequent Cytotoxic Therapy ¹				
	Radium-223 N = 269		Placebo N = 93	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Hemoglobin	91%	5%	82%	2%
Neutrophils	5%	1%	6%	0
Platelets	23%	6%	18%	3%

¹Follow up visit #1 was ~ 90 days after the last dose

Data Cutoff July 15, 2011

In the safety database, 5 patients received 250 kBq/kg (N=5) as a single dose. The lowest laboratories recorded in these 5 patients were a neutrophil count of $0.7 \times 10^9/L$ and a platelet count of $92 \times 10^9/L$.

Adverse Events and Issues of Special Interest

Secondary Malignancies: The Phase 3 study continued long-term follow up for secondary malignancies for 3 years after the last dose of study drug (median OS 14 mos in the radium-223 arm). At 3 years, patients could consent to additional follow up. However, at present, long-term follow up is limited to 22 patients who have been followed for 3 years. The other radium-223 trials in the safety database provided for limited follow up for long-term toxicities. In the Phase 3 trial, 5 patients treated with radium-223 [bladder cancer (1), squamous cell

carcinoma of the skin (2), and non-melanoma skin cancer (2)] and 5 patients treated with placebo [squamous cell carcinoma of the skin (1), skin cancer (2), gastric cancer (1), and rectal cancer (1)] have developed second primary tumors. In the safety database, 4 patients have developed a second malignancy [squamous cell carcinoma of unknown primary (1), rectal cancer (1), bladder cancer (1), and pancreatic cancer (1)]. The patient who developed a squamous cell carcinoma of unknown primary was also diagnosed with cancer of the penis 1 month after study entry.

Osteonecrosis: Osteonecrosis is a theoretical concern in patients receiving radium-223. Osteonecrosis of the jaw (ONJ) was reported in 4 patients receiving radium-223, but was not reported in other areas of the bone. All 4 patients had received bisphosphonates. However, the last dose of bisphosphonate in 1 of the 4 patients was 8 months prior to the diagnosis of ONJ. This patient received 1 dose of radium-223 after the diagnosis of ONJ. The investigator reported that the area of osteonecrosis did not seem to progress following this dose of radium-223. The safety database of all patients who received radium-223 was examined for additional reports of osteonecrosis. There was 1 additional report of jaw pain in the safety database.

Injection Site Reactions: Although alpha particles have a 100 micron path length, it is possible that extravasation could result in local injury. There were no reports of extravasation. Injection site reactions (injection site pain, rash, reaction, swelling, and erythema) were reported in 6 patients in the radium-223 arm of the Phase 3 study. All reactions were grade 1 and all resolved without sequelae. There was 1 additional report of grade 1 injection site pruritus in the safety database.

Use of Cytotoxic Chemotherapy: Ninety-three patients in the Phase 3 study received cytotoxic chemotherapy after their last dose of radium-223. Limited information is available concerning the laboratory abnormalities in these patients and firm conclusions cannot be drawn.

The Applicant is conducting an ongoing Phase 1-2 study of docetaxel 75 or 60 mg/m² every 3 weeks with 25 or 50 kBq/kg radium-223 every 6 or 3 weeks for 2 to 4 doses. Additional information was not included in the Safety Update. In the original NDA submission, the Applicant reported that 17 patients had been treated (doses unknown) and that 6 patients had experienced febrile neutropenia.

9. Advisory Committee Meeting

This application presented a clear benefit for treatment with radium-223 and was not discussed at an Advisory Committee meeting.

10. Pediatrics

Since prostate cancer rarely occurs in children, a pediatric waiver was granted for this indication.

11. Other Relevant Regulatory Issues

- Clinical Inspections of 4 clinical sites and the Applicant by the Office of Scientific Investigation found that the data submitted in the NDA was adequate for review.

- Applicant Audit: On routine audit prior to the submission of the NDA, the Applicant found a potential under-reporting of adverse events. This prompted further auditing and ~ 75% of patients randomized prior to the cutoff date for the interim analysis were reviewed for the completeness of adverse event reporting. The Applicant found 12 serious adverse events and 565 adverse events that had not been reported on their case report form. Bias was not found (by arm) in the under-reporting of adverse events. The Applicant initiated additional training and planned to conduct additional audits. The auditing program was discussed with the Applicant and the review team was satisfied that the data submitted in the NDA was adequate for review.
- Establishment inspections are pending.

12. Labeling

Please see final labeling. The Applicant's indication statement was changed to specifically state that this product is not indicated in patients with visceral metastases. Radium-223 targets areas of bone turnover and is not thought to be active in areas of visceral metastases.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval
- Risk Benefit Assessment

Table 13: Risk-Benefit Assessment		
	Evidence	Conclusions
Analysis of Condition	Metastatic castration-resistant prostate cancer is a serious and life-threatening disease.	Despite the availability of an increasing number of therapeutic options, metastatic castration-resistant prostate cancer remains a serious and life-threatening disease.
Unmet Medical Need	Metastatic castration-resistant prostate cancer remains an incurable disease. Additional treatment options are needed.	Radium-223 provides an additional option, but is limited to patients with bone-only disease. It is likely that radium-223 can be added to other therapeutic options which are not cytotoxic.
Clinical Benefit	Radium-223 improved overall survival with a hazard ratio of 0.70, p = 0.0012. Radium-223 lengthened the time to the development of a symptomatic skeletal event.	Radium-223 has demonstrated clinical benefit in patients with metastatic castration-resistant prostate cancer.
Risk	Adverse drug reactions in $\geq 10\%$ of patients included nausea, diarrhea, vomiting and peripheral edema. Hematologic laboratory abnormalities in $\geq 10\%$ of patients included anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Whether late toxicities such as the development of bone marrow suppression and second primary malignancies will occur with radium-223 remains unknown.	The adverse reaction profile of radium-223 is acceptable. Post-marketing requirements will assess the late toxicities associated with radium-223.

- Recommendation for Postmarketing Risk Management Activities
 - The Applicant will be required to conduct a study to fully assess the risk of secondary malignancies.
 - The Applicant will be required to conduct a study to further assess late hematological toxicities.
 - The Applicant plans to conduct a pilot study of retreatment with radium-223. The Applicant will be required, as part of this study, to collect data concerning acute and long-term hematologic toxicity.
- Recommendation for other Postmarketing Study Commitments
 - The Applicant will be asked to conduct a study to fully assess the dose-response relationship of radium-223.
- Recommended Comments to Applicant: Please see final letter.

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/s/

VIRGINIA E MAHER
04/22/2013