

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203971Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 203-971
Product Name: Radium Ra 223 dichloride

PMR Description: An observational study (N = 1200) to assess the long-term safety of radium Ra 223 dichloride 50 kBq/kg every 4 weeks for 6 doses in patients with castration-resistant prostate cancer with bone metastases

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2013</u>
	First Interim Analysis Report:	<u>09/30/2017</u>
	Second Interim Analysis Report:	<u>09/30/2019</u>
	Study/Trial Completion:	<u>12/31/2023</u>
	Final Report Submission:	<u>09/30/2024</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The post-marketing requirement will examine the long-term risk of secondary malignancies and drug-related serious adverse events.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Xofigo is an alpha-emitting radioisotope. In animal studies, secondary malignancies have developed following administration of Xofigo. In human, secondary malignancies and long-term bone marrow suppression have developed following treatment with related compounds.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 203971
Product Name: Radium Ra 223 dichloride

PMR Description: A randomized clinical trial to assess the safety of radium Ra 223 dichloride in patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease

PMR/PMC Schedule Milestones:	Final Protocol Submission:	12/31/2013
	Study/Trial Completion:	12/31/2017
	Interim Report Submission:	09/30/2018
	Final Report Submission:	03/31/2025

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The post-marketing requirement will examine the long-term risk of secondary malignancies and drug-related serious adverse events.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Xofigo is an alpha-emitting radioisotope. In animal studies, secondary malignancies have developed following administration of Xofigo. In human, secondary malignancies and long-term bone marrow suppression have developed following treatment with related compounds.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)



Required

- Observational pharmacoepidemiologic study
- Registry studies

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 203971
Product Name: radium Ra 223 dichloride

PMR Description: A trial of the short and long-term safety of re-treatment of patients with castration-resistant prostate cancer with bone metastases with radium Ra 223 dichloride

PMR/PMC Schedule Milestones: Final Protocol Submission: 08/31/2013
Study/Trial Completion: 09/30/2016
Interim Report: 03/31/2017
Final Report Submission: 01/31/2024

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This post-marketing requirement will examine the risk of retreatment with Xofigo.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Xofigo is an alpha-particle emitting radioisotope. An initial course of 6 cycles has been associated with high grade hematological toxicity in a small percentage of patients. The safety of retreatment, particularly in terms of its hematological toxicity is unknown.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant intends to conduct a clinical trial of retreatment with an additional 6 cycles of Xofigo in patients who have already received 50 kBq/kg of Xofigo every 28 days for 6 cycles. This PMR will examine the hematological toxicity associated with retreatment. Patients will also be followed for long-term bone marrow suppression and the development of secondary malignancies.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA203971
Product Name: Xofigo

PMC Description: Optimize the dosing regimen of Xofigo by conducting a randomized Phase 2 clinical trial to evaluate the efficacy and safety of Xofigo at a dose higher than 50 kBq/kg in patients with castration-resistant prostate cancer with bone metastases.

Depending on the results of the Phase 2 trial, a randomized Phase 3 trial may be needed to further confirm the appropriateness of the dosing regimen determined in the Phase 2 trial.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2013</u>
	Study/Trial Completion:	<u>09/30/2018</u>
	Final Report Submission:	<u>03/31/2019</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This trial is recommended as a PMC trial instead of pre-approval requirement because it was based on post-hoc exploratory analyses suggesting that the proposed dosing regimen may not be optimal. Given the safety and efficacy of Xofigo demonstrated in the randomized trial BC1-06, a dose higher than 50 kBq/kg (e.g., 80 kBq/kg for 6 cycles) may further improve the OS in the indicated patient population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Initially, the applicant may conduct a randomized Phase 2 clinical trial to evaluate the efficacy and safety of Xofigo at a higher dose (e.g., 80 kBq/kg for 6 cycles) in patients with castration-resistant prostate cancer with bone metastases.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

ELLENI K ALEBACHEW
05/14/2013
PMC/PMR Set# 2041

KATHERINE M FEDENKO
05/14/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 9, 2013

TO: Elleni Alebachew, Regulatory Project Manager
Paul Kluetz, M.D., Medical Officer
Division of Oncology Products 1

FROM: Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203971
APPLICANT: Bayer HealthCare Pharmaceuticals, Inc.
DRUG: Alpharadin [radium-223 chloride] Injection (Xofigo[®] Injection)
NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review (anticipated 4-month expedited review)

INDICATION(S): For the treatment of castration-resistant (hormone refractory) prostate cancer in patients with bone metastases.

CONSULTATION REQUEST DATE: December 14, 2012
INSPECTION SUMMARY GOAL DATE: April 4, 2013

DIVISION ACTION GOAL DATE: May 17, 2013
PDUFA DATE: August 14, 2013

I. BACKGROUND:

Bayer Healthcare Pharmaceuticals [Bayer], Inc., seeks approval to market alpharadin for the treatment of patients with symptomatic castration-resistant prostate cancer (CRPC) and symptomatic bone metastases. Alpharadin injection (radium-223) is a novel alpha emitting pharmaceutical developed by Algeta ASA. The product is based on the alpha-particle emitting radionuclide radium-223. The bone targeting property of radium-223 is similar to that of other alkaline elements, such as strontium-89. An alpha-emitting radiation source located in a target tissue, such as skeletal metastases, will deliver the radiation to a more localized area than beta emitters, thereby reducing exposure of surrounding normal tissues.

The application is largely based on the results of the pivotal Phase 3 study BC1-06 (a.k.a., ALSYMPCA trial). ALSYMPCA was a randomized (2:1), double-blind, multi-dose, placebo-controlled international study of radium-223 plus standard of care (SOC) compared with placebo plus SOC in castration-resistant prostate cancer (CRPC) patients with symptomatic bone metastases. The ALSYMPCA trial was stopped early based on Independent Data Monitoring Committee (IDMC) review of a pre-planned interim analysis of overall survival (two-sided p-value = 0.00185, HR = 0.695; the median overall survival was 14.0 months for radium-223 chloride and 11.2 months for placebo). The secondary endpoints time to skeletal related event (SRE), time to PSA progression, and PSA response also favored the radium-223 treatment arm compared to placebo.

The most frequently reported AEs in the ALSYMPCA trial that occurred at an increased incidence on the radium-223 arm compared to placebo were nausea (34%), diarrhea (22%), vomiting (17%), thrombocytopenia (8%), and neutropenia (4%).

The planned sample size for this study was 640 events and a total of 900 patients (radium- 223, n = 600; placebo, n = 300) from multiple international centers to achieve the number of events required for analysis. Enrollment in the trial was completed in February 2011 with 922 patients randomized. The study was conducted at approximately 155 centers worldwide. This study was conducted under IND 067521.

Four clinical sites, chosen on the basis of number of patients enrolled at each site, and based on Grade 3-4 AE reporting, major protocol violations, and efficacy results of the 137 individual sites accruing patients for the pivotal trial BC1-06 ("ALSYMPCA"), were inspected for this NDA. Because this is a new molecular entity, the sponsor was also inspected.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Dates	Final Classification
CI#1: Dr. Svein Inge Helle Kreftpolikliniken, Haukeland University Hospital Jonas Liesvei 65 Bergen 5021 Norway	Protocol: Study BC1-06 (ALSYMPCA) Site Number: 006 Number of Subjects: 45	February 11-15, 2013	Pending Interim classification: NAI
CI#2: Dr. Christopher Parker Department of Oncology The Royal Marsden Hospital Downs Road Sutton Surrey SM2 5PT UK	Protocol: Study BC1-06 (ALSYMPCA) Site Number: 033 Number of Subjects: 27	February 25 - March 1, 2013	Pending Interim classification: NAI
CI#3: Dr. Joe O'Sullivan Cancer Centre, Belfast Hospital Lisburn Road Belfast BT9 7AB UK	Protocol: Study BC1-06 (ALSYMPCA) Site Number: 035 Number of Subjects: 32	March 3-8, 2013	Pending Interim classification: VAI
CI#4: Dag Clement Johannessen Dep of Oncology, Ullevål University Hospital Kirkeveien 166 Oslo N-0407 Norway	Protocol: Study BC1-06 (ALSYMPCA) Site Number: 002 Number of Subjects: 17	February 18-22, 2013	Pending Interim classification: NAI
Sponsor: Bayer HealthCare Pharmaceuticals Inc 340 Changebridge Road Pine Brook, New Jersey 07058	Protocol: Study BC1-06 (ALSYMPCA) Site#: 18 Sites (including Sites 002, 006, 033, 035) Subjects Records Reviewed: 137	March 1-28, 2013 (14 days on-site)	Pending Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. CI#1: – Dr. Svein Inge Helle

Kreftpolikliniken, Haukeland University Hospital
Jonas Liesvei 65
Bergen 5021 Norway

- a. What was inspected:** The site screened 55 subjects, and 45 subjects were enrolled and treated. Portions of all subjects' study records were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, monitoring and safety reports, and financial disclosure forms.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records were adequate and well organized. The primary efficacy endpoint data, overall survival, for the subjects enrolled at this site were verified. At the time of this inspection there were two subjects that lived beyond three years, and two subjects that were still alive and in follow-up. There was no evidence of under-reporting of AEs. No Form FDA 483 was issued.
- c. Assessment of data integrity:** The data for Dr. Helle's site, associated with Study BC1-06 (ALSYMPCA) submitted to the Agency in support of NDA 203971, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: – Dr. Christopher Parker

Department of Oncology, The Royal Marsden Hospital Downs Road
Sutton Surrey SM2 5PT
UK

- a. What was inspected:** The site screened 32 subjects, and 27 subjects were enrolled and treated. The study records of all 27 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, monitoring and safety reports, and financial disclosure forms.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data, overall survival, for the subjects enrolled at this site were verified. There was no evidence of under-reporting of AEs. The record review revealed that one subject was unblinded during the study.

Briefly, a letter dated February 10, 2009, was found in the site's study records. The letter, addressed to Dr. Parker, was from the daughter of Subject #1 and, in part, revealed that the daughter of Subject #1 had learned that her father was on the placebo arm of the alpharadin study. Subject #1 had died on [REDACTED] (b) (6) [REDACTED] and the question of whether it was safe to cremate the remains was of issue. The subject's General Practitioner (GP) had phoned the site requesting guidance on whether the deceased could be cremated, given the possibility that the subject may have received radium-223 on study. Dr. Parker himself was blinded and informed the sponsor of this request. The sponsor then contacted the site's nuclear medicine staff, the only site personnel authorized to be unblinded, for assistance. The site nuclear medicine staff then contacted the GP to inform of the decedent's treatment regimen. No Form FDA 483 was issued.

- c. Assessment of data integrity:** Notwithstanding the minor observation noted above, the data for Dr. Parker's site, associated with Study BC1-06 (ALSYMPCA) submitted to the Agency in support of NDA 203971, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. CI#3: – Dr. Joe O'Sullivan

Cancer Centre, Belfast Hospital Lisburn Road
Belfast BT9 7AB
UK

- a. What was inspected:** The site screened 37 subjects, and 32 subjects were randomized. Nineteen subjects completed the study. Portions of all subjects' study records were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, monitoring and safety reports, and financial disclosure forms.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data for the subjects enrolled at this site were verified. There was no evidence of under-reporting of AEs. There were minor protocol deviations noted by the FDA field investigator regarding not always reporting serious adverse events (SAEs) within the protocol specified timeframe of 24 hours of discovery of the event. A Form FDA 483 was issued citing one inspectional observation.

1. An investigation was not conducted in accordance with the investigational plan.

Specifically, Protocol BC1-06 specifies in *Section 10.1.2.1 Investigator's Responsibilities [Adverse Event and Serious Adverse Event]*, that Serious Adverse Events were to be reported to the sponsor's representative by telephone or facsimile immediately (within 24 hours of the investigator becoming aware of the event). The site did not ensure that all SAEs were reported to the sponsor, or their representative, within 24 hours of discovery by site personnel.

- a. Subject #015 had neck pain and the site staff became aware of the event on July 9, 2010, but did not report the SAE to the sponsor until October 18, 2010.
- b. Subject #016 had back pain and the site staff became aware of the event on May 18, 2010, but did not report the SAE to the sponsor until May 21, 2010.
- c. Subject #016 had diarrhea and the site staff became aware of the event on December 29, 2010, but did not report the SAE to the sponsor until January 5, 2011.
- d. Subject #017 had pneumonia and the site staff became aware of the event on September 15, 2010, but did not report the SAE to the sponsor until September 17, 2010.
- e. Subject #022 had back pain and the site staff became aware of the event on May 18, 2010, but did not report the SAE to the sponsor until May 21, 2010.
- f. Subject #023 had diarrhea and the site staff became aware of the event on July 13, 2010, but did not report the SAE to the sponsor until July 15, 2010.
- g. Subject #028 had back pain and the site staff became aware of the event on September 3, 2010, but did not report the SAE to the sponsor until September 17, 2010.

OSI Reviewer Notes: *Dr. O'Sullivan promised corrective actions to prevent these inspectional observations moving forward. Albeit not compliant with protocol reporting requirements for SAEs, all were eventually reported to the sponsor's representative, and should not impact data reliability for this site.*

- c. Assessment of data integrity:** Notwithstanding the observations noted above, the data for Dr. O'Sullivan's site, associated with Study BC1-06 (ALSYMPCA) submitted to the Agency in support of NDA 203971, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. CI#4: – Dag Clement Johannessen
Dep of Oncology, Ullevål University Hospital
Kirkeveien 166 Oslo N-0407
Norway

- a. What was inspected:** The site screened 19 subjects, 17 subjects were enrolled and treated, and 1 subject completed the study. Portions of all subjects' study records were audited in accordance with the clinical investigator compliance program, CP 7348.811. Of the 19 subjects screened all were audited for informed consent procedures and disposition. Of the 17 subjects randomized all records were reviewed for the primary efficacy endpoint source data verification (date of randomization and date of death or the cutoff date of July 15, 2011), randomization, study drug administration, primary reason for not completing all 6 cycles, screening date and protocol violations. Of the 17 subjects randomized, 7 subject's records were reviewed for concomitant medications, AE/SAEs, eligibility and overall protocol adherence. The FDA investigator also assessed test article accountability, monitoring and safety reports, and financial disclosure forms.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data for the subjects enrolled at this site were verified. There was no evidence of under-reporting of AEs. There were minor protocol deviations noted by the FDA field investigator but all deviations were properly reported to the sponsor either by the site or the site monitors. There was one instance where use of a concomitant medication was reported to the sponsor but was not listed in the data listings submitted to NDA 203971. Subject #003 was being treated with Zoladex throughout the study (ongoing after the study), yet it was not found in the data listings submitted to NDA 203971. No Form FDA 483 was issued.
- c. Assessment of data integrity:** Notwithstanding the observations noted above, the data for Dr. Johannessen's site, associated with Study BC1-06 (ALSYMPCA) submitted to the Agency in support of NDA 203971, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

5. Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

340 Changebridge Road
Pine Brook, New Jersey 07058

- a. What was inspected:** The sponsor, Bayer, was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection covered adherence to protocol, and review of the firm's SOPs, monitoring reports, actions related to monitoring deficiencies, Ethics Committee/IRB approvals, completed Form FDA 1572s, communications with the sites, drug accountability, and review of data management from the clinical study sites to the submission of the NDA to the Agency. The FDA field investigator specifically audited subject records (137 subjects) from 18 clinical study sites, and assessed the SAEs and primary efficacy endpoints. The 18 audited sites included the 4 clinical sites listed in the table above; Site 006 (Dr. Svein Inge Helle; 45 subjects), Site 033 (Dr. Christopher Parker; 27 subjects), Site 035 (Dr. Joe O'Sullivan; 32 subjects), and Site 002 (Dr. Dag Clement Johannessen; 17 subjects), and compared copies of subject case report forms (CRFs) against the data listings submitted to NDA 203971 from the October 14, 2010 and July 15, 2011 Clinical Study Reports (CSR).

Additional Clinical Sites Audited:

Foreign Sites (Site #/PI)	Domestic Sites (Site #/PI)
#209/Pittman	#240/Sartor
#028/Billiet	#241/Vogelzang
#170/Damiano	#242/Hudes
#173/Murad	#244/Vanderstreek
#181/Dal'Oglio	#251/Michalski
#155/Kuffer/Schrader	#253/Sandler
#071/Donas	#254/Tomblyn

- b. General observations/commentary:** Records and procedures were clear, and generally well organized. This inspection had to rely on the review of CRFs from PDF files. The sponsor informed the inspector that original CRFs are kept at a contract research organization (b) (4) archive near London, UK. There were no discrepancies between audited subject CRFs and the data listings submitted to NDA 203971; all primary endpoints and SAEs from the CRFs appear to have been correctly reported in the CSR. There was nothing to indicate systemic under-reporting of AEs/SAEs.

Overall site monitoring appeared adequate. The sponsor conducted monitoring activities according to the Monitoring Plan developed prior to the initiation of the clinical trial. Monitoring of each clinical site appeared adequate. The firm identified a number of under-reported AEs at multiple sites and as a result developed and implemented a re-monitoring plan. However, the firm did not prepare any formal written guidance for this additional monitoring plan. According to Bayer representatives, the firm was trying to identify and clean-up the data for the FDA review and did not have enough time to create the formal SOP documents for the re-monitoring. Instead, written guidance was provided on a PowerPoint presentation. Additionally, there was no approval documentation from Bayer upper management specific to this re-monitoring effort. The re-monitoring audit identified a number of missed AEs that were then corrected in study records. The FDA field investigator stated that all AEs that were reported on reviewed CRFs appear to have been adequately reported in the study CSR.

The FDA field investigator issued a Form FDA 483 for the following inspectional observations:

1. Failure to ensure that an investigation was conducted in accordance with the investigational plan and protocols as specified in the IND.
 - a. A supplemental re-monitoring plan was developed and implemented that required additional monitoring visits to be conducted at selected clinical investigators' sites. The original monitoring plan, Version 1.5 dated, May 20, 2008, was not updated or amended to reflect this new three-part re-monitoring plan. Consequently, 10 re-monitoring visit reports were produced that did not follow the directives as set forth in the original written monitoring plan from 8 out of 18 clinical sites selected for review.
 - b. Two SAE expedited reports, from Sites ALG-BC1-06-0005 and ALG-BC1-06-0538, were not submitted by the sponsor to the FDA within the required 15-day requirement.
 - c. One SAE expedited report, from Site ALG-BC1-06-0020, requiring 15 day reporting was not submitted to FDA.
 - d. The monitor failed to document comments for disagreements between the monitor and the principle clinical investigator on the medical evaluation form for Site ALG-BC1-06-0909.

OSI Reviewer Notes: *With respect to item 1.a., the issue of concern is that the sponsor failed to prepare a written modification to the original monitoring plan for procedures and conduct of re-monitoring selected clinical sites for AE reporting. Therefore, while re-monitoring was conducted, and based on those findings the CSR included corrected AE reporting, the FDA field investigator was unable to verify the integrity of the procedures, and standardized conduct of the re-*

monitoring effort. The OSI reviewer, Lauren Iacono-Connors, communicated this inspectional finding to the DOP1 Clinical Reviewer Paul Kluetz and CDTL Ellen Maher in order to obtain feedback on potential impact of AE reporting. Dr. Kluetz informed that he understood the observation but did not feel that there would be an impact on study data reliability because study subjects were randomized and all monitoring and AE re-monitoring remained blinded to subject treatments. Furthermore, there were no signals of AE bias between the active test article and the active control arms. The remaining inspectional observations were not systemic and should not importantly impact data reliability for Study BC1-06.

- c. Assessment of data integrity:** The data generated at this site, as it pertains to Study BC1-06 (ALSYMPCA) were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Notwithstanding the inspectional observations noted above, the findings are that the data from this sponsor submitted to the Agency in support of NDA 203971 appear reliable.

Note: Observations noted for this site are based on preliminary communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Johannessen, Dr. Helle, Dr. Parker, and Dr. O'Sullivan, and study sponsor, Bayer HealthCare Pharmaceuticals Inc., the study data collected appear reliable.

The clinical site of Dr. O'Sullivan (Site 035) and the study sponsor, Bayer, were issued a Form FDA 483 citing inspectional observations and preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). The preliminary classifications for the remaining inspections of Drs. Johannessen, Helle, and Parker are No Action Indicated (NAI).

The four inspected clinical sites revealed nothing to indicate under-reporting of AEs/SAEs. In addition, the primary efficacy endpoint data were verifiable for those sites. The inspection of Dr. O'Sullivan's site (035) found that there were minor protocol deviations noted by the FDA field investigator regarding not always reporting SAEs within the protocol specified timeframe of 24 hours following discovery of the event. Of the 7 SAEs reported late, 5 were reported between 2 and 7 days after site discovery, 1 was reported within two weeks of site discovery, and 1 was reported approximately three months after site discovery. Dr. O'Sullivan promised corrective actions to prevent these inspectional observations moving forward. Though not compliant with protocol reporting requirements for SAEs all were eventually reported to the sponsor's representative, and should not impact data reliability for this site.

The inspection of the sponsor found that they adequately controlled the study. However, there were two issues of concern. First, the inspection had to rely on the review of copies of Case Report Forms (CRFs) in PDF files. The sponsor informed that the original CRFs are kept at a contract research organization (b) (4) archive near London, UK. There were no discrepancies between the audited subject's CRFs and the data listings submitted to NDA 203971, and all primary endpoints and SAEs from the CRFs appear to have been correctly reported in the CSR. There was nothing to indicate systemic under-reporting of AEs/SAEs.

Second, the sponsor conducted monitoring activities according to the Monitoring Plan developed prior to the initiation of the clinical trial. The firm identified a number of under-reported AEs at multiple sites and as a result developed and implemented a re-monitoring plan. However, the firm did not prepare any formal written guidance for this additional monitoring plan. According to Bayer representatives, the firm was trying to identify and clean-up the data for the FDA review and did not have enough time to create the formal SOP documents for the re-monitoring effort. Instead, written guidance was provided to site monitors on a PowerPoint presentation.

Therefore, while re-monitoring was conducted, and based on those findings the CSR included corrected AE reporting, the FDA field investigator was unable to verify the integrity of the procedures, and standardized conduct of the re-monitoring effort. The re-monitoring audit identified a number of missed AEs that were then corrected in study records. The FDA field investigator informed that all AEs that were reported on reviewed subject CRFs appear to have been adequately reported in the study CSR.

The OSI reviewer, Lauren Iacono-Connors, communicated this inspectional finding to the DOP1 Clinical Reviewer Paul Kluetz and CDTL Ellen Maher in order to obtain feedback on potential impact of AE reporting. Dr. Kluetz informed that he did not feel that there would be impact on study data (AE) reliability because study subjects were randomized and all monitoring and AE re-monitoring remained blinded to subject treatments. Furthermore, there were no signals of AE bias between the active test article and the active control arms.

Although regulatory violations were noted for the sponsor, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data for Study BC1-06 in support of this application may be considered reliable based on available information.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{ See appended electronic signature page }

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

/s/

LAUREN C IACONO-CONNORS
04/09/2013

JANICE K POHLMAN
04/09/2013

SUSAN D THOMPSON
04/09/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 8, 2013

To: Elleni Alebachew – Regulatory Project Manager
Division of Oncology Products 1 (DOP 1)
Office of Hematology Oncology Products

From: Michelle Safarik, MSPAS, PA-C – Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on draft labeling (PI) for Xofigo
(radium Ra 223 dichloride) Injection, for intravenous use (Xofigo)
NDA 203971

As requested in your consult dated December 14, 2012, OPDP has reviewed the draft PI for Xofigo. Reference is made to OPDP's comments on the proposed carton and container labeling for Xofigo dated March 7, 2013.

OPDP's comments are based on the draft PI accessed via the DOP 1 eRoom on April 8, 2013, and are included in the proposed, marked-up, substantially complete version of the PI below.

Thank you for your consult.

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MICHELLE L SAFARIK
04/08/2013

**Division of Medical Imaging Products
Medical Officer Consultative Review
March 15, 2013**

NDA	203971
Sponsor	Bayer
Product	Radium-223 dichloride solution for injection (BAY 88-8223) Xofigo (previously known as alpharadin)
Proposed Indication	Treatment of castration-resistant prostate cancer (CRPC) patients with bone metastases
Requesting Office	OODP/DOP1
Requestor	Elleni Alebachew
Request Date	12/19/12
Requested Due Date	4/1/13
Primary Reviewer	Cindy Welsh, M.D.
Team Leader	Lucie Yang, M.D., Ph.D.
Through	Louis Marzella, M.D., Ph.D.
Items Reviewed	Clinical overview, summary of clinical safety, label
Request from Division	Review of the adverse event profile of alpharadin and patient monitoring for the effects of alpharadin Email request: “Adverse events that might be radiation-related...” “Assessment of any exposure risks to administration site personnel and caregivers [e.g., exposure from gamma decay, secondary alpha exposure (if applicable), or potential contamination] is important to ensure the labeling covers these concerns if they are significant...”

DMIP Response:

1. Adverse Event (AE) Profile – long term radiation related:

Based on review of the adverse events as well as the nature of the patient population (end-stage, multiple prior therapies including chemotherapy, external beam radiation therapy to prostate and bone metastases, as well as beta emitters) studied in this phase 3 trial, it is difficult to draw any definitive conclusions regarding the long term toxicity of the product. The follow up time frame was short (only 22 patients had 3 years follow up and only 10 of those patients agreed to survival follow up > 3 years), many of the patients have died, and the adverse event collection requirements, per protocol, after the 12 week post-injection AE reporting period resulted in incomplete data on which to draw conclusions and make recommendations as the AEs were not actively sought and were only reported to the sponsor if the investigator thought the AE was related to the drug product.

DMIP recommends a commitment on the part of the sponsor for long term follow up (at least 5 years or ideally until death) of patients previously enrolled who will

provide consent as well as patients who may be enrolled in their current and future trials. This information will be useful in determining the long term toxicity of the first in class alpha emitter with respect to chronic toxicity and tumor formation, both solid and liquid, of the higher dose organ regions based on dosimetry (bone, marrow, kidneys/urinary system, and intestine) that may impact the safety profile of the product, particularly for less end stage patient populations that may be studied in the future. Of note, one may wish to also follow patients for osteonecrosis, renal failure, and retinal detachment.

2. Exposure Risk to Personnel and Caregivers:

Based upon the physical properties of the product, medical personnel and caregivers should not require special procedures other than those that are traditionally recommended by professional societies for nuclear pharmacists. Simply wearing gloves and hand washing will protect caregivers who may have to interface with bodily fluids.

Consider modifications for clarity and consistency to section 17 of the sponsor’s proposed label.

This consult is not a primary review for approval but a supplementary consulting review that focuses on the radiation aspects of the product.

- Drug Product
- Physics/radiobiology
- Approved Drug Products for Similar Indication with Labeled Dosimetry
- Dosimetry of Radium-223
- Potential Long Term Adverse Events Expected Based on Dosimetry
- Assessment of any exposure risks to administration site personnel and caregivers

Drug Product:

Radium-223 dichloride solution for injection (BAY 88-8223) is a therapeutic alpha-particle emitting pharmaceutical targeted on bone metastases administered according to the following recommendations:

- Dose: 50 kilobecquerel (kBq) (= 0.00135 mCi) per kilogram body weight
- Regimen: every 4 weeks for a regimen consisting of 6 cycles
- Administration: slow intravenous injection (generally up to 1 minute)

Doses of radiation administered activity are given in kilobecquerels (kBq). Conversion of kBq to millicuries (mCi) is shown below:

kBq	5	25	46	50*	80	100	93	125	163	213	250
mCi	0.00014	0.00068	0.00124	0.00135	0.00216	0.00270	0.00251	0.00338	0.00441	0.00576	0.00676

* recommended dose (per kg BW)

Radium-223 dichloride:

- physical half-life: 11.4 days
- target : hydroxyapatite
- high linear energy transfer (LET) resulting in short path length:
 - The maximum range of alpha particles from radium-223 and its daughters is approximately 6.2 cm in air and <100 μm in water/tissue.
 - The range for beta particles is approximately 1 m in air and 50-8000 μm in water/tissue.
 - The alpha particles and most of the beta particles are stopped by the wall of a glass vial. The small fraction of gamma energies emitted, will cause a dose rate of <6 uSv/h per MBq at ten centimeters from the glass vial.

Standard radio-pharmacy practices should provide adequate protection for the health care staff.

The fraction of energy emitted from radium-223 and its daughters is:

Table 1-3 Radium-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

Physics/radiobiology

Some background physics (unit conversion) from ORISE (<http://orise.orau.gov/reacts/guide/measure.htm>) for reference when reading this document:

Radiation Measurements

	Radioactivity	Absorbed Dose	Dose Equivalent	Exposure
Common Units	curie (Ci)	rad	rem	roentgen (R)
SI Units	becquerel (Bq)	gray (Gy)	sievert (Sv)	coulomb/kilogram (C/kg)

From the chart above note that radioactivity or Becquerel would be the activity (in the syringe) administered to the patient while Gray would be the amount of absorbed dose for that patient from that administered dose.

Conversion Equivalence

1 curie = 3.7×10^{10} disintegrations per second	1 becquerel = 1 disintegration per second
1 millicurie (mCi)	= 37 megabecquerels (MBq)
1 rad	= 0.01 gray (Gy)
1 rem	= 0.01 sievert (Sv)
1 roentgen (R)	= 0.000258 coulomb/kilogram (C/kg)
1 megabecquerel (MBq)	= 0.027 millicuries (mCi)
1 gray (Gy)	= 100 rad
1 sievert (Sv)	= 100 rem
1 coulomb/kilogram (C/kg)	= 3,880 roentgens

An overly simplified background radiobiology lesson on what makes an alpha particle special

What is an alpha particle?

An alpha particle is a nucleus of a helium atom that consists of 2 protons and 2 neutrons with a net positive charge and is about 8000 times greater in mass than an electron. An alpha particle is emitted during decay of uranium and radium. An alpha particle is large and heavy compared to an electron or a proton. An alpha particle is the least penetrating (**microns**) of the particles because of its size/weight. In other words, it is so heavy that it can't go far in tissue. An alpha particle can be stopped by a piece of paper.

What is an electron?

An electron is a small negatively charged particle. The mass is very small (~1/837 the mass of a proton). The degree of penetration (**millimeters** or more) is determined by its energy. In general, the higher the energy of the electron, the greater depth the energy penetrates. An electron will pass through a sheet of paper. Electrons of various energies are used in radiation oncology clinics on a daily basis.

What is a proton?

A proton is a positively charged particle that is about 2000 times larger than an electron. In general, the higher the energy of the proton, the greater depth the energy penetrates. A proton will also pass through a sheet of paper. Protons were traditionally used in a few radiation oncology clinics in the U.S. for specific indications (e.g. brain tumors). However, with the improvements in technology, proton machines are smaller and are becoming readily available. The clinical scenarios for use are evolving but mainly are being utilized for prostate cancer treatment.

What is a neutron?

A neutron is particle slightly greater than the size of a proton but without electrical charge. We won't discuss neutrons further.

What is LET?

LET, or linear energy transfer, is the (average quantity due to variability) rate of energy loss along the track of an ionizing particle, usually expressed in keV/um. A high LET

particle, such as an alpha particle, will deposit a greater amount of energy/um as compared to a low LET particle such as an electron. For example:

Radiation Type	LET (keV/um)
Cobalt-60 gamma	0.2
10 MeV proton	4.7
2.5 MeV alpha particle	166

What is RBE?

RBE, or relative biologic effectiveness, is a factor used to compare the biological effectiveness of different types of ionizing radiation. RBE depends upon the radiation quality (LET), radiation dose, number of dose fractions, dose rate, and the biological system/endpoint chosen.

What is a radiation weighting factor?

A radiation weighting factor is a dimensionless multiplier used to place biological effects from exposure to different types of radiation on a common scale with respect to stochastic (probability of occurring rather than severity, for example, a probability that cancer can occur but that when it does, severity is not the issue) late effects.

Radiation Type	Radiation weighting factor (ICRP 2007) for stochastic effects
photons	1
electrons	1
protons	2
Alpha particles	20* stochastic effects 3-7 toxicity (most people use 5)

* Some argue that a smaller value for alpha may be used when considering deterministic effects (such as 3 – 7)

“Alpha-particles for targeted therapy” in Advanced Drug Delivery Reviews Vol 60 Issue 12, 15 September 2008 by George Sgouros

The RBE of alpha-particles therefore depends upon the reference radiation and also, more importantly, upon the biological effect considered. RBE is used as a multiplicative term to adjust the estimated absorbed dose so that it reflects the likelihood or severity of a biological effect. *If the biological end-point is stochastic such as cancer induction, then the RBE is approximately 20. In targeted therapy the relevant biological end-point is not carcinogenesis, but rather, efficacy or toxicity. Such therapeutic end-points are deterministic and the measure associated with them is not probability of occurrence (i.e., risk) but severity of toxicity or level of response. The RBE for such end-points is in the range of 3 to 7.*

Now that we have this background physics knowledge let’s sum up the special qualities of an alpha particle in tissue:

- It is large and charged (2+)
- It has a heavy mass

- It does not travel far and thus deposits its energy quickly and densely (over a short distance)

Approved Products for Similar Indication

Other drugs approved for bone pain palliation are beta emitters:

- **Metastron (strontium-89):**
 - Half life: 50.5 days
 - Maximum beta energy: 1.463 MeV
 - Maximum range in tissue: 8 mm
 - Excretion 2/3 urinary; 1/3 fecal
 - Predominant adverse events:
 - Leukopenia
 - Thrombocytopenia
 - *Note that the label has not been updated or converted to the currently recommended format. There is no post-marketing AE section.*
 - *2012 annual report: nothing to report*
 - *2011 PSUR: The sponsor has received 220 individual case safety reports with a total of 268 adverse drug reactions (ADRs) in connection with the use of Metastron. Ninety of the ADRs were serious, and the remaining 178 ADRs were non-serious. A total of 93 ADRs were unlisted, of which 26 were serious and 67 were non-serious. One of the reports was identified in the scientific literature, and the remaining 219 were received from healthcare professionals.*

Fatal adverse drug reactions were reported in 10 patients and include:

- *Disseminated intravascular coagulation (DIC, gastrointestinal hemorrhage and bone marrow failure,*
- *bone marrow failure,*
- *bone marrow failure, malaise and bone pain,*
- *disseminated intravascular coagulation and bone marrow failure,*
- *bone marrow failure,*
- *death,*
- *death,*
- *multi-organ failure, DIC, subdural hematoma, transaminase increased, pain, and bone marrow failure,*
- *cerebellar hemorrhage, and*
- *shock, depressed level of consciousness and blood pressure decrease.*
- Post-marketing commitments: According to the most recent annual report (SDN 110) received 7/30/12, there are no postmarketing studies or phase 4 commitments to report.

Note: Excerpts from labels deemed relevant by DMIP clearance officials are included in this review. Please note that some excerpts do not include the section texts in their entirety. We refer you to the Metastron and Quadramet labels for the complete text from these sections.

From the Metastron label:

DOSAGE AND ADMINISTRATION

The recommended dose of Metastron is 148 MBq, 4 mCi, administered by slow intravenous injection (1-2 minutes). Alternatively, a dose of 1.5 - 2.2 MBq/kg, 40-60 µCi/kg body weight may be used. Repeated administrations of Metastron should be based on an individual patient's response to therapy, current symptoms, and hematologic status, and are generally not recommended at intervals of less than 90 days...

RADIATION DOSIMETRY

The estimated radiation dose that would be delivered over time by the intravenous injection of 37 MBq, 1 mCi of Strontium-89 to a normal healthy adult is given in Table 4. Data are taken from the ICRP publication "Radiation Dose to Patients from Radiopharmaceuticals"-ICRP #53, Vol. 18, No. 1-4, Page 171, Pergamon Press, 1988.

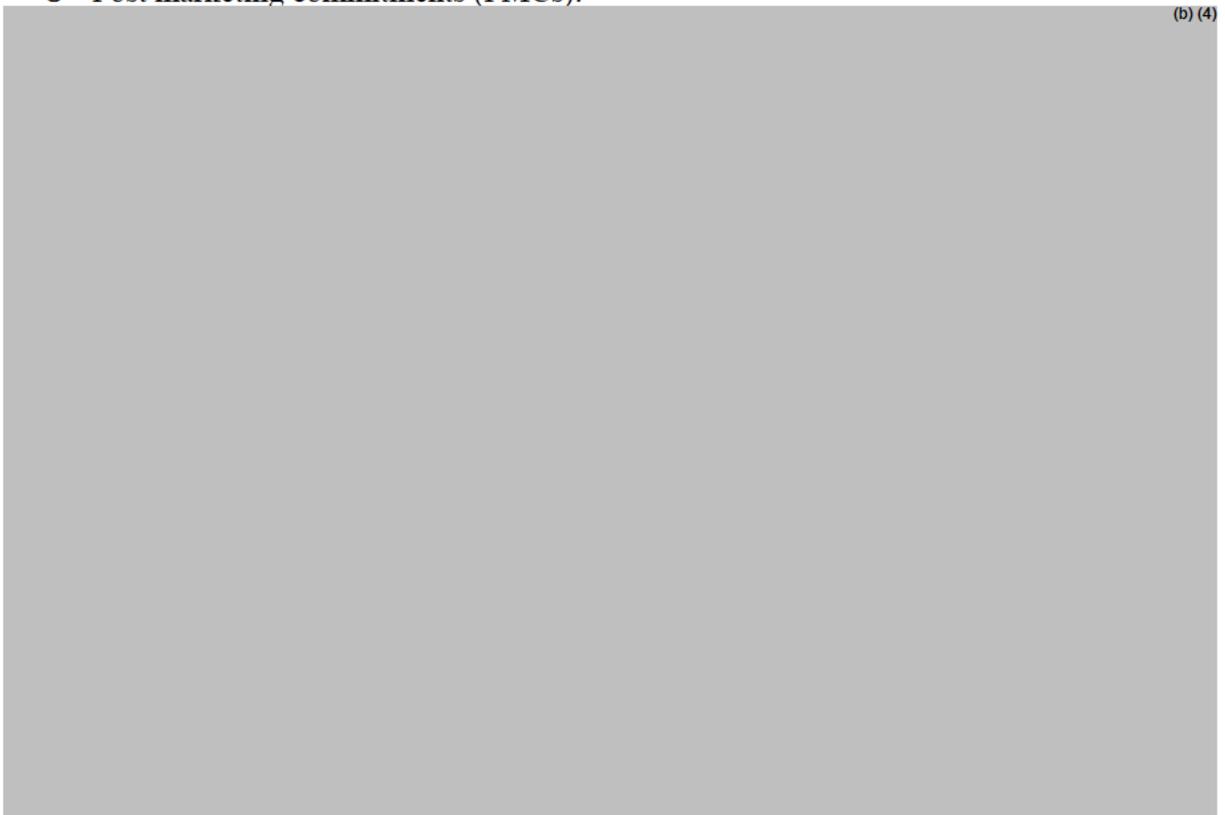
Table 4: Strontium-89 Dosimetry

Organ	mGy/MBq	rad/mCi
Bone Surface	17.0	63.0
Red Bone Marrow	11.0	40.7
Lower Bowel Wall	4.7	17.4
Bladder Wall	1.3	4.8
Testes	0.8	2.9
Ovaries	0.8	2.9
Uterine Wall	0.8	2.9
Kidneys	0.8	2.9

- Quadramet (samarium-153 EDTMP)
 - Half life: 46.3 hours
 - Energy
 - Beta energy: 640-810 keV (average 233 keV)
 - Gamma energy: 103 keV
 - Maximum beta range in tissue: 3 mm
 - Excretion: renal
 - Predominant adverse events:
 - Leukopenia
 - thrombocytopenia
 - *Note that the label has not been updated or converted to the currently recommended format. There is no post-marketing AE section.*
 - *Most recent annual report*

- Hemoglobin ↓ (*IJROBP* 2011; 79: 732-737)
- Thrombocytopenia x2 (*Urologic Oncology: Seminars and Original Investigations* 29 (2011): 670-675)
- Dermatitis (*IJROBP* 2011; 79: 732-737)
- Pancytopenia (fatal) – spontaneous report
 - 46 year old woman with metastatic breast cancer who had prior history of chemotherapy (b) (6)
 - Quadramet 52 mCi on 2/3/11
 - Treated with paclitaxel 2/8/11
 - Patient died (b) (6)
 - Pancytopenia developed sometime between last chemotherapy and date of death

○ Post marketing commitments (PMCs):



From the Quadramet label:

DOSAGE AND ADMINISTRATION

The recommended dose of QUADRAMET® is 1.0 mCi/kg, administered intravenously over a period of one minute through a secure in-dwelling catheter and followed with a saline flush. Dose adjustments in patients at the extremes of weights have not been studied. Caution should be exercised when determining the dose in very thin or very obese patients... Patients should not be released until their radioactivity levels and exposure rates comply with federal and local regulations. The patient should ingest (or receive by i.v. administration) a minimum of 500 mL (2 cups) of fluids prior to injection

and should void as often as possible after injection to minimize radiation exposure to the bladder...

Radiation Dosimetry

The estimated absorbed radiation doses to an average 70 kg adult patient from an i.v. injection of QUADRAMET® are shown in Table 7. The dosimetry estimates were based on clinical biodistribution studies using methods developed for radiation dose calculations by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine. Radiation exposure is based on a urinary voiding interval of 4.8 hours.

TABLE 7 RADIATION ABSORBED DOSES

70 kg ADULT		
Target Organ	Rad/mCi	mGy/MBq
Bone Surfaces	25.0	6.76
Red Marrow	5.70	1.54
Urinary Bladder Wall	3.60	0.097
Kidneys	0.065	0.018
Whole Body	0.040	0.011
Lower large intestine	0.037	0.010
Ovaries	0.032	0.0086
Muscle	0.028	0.0076
Small Intestine	0.023	0.0062
Upper Large Intestine	0.020	0.0054
Testes	0.020	0.0054
Liver	0.019	0.0051
Spleen	0.018	0.0049
Stomach	0.015	0.0041

Reviewer comment: In the dosimetry section below you will find a dosimetry comparison between the beta emitters and radium-223. The most important distinction between the beta emitters and the alpha emitter is the range of activity of the particle – millimeters for the beta products and microns for the alpha product resulting in lower dose to the red marrow and the potential less hematologic toxicity.

In the updates for the beta emitters, the predominant AE is bone marrow related. There do not appear to be secondary malignancies reported (via information available in darrrts). This may be due to the end stage nature of patients who receive this product and their limited survival.

Dosimetry of Radium-223

Clinical Studies included in the NDA package include two small studies evaluating biodistribution and dosimetry [BC1-05(EU) and BC1-08(USA)].

BC1-08 (USA)

Phase 1, open-label, single ascending-dose study to assess safety, pharmacokinetics, biodistribution and radiation dosimetry

Primary Objective

To investigate the safety including long-term radiation toxicity, biodistribution, radiation dosimetry and pharmacokinetics of three intravenous escalating dose levels of Alpharadin

Reviewer comment: It is unlikely that the sponsor completely captured the long term radiation toxicity based upon their definition of AE reporting (voluntary after 12 weeks).

Design/study procedures:

Three dose levels of Alpharadin (50, 100 and 200 kBq/kg [0.0014, 0.0027 or 0.0054 mCi/kg] body weight) were studied in escalating order using a conventional 3+3 dose-escalation study design for oncology products. A single injection was given per patient. An optional second injection of Alpharadin was permitted after the 6 week safety assessment had been performed. Six of the 10 patients received this second injection. Three died (1 at each dose level) and 1 withdrew.

The protocol included a 2 week screening period --> 12 week treatment period -->12 month follow up. Biodistribution, radiation doses and pharmacokinetics were assessed at multiple time points after injection.

All AEs were collected for 12 weeks after injection. *Any AEs after that point were reported only if they came to the investigator's attention and were felt to be related to the drug.*

Results:

Biodistribution

- Ra-223 was rapidly eliminated from the circulation. The median fraction of administered activity remaining in blood:
 - 15 minutes after injection was 10 % (range: 6 - 21 %)
 - 4 h was 2 % (1 - 5 %)
 - 24 h was 0.5 % (0.3 - 1 %)
- The median percentage of injected activity retained in the body the day after injection (23 ± 2 h) was 86 % (range 72-94 %) corresponding to a decay corrected value of 90 % (range 76-99 %) of injected activity.
- The major route of elimination from body was fecal
 - ~24 h after injection, a median of 52 % (range 40-61 %) of total activity present was in the gastrointestinal tract (in large intestine)

- A median of 76 % (range 2-82 %) of decay-corrected administered activity had been excreted from the body by the time of the last whole body count (approximately 7 days after administration).
- Ra-223 enters the intestines, predominantly through the SI wall and remains in the gut content until excretion in the feces with defecation. Almost half of the amount that reached the bowel did so by 10 minutes after administration, increasing to approximately 50 % of administered activity by 24 hours
- The calculated absorbed doses from α -irradiation to:
 - red marrow = 0.9 ± 0.3 mGy/MBq
 - small intestine wall = 5.2 ± 0.7 mGy/MBq
 - kidney = 1.8 ± 0.6 mGy/MBq
 - liver = 1.6 ± 0.5 mGy/MBq

Reviewer comment:

Now that we have the dosimetry of the 2 categories (beta and alpha) of product available, let's compare (keeping in mind that alpha emitters differ in radiation quality (weighting factor – let's use a value of 5 for alpha and 1 for beta) from beta emitters [high LET vs. low LET respectively]). Let's look at red marrow estimations:

- Radium-223 - 0.9 ± 0.3 mGy/MBq
- Metastron - 11 mGy/MBq
- Quadramet - 1.54 mGy/MBq

When evaluating these numbers one must also consider the range of the particle in tissue. Due to the limited range of radium-223 and the lower dose, one would expect decreased red marrow toxicity compared to the beta emitters.

- Radium-223: 2-10 **cell diameters*** (microns)
- Metastron: 8 **mm**
- Quadramet: 3 **mm**

*Oncology Vol 26 No. 4 April 17, 2012 Alpha Particles as Radiopharmaceuticals in the Treatment of Bone Metastases: Mechanism of Action of Radium-223 Chloride (Alpharadin) and Radiation

A Radium-223 example:

*Administered 100 kBq/kg x 70 kg = 7000 kBq
 1000 kBq = 1 MBq so 7000 kBq = 7 MBq
 7 MBq x 5.2 mGy/MBq = 36.4 mGy = 0.0364 Gy x 5 (deterministic α weighting factor) = 0.182 Gy or
 0.0364 Gy x 20 (stochastic α weighting factor) = 0.728 Gy*

A Quadramet example:

*Administered 1 mCi/kg x 70 kg = 70 mCi
 1 mCi = 37 MBq
 70 mCi x 37 MBq/mCi = 2590 MBq
 2590 MBq x 1.54 mGy/MBq = 1398.6 mGy = 1.398 Gy*

A Metastron example:

*Administered 148 MBq (not weight based)
 11 mGy/MBq x 148 MBq = 198 mGy = .198 Gy*

Drug	Marrow dosimetry	Administered dose (70 kg)	Absorbed dose to marrow (Gy)
Radium-223	$\sim 0.9 \text{ mGy/MBq}$	7 MBq	0.182* toxicity risk
Radium-223	$\sim 0.9 \text{ mGy/MBq}$	7 MBq	0.728^ cancer risk
Quadramet	1.54 mGy/MBq	2590 MBq	1.398
Metastron	11 mGy/MBq	148 MBq	0.198

*includes a weighting factor of 5

^ includes a weighting factor of 20

Potential Long Term Adverse Events Expected Based on Dosimetry and Adverse Event Profile from Phase 3 Study

Dosimetry

Based on the dosimetry of Alpharadin, one would anticipate that the long term adverse effects from the radiation component of the product would be related to the higher dosed organs such as the bone, intestine, kidney, and bone marrow. In order to potentially minimize dose to the kidney and intestine, the patient should drink plenty of water to flush the urinary system and use bowel stimulants to encourage bowel elimination as these patients were in pain and most likely on narcotics that slow the bowel.

From experience with radiation therapy, in addition to both solid and liquid tumor formation, the long term effects of the radiation to the high dose organs may be:

- Bone: fracture
- Marrow: various cytopenias
- Kidney/urinary system: renal failure
- Intestine: fistula, volvulus, intussusception/obstruction, necrosis (unlikely at doses administered)

Adverse events

Please remember that AEs were collected for 12 weeks after injection in the dosimetry studies. The remaining AEs have limited reporting as *AEs, after the 12 week reporting period, were reported only if they came to the investigator's attention and were felt to be related to the drug. Additionally, as these were metastatic, hormone refractory, end-stage patients, there is a considerable amount of background AEs as was demonstrated by the placebo arm of the trial.*

Osteonecrosis: was found in 3/600 treated patients - confounded by treatment with prior chemotherapy, bisphosphonate administration, and/or tooth extraction.

- The 3 patients with osteonecrosis were in the group of patients who were treated with radium + docetaxel.

Renal failure: While overall percentages were roughly equivalent, there were 18 patients in the radium arm and 4 in the placebo arm.

Preclinical studies revealed retinal detachment in dogs after a single injection of doses of 150 and 450 kBq/kg BW (3 and 9 times the clinically recommended dose), but not after repeated administration of the clinically recommended dose (i.e. 50 kBq/kg BW once every 4 weeks for a total of 6 injections) in a part of the eye that does not exist in humans.

One may wish to be cognizant of the eye finding when evaluating long term toxicity and post-marketing reports of treatment in humans as more subjects are exposed to the product as well as potential off label usage (larger number of administrations, earlier in disease course, etc.). No cases of retinal detachment were seen in the phase 3 trial (short follow up). There was one case of cataract in a treated patient and one glaucoma case in a placebo patient. Both of these findings may be age related. Cataract formation is a known long term radiation toxicity.

Safety and efficacy of radium-223 dichloride in patients with concomitant Crohn’s disease or ulcerative colitis have not been studied. *Note that in the radiation literature, patients with a history of Crohn’s disease or ulcerative colitis may be at risk for increased toxicity from the radiation and if alternative therapies exist, the patients are counseled in that direction or informed of the potential for increased risk.*

Follow up was up to 2 years for the phase 2 studies and will be up to 3 years in the phase 3 study. *Note that this follow up period is too short to make any statements regarding the long term toxicity of this drug product.*

Update of patients in the trial who have reached follow up benchmarks:

	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%)

One can see from this follow up table that there is insufficient follow up duration on which to draw any conclusions regarding the long term toxicity of this product. The sponsor has a subset of patients who have consented to follow up > 3 years for survival only.

From the submission: “Of the 22 patients who had reached 3 years follow-up as of January 2013, 10 patients have consented to be followed up further for survival, 6 patients died shortly after the 3 years follow-up visit without signing the survival

consent form, and 6 patients have not signed the survival consent form yet. When patients are reconsented for follow-up beyond 3 years, they are only asked to consent to collection of survival information”.

Recommendation: A commitment from the sponsor to obtain long term follow up safety data on remaining patients as well as patients currently enrolled in their clinical studies. Long term toxicity from radiation evolves over years, thus, the sponsor should commit to an extended time frame (minimum 5 years but up to 10 years if feasible). If approved this drug might be used in patients with longer life expectancy than the patients in the phase 3 study.

Assessment of any exposure risks to administration site personnel and caregivers [e.g., exposure from gamma decay, secondary alpha exposure (if applicable), or potential contamination] is important to ensure the labeling covers these concerns if they are significant...

This topic is regulated by the Nuclear Regulatory Commission (NRC) and is usually delegated to the radiation safety officer or health physicist of the administering facility (typically a nuclear medicine department or, in some cases, a radiation oncology department) who performs the task according to NRC guidelines. Typically, there is an information sheet that is given to the patient at the time of discharge with instructions for interactions with family/public, and how to manage bodily fluids, if applicable.

Excerpted from a letter from the NRC to Bayer dated 1/10/13:
“...the U. S. Nuclear Regulatory Commission’s (NRC) staff has reviewed the radiation safety aspects of radium-223 dichloride ($^{223}\text{RaCl}_2$) and determined, based on available information, that licensing under Title 10 of the Code of Federal Regulations (10CFR) Part 35, Subpart E “Unsealed Byproduct Material – Written Directive Required” is appropriate. Under current regulations, physicians who are approved for the use of any beta emitter or any photon-emitting radionuclide with a photon energy less than 150 keV under 10 CFR 35.390 “Training for use of unsealed byproduct material for which a written directive is required” or 10 CFR 35.396 “Training for the parenteral administration of unsealed byproduct material requiring a written directive” can be authorized for the medical use of $^{223}\text{RaCl}_2$ ”. See NRC title 10:
<http://www.nrc.gov/reading-rm/doc-collections/cfr/>

Reviewer comment: For the administration of brachytherapy in the radiation oncology clinic, the physician and the technologist both confirm the identity of the patient by verbally asking the patient their name as well as comparing the patient’s face to a photograph taken at the time of treatment planning or initial consultation.

Handling of alfaradin and radiation protection (from Oncology Vol 26 No. 4 April 17, 2012 Alpha Particles as Radiopharmaceuticals in the Treatment of Bone Metastases: Mechanism of Action of Radium-223 Chloride (Alfaradin) and Radiation)

The ultra-short penetration of alpha particles, the fact that alpha radiation is readily blocked (e.g., by a sheet of paper) along with the favorably low irradiation, allow for ease of handling of alphas and administration through simple plastic tubing. There is no requirement for complex shielding or handling during shipping or administration, and no radiation protection procedures are required. Alphas require no additional specialized detection equipment. Standard equipment for contamination monitoring can be used; no specialized alpha-monitoring equipment is required. For Alpha waste disposal, radioactive waste should be stored for 4 months, and then discarded as normal clinical waste.

Let's look at the labels of other approved therapeutic radioactive drug products -

From Metastron label:

Radiopharmaceuticals should only be used by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Metastron, like other radioactive drugs, must be handled with care and appropriate safety measures taken to minimize radiation to clinical personnel.

From the Quadramet label:

Radiopharmaceutical agents should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

QUADRAMET®, like other radioactive drugs, must be handled with care, and appropriate safety measures must be taken to minimize radiation exposure of clinical personnel and others in the patient environment.

Special precautions, such as bladder catheterization, should be taken with incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen, and the patient's environment. Urinary excretion of radioactivity occurs over about 12 hours (with 35% occurring during the first 6 hours). Studies have not been done on the use of QUADRAMET® in patients with renal impairment.

INFORMATION FOR PATIENTS

Patients who receive QUADRAMET® should be advised that for several hours following administration, radioactivity will be present in excreted urine. To help protect themselves and others in their environment, precautions need to be taken for 12 hours following administration. Whenever possible, a toilet should be used, rather than a urinal, and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely and patients should wash their hands thoroughly. If blood or urine gets onto

clothing, the clothing should be washed separately, or stored for 1-2 weeks to allow for decay of the Sm-153...

From the Iodine-131 label:

2.1 Radiation Safety

Sodium iodide I-131 solution emits radiation and must be handled with safety measures to minimize inadvertent radiation exposure to clinical personnel and patients [see *Warnings and Precautions (5.7)*].

- Radiopharmaceuticals should be used only by or under the direction of physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.
- Wear waterproof gloves during the entire sodium iodide I-131 solution handling and administration procedure.
- Maintain adequate shielding during the radiation-emitting life of the product.
- Measure the patient dose using a suitable radioactivity calibration system immediately prior to administration.

5.7 Radiation Exposure Risk to Other Individuals

Unwanted radiation exposure can occur from handling and administration of radiopharmaceuticals or from contaminated waste products, including urine and feces. Follow safe administration instructions to minimize unnecessary radiation exposure to patients and health care workers [see *Dosage and Administration (2.1)*]. Instruct patients on how to reduce unnecessary radiation exposure to others, especially family members following treatment.

Review the most recent professional society guidelines and publications that describe the procedures for the safe use of sodium iodide I-131 therapy to minimize radiation toxicity risks to patients, radiation exposure risks to other individuals, and environmental radiation contamination risks.

17 PATIENT COUNSELING INFORMATION

Review the most recent professional society guidelines and publications that describe important components of the patient counseling process.

- Discuss the measures to minimize inadvertent radiation exposure to the patient, members of the patient’s household, the public, and the environment.

Proposed **radium-223** labeling:

2.2 Instructions for use / handling



2 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CYNTHIA A WELSH
04/03/2013

LUCIE L YANG
04/03/2013

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	203971
Brand Name	Xofigo
Generic Name	Radium-223 dichloride (Alpharadin)
Sponsor	Bayer Healthcare Pharmaceuticals
Indication	Castration-resistant prostate cancer patients with bone metastases
Dosage Form	Injection/IV
Drug Class	Targeted alpha-pharmaceutical
Therapeutic Dosing Regimen	50 kBq/kg
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Not determined
Submission Number and Date	SDN 001, 14 Dec 2012
Review Division	DOP1

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

We conclude that the current QT study is inconclusive in its objective to adequately characterize the Xofigo's liability to prolong the QT interval. We note the following limitations in the trial design:

- ECGs were only collected up to 4-6 hours post-dose. The sampling time points were inadequate to cover the potential delayed effect over the dosing interval (i.e., 24 hours)
- No time-matched PK samples were obtained.

We also note that recommendations to address these limitations were previously conveyed to the Sponsor in our previous review (5/05/2011).

1.2 QT-IRT RECOMMENDATIONS

- The Sponsor should repeat an ECG assessment with time-matched ECG and PK sampling to cover immediate and delayed effects with Xofigo as per our previous recommendations. The QT-IRT would like to review the protocol prior to study initiation.

- From the QT-IRT's perspective, this can be as a post-marketing requirement because there were no AEs of concern in the clinical program and we did not observe any large effects on the QTc interval in the current study.

2 BACKGROUND

2.1 PRODUCT INFORMATION

Alpharadin Injection, a targeted alpha-pharmaceutical (alpha emitting pharmaceutical) is being developed for the treatment of bone metastases. Alpharadin is a ready-to-use, sterile solution of radium-223 chloride ($^{223}\text{RaCl}_2$) for intravenous injection.

2.2 MARKET APPROVAL STATUS

Xofigo is not approved for marketing in any country

2.3 PRECLINICAL INFORMATION

Reviewer's comments: hERG studies have not been conducted. Sponsor states that Alpharadin does not affect ECG intervals in conscious telemetered dog studies.

2.4 PREVIOUS CLINICAL EXPERIENCE

From 2.7.4

A summary of the study descriptors and main efficacy data generated from the clinical trials is presented in Table 1

Table 1: Radium-223 dichloride efficacy studies: Overview

Study no.	Study design	Key objectives	Treatment dose and regimen
Phase 1			
ATI-BC-1	Open-label, dose-escalation study with repeated dosing Part Ia (single dose) Part Ib: (retreatment and multiple dosing)	Primary: safety, tolerability and identify possible DLTs of radium-223 dichloride. Secondary: PK /blood clearance of radioactivity, effect on ALP	Part Ia: single doses: Actual: 46, 93, 163, 213 and 250 kBq/kg BW Part Ib: 5 x 50 kBq/kg at 3 week intervals and 2 x 125 kBq/kg BW at 6-week intervals
BC1-05	Open-label	Primary: safety, PK, radiation dosimetry, and biodistribution	Radium-223 dichloride 100 kBq/kg x 2 at 6 week intervals
BC1-08	Open-label, single ascending-dose	Primary: safety, PK, bio-distribution and radiation dosimetry	Single doses: 50 or 100 or 200 kBq/kg BW increased by cohort Note: 50 kBq/kg once 6 weeks after first administration optional
Phase 2			
BC1-02	Double-blind, exploratory, randomized (1:1), placebo-control	Primary: time to new SRE and change in bone-ALP values	Radium-223 dichloride 50 kBq/kg BW vs placebo 4 injections at 4-weeks intervals
BC1-03	Double-blind, randomized, dose-response	Primary: investigate dose-response relationship for palliation of bone pain. Secondary: find the most efficacious dose of radium-223 dichloride with an acceptable safety profile	4 dose groups: 5, 25, 50 or 100 kBq/kg BW administered as a single injection Note: Second injection, set to 50 kBq/kg BW could be administered after Wk 16 at discretion of investigator
BC1-04	Double-blind, randomized, parallel group, repeat dose, dose-finding	Primary: compare proportion of patients with a protocol defined PSA response	3 dose groups: 25, 50 or 80 kBq/kg 3 injections at 6-weeks intervals
Phase 3			
BC1-06	Double-blind, placebo-controlled, randomized 2:1	Primary: Overall survival Secondary: Time to ALP progression; ALP response; Time to SRE; ALP normalization; Time to PSA progression; PSA response; FACT-P; QoL	Radium-223 dichloride 50 kBq/kg BW vs placebo 6 injections at 4-weeks intervals Note: Post-interim analysis Investigators could offer placebo patients still participating in the study and eligible a course of radium-223 dichloride

ALP = alkaline phosphatase; BW = body weight; CRPC = castration refractory or resistant prostate cancer; DLT = dose-limiting toxicity; FACT-P = Functional Assessment of Cancer Therapy - Prostate;; kBq = kilobecquerel; PK = pharmacokinetics; PSA = prostate specific antigen; QoL = quality of life; SRE = skeletal-related events

Source: eCTD, 2.7.4, table 1-2, page 12

Reviewer's comments: no seizures, sudden cardiac death or ventricular arrhythmias were reported. No clinically relevant ECGs were reported.

2.5 CLINICAL PHARMACOLOGY

Appendix 5.1 summarizes the key features of alpharadin's clinical pharmacology.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 67521. The sponsor submitted the study report A58800 (including sub-study BC1-06) for Xofigo, including electronic datasets and waveforms to the ECG warehouse.

3.2 TQT STUDY

3.2.1 Title

Study A58800: “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”

Sub-study BC1-06: “Sub-study for Clinical Evaluation of QTc Interval Prolongation in a Subgroup of the Patient Population”

3.2.2 Protocol Number

BC1-06

3.2.3 Study Dates

Study A58800: 12 June 2008 – 15 July 2011*

* Study ongoing as of 1 Feb 2011

3.2.4 Objectives

The primary objective of the BC1-06 ECG substudy was to obtain information regarding any clinically relevant effects of Alpharadin on QTc prolongation and proarrhythmic potential.

The secondary endpoints were to assess the:

- Analysis of central tendencies of QRS and PR interval, HR and QTcB duration
- New onset of ECG abnormalities
- Description of patients with absolute QT values above 500 msec
- Categorical Analyses of QTc values
- Absolute QTc prolongation:
 - QTc greater than 450 msec
 - QTc greater than 480 msec
 - QTc greater than 500 msec
- QTc change from baseline:
 - QTc greater than 30 msec
 - QTc greater than 60 msec
- Categorical analysis of HR values:
 - HR greater than 100 bpm and an increase from baseline of more than 20 bpm
 - HR less than 50 bpm and a decrease from baseline of more than 20 bpm
- Categorical analysis of PR values:
 - PR above 220 msec and more than 10 percent change from baseline
- Categorical analysis of QRS values:
 - QRS above 120 msec and more than 10 percent change from baseline

Source: Sponsor’s study report, appendix 16.1.9.4, pages 14-15.

3.2.5 Study Description

3.2.5.1 Design

This is a two-arm parallel design with six dosing occasions. Each dosing occasion was followed by a 4-week washout period.

3.2.5.2 Controls

The sponsor used a placebo control.

3.2.5.3 Blinding

All treatment arms were administered blinded.

3.2.6 Treatment Regimen

3.2.6.1 Treatment Arms

There were two treatment arms: intravenous administrations of Xofigo or best standard of care (BSoC) and matching placebo (normal saline).

3.2.6.2 Sponsor's Justification for Doses

The proposed dosing regimen for the Phase III trial is 50 kBq/kg b.w. every four weeks for a 6-month treatment period (6 injections). In the completed Phase I safety, tolerability and pharmacokinetic clinical study (ATI-BC-I), prostate or breast carcinoma patients with skeletal metastases were administered Alpharadin in single doses of 46, 93, 163, 213 or 250 kBq/kg b.w. (25 subjects) or multiple doses of five administrations of 50 kBq/kg b.w. at three week intervals (3 subjects) or two administrations of 125 kBq/kg b.w. at six week intervals (3 subjects). In the completed Phase II study, 64 hormone-refractory prostate cancer patients with painful skeletal metastases referred for external radiotherapy, received four injections of 50 kBq/kg b.w. Alpharadin (33 subjects) or placebo (31 subjects) at four weeks intervals, to examine the effects of Alpharadin on biomarkers of disease progression, skeletal related events, pain palliation, survival and safety parameters.

The efficacy and safety data from Phase II support the selection of a dosing regimen of multiple doses of 50 kBq/kg b.w. of Alpharadin given at four weeks intervals. Clinically relevant efficacy was observed, with only minor side effects and no indication of cumulative effect on bone marrow suppression upon multiple administration of Alpharadin. Currently, no data are available to assess if similar effects could be achieved with a dose lower than 50 kBq/kg b.w. However, HRPC patients have a poor prognosis with a median survival of only 1-2 years and since no curative treatment is available it is important that the dose administered is effective and well tolerated. The highly promising phase II results for Alpharadin make it a priority to make this treatment available to larger patient populations as soon as possible. Thus, the data to support selection of individual dose is considered adequate, with only minor side effects being seen with this dose and no increase in frequency or severity of adverse events being observed upon multiple administrations.

In the Phase II study BC 1-02, the duration of the benefit appeared to be related to duration of treatment, consequently the treatment period is planned to be extended in Phase II to prolong the anticipated benefit to the patients. A 6-month treatment period (6 administrations) is reasonable since it is comparable to the treatment duration of other approved treatments used in this patient group. Blood samples will be assessed before dosing to ensure normal hematology. The study will be supervised by an independent data monitoring committee (IDMC).

Reviewer’s Comment: The review of the protocol for this study indicates: “The selected dose appears to be reasonable. It reflects the dose tested in the currently on-going phase 3 clinical trials” However, since pharmacokinetic exposures were not collected in this sub-study, the dose cannot be evaluated for comparison of exposures between what was studied and the intended clinical population. See the protocol review for IND 67521, dated March 2011 for further details on the protocol recommendations.

3.2.6.3 Instructions with Regard to Meals

Reviewer’s Comment: Not applicable since alpharadin will be administered as an i.v. infusion.

3.2.6.4 ECG and PK Assessments

PK Assessments:

No PK assessments were made during trial A58800.

ECG Assessments:

	Screening	Prior to Injection			After Injection						Follow-up		Treatment Discontinuation If relevant
		≥1 hr	-45 min	-30 min	≤1 min	30 min*	1 hr*	2 hr*	3 hr*	4-6 hrs	4 wks	24 wks	
ECG performed according to ECG substudy protocol addendum:													
12-lead ECG **		X	X	X	X	X	X	X	X	X			
ECG performed according to main protocol BC1-06:													
12-lead ECG	X										X	X	X

* (+/- 15 min)

** Performed after the first administration cycle of Alpharadin.

Reviewer’s Comment: Exclusion of PK sampling was done against the Agency’s recommendations. See clinical pharmacology comments in the protocol review for IND67521, dated March 5, 2011. This gives the reviewer no information regarding exposure-response at the studied dose.

ECGs were only collected four hours after the first dose administration. This is not a sufficient time interval for evaluating the potential for QT prolongation as for some drugs there is a delay in the effect. ECGs were taken after the first administration of alpharadin based on the Agency’s recommendations in the protocol review.

3.2.6.5 Baseline

The sponsor used a within-day baseline.

3.2.7 ECG Collection

All ECGs were collected in triplicate. A copy of all ECG measurements was to be sent electronically to the core laboratory for interpretation. Analysis of the ECG was performed by a Board-Certified independent cardiologist in a blinded manner.

3.2.8 Sponsor's Results

3.2.8.1 Study Subjects

A total of 29 patients were included (21 receiving Alparadin and 8 receiving placebo).

Two patients 017026 (placebo) and 017030 (Alparadin) had a history of cardiac arrhythmia, which could be considered as a violation of exclusion criterion No. 3.

Four patients, 001039 (Alparadin), 017026 (placebo), 148019 (Alparadin) and 148021 (placebo) had been treated with concomitant medication that could prolong the QT interval and/or induce Torsade de Pointes (TdP).

Table 2: Patients treated with drugs that prolong the QT interval or induce TdP

Patient ID	Treatment	Drug Generic Name	Indication	Risk
001039	Alparadin	Escitalopram	Depression	Possible risk of TdP
017026	placebo	Amiodarone	Cardiac arrhythmia	Risk of TdP
148019	Alparadin	Ketoconazole	Prostata ca	Conditional TdP risk
148021	placebo	Doxepin	Depression	Conditional TdP risk
		Amitriptyline	Depression	Conditional TdP risk
		Ciprofloxacin	Infection urinary	Conditional TdP risk

Source: CSR, Table 3

3.2.8.2 Statistical Analyses

3.2.8.2.1 Primary Analysis

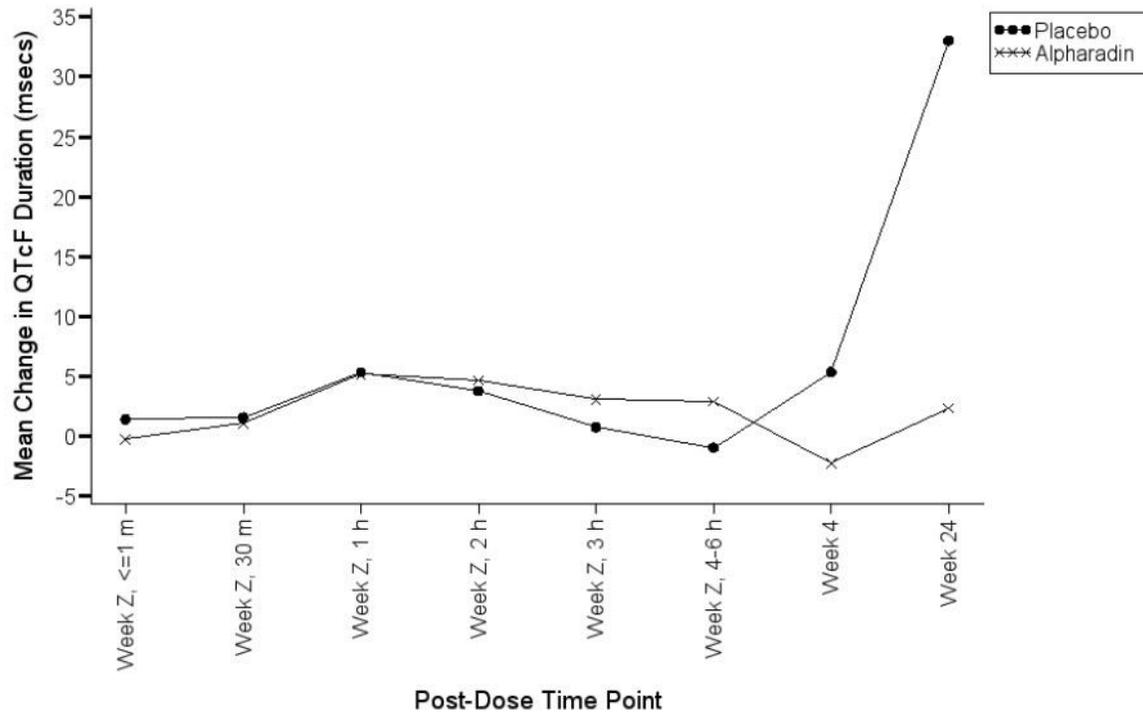
The sponsor found that there was no significant QT prolongation:

On the basis of the data, there is no evidence that intravenous injection of Alparadin at a dose of 50 kBq/kg prolongs the QTc interval. The data shows both increases and decreases from baseline. In the Alparadin group, the highest mean increase in QTcF was 5.2±6.5 msec at the one hour post-injection time point (the upper limit of the 90% Confidence Interval (CI) of the mean change from baseline in QTcF was 7.6 msec). This was almost identical to the results in the placebo group during the intensive ECG monitoring day. The highest mean increase in QTcF was 5.4±4.5 msec occurring at the one hour post-injection time point (the upper limit of the 90% confidence interval of the mean change from baseline in QTcF was 8.4 msec).

Source: Sponsor's study report, appendix 16.1.9.4, page 23.

Figure 1: Sponsor's QTcF Timecourse

Plot of Mean Change from Baseline in QTcF Duration by Time Point
Safety Population



Source: Sponsor's study report, appendix 16.1.9.4, Figure 1.3.1.

Reviewer's Comments: This result agrees with the FDA analysis. See section 4.2.

3.2.8.2.2 Assay Sensitivity

The sponsor did not use a positive control and hence did not perform an assay sensitivity analysis.

3.2.8.3 Safety Analysis

There were no clinically relevant morphological changes in the ECGs. No adverse events as per ICHE14 guidance were reported.

3.2.8.4 Clinical Pharmacology

No pharmacokinetic concentrations were collected during study A58800. Therefore, no pharmacokinetic or exposure-response analyses were conducted by the sponsor.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcB distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcB), and the interaction term of RR and correction type. The slopes of QTcF and QTcB versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 3, it appears that QTcF had smaller absolute slopes than QTcB. Therefore, QTcF is a better correction method for the study data.

Table 3: Comparison of QTcF and QTcB Using the Mixed Model

Treatment Groups	Slope of QTcB	Slope of QTcF	P-value
Xofigo	-0.0648	0.0138	0.0000
Placebo	-0.0703	0.0155	0.0000
All	-0.0673	0.0138	0.0000

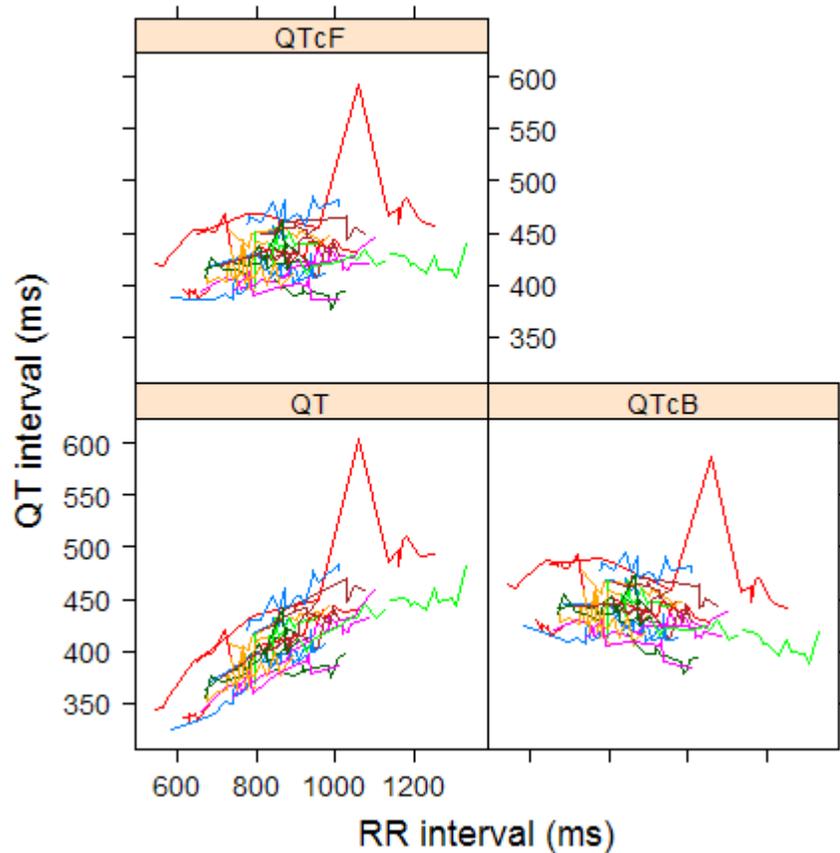
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 4, it appears that QTcB and QTcF have approximately equivalent MSSS. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcB		QTcF	
	N	MSSS	N	MSSS
Xofigo	21	1.5010	21	1.6029
Placebo	8	0.0144	8	0.0117
All	29	1.0909	29	1.1639

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



4.2 STATISTICAL ASSESSMENTS

4.2.1 QTc Analysis

4.2.1.1 The Primary Analysis for Xofigo

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as a fixed effect and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in Table 5.

Table 5: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group A: Xofigo x 6 days

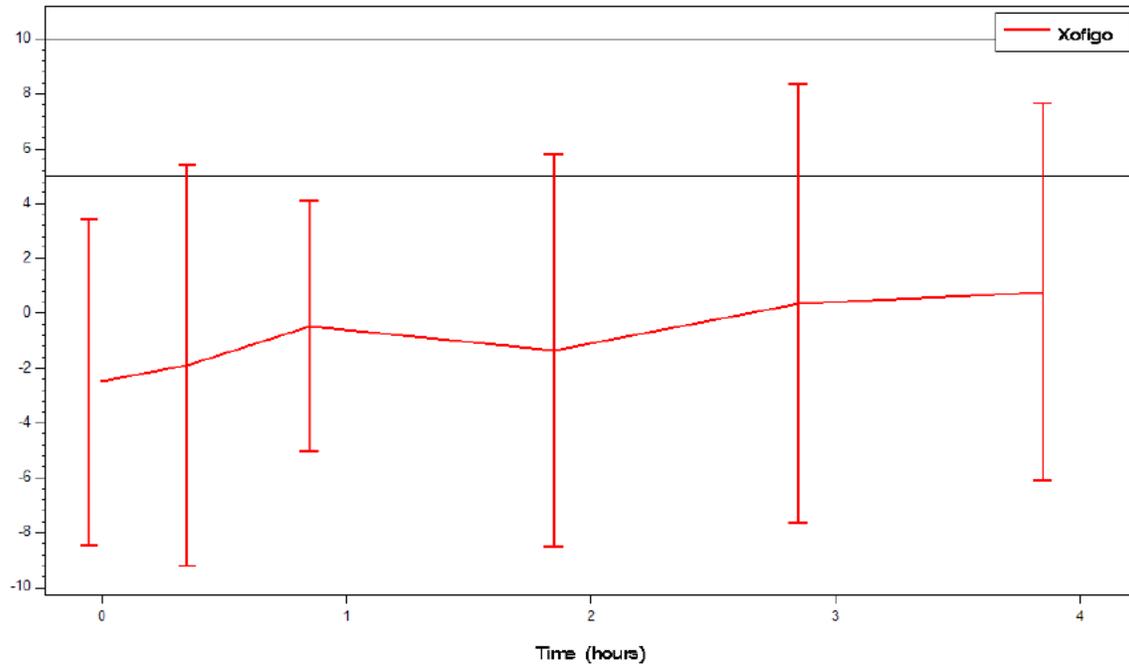
Time	Δ QTc: Xofigo			Δ QTc: Placebo			$\Delta\Delta$ QTc		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.1	21	-0.5	1.8	8	2.1	2.9	8	-2.5	(-8.5, 3.4)
0.5	21	0.8	2.2	8	2.7	3.6	8	-1.9	(-9.2, 5.4)
1	21	5.1	1.4	8	5.6	2.3	8	-0.5	(-5.0, 4.1)
2	21	4.1	2.1	8	5.4	3.5	8	-1.4	(-8.5, 5.8)
3	21	2.6	2.4	8	2.2	3.9	8	0.3	(-7.7, 8.3)
4	21	2.1	2.0	8	1.3	3.4	8	0.8	(-6.1, 7.6)

The largest upper bound of the 2-sided 90% CI for the mean difference between Xofigo and placebo was 8.3 ms.

4.2.1.2 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for Xofigo.

Figure 3: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



All CIs are unadjusted.

4.2.1.3 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. No

subject's QTcF was above 480 ms in the Xofigo treatment group. There is 1 (12.5%) subject who experienced QTcF greater than 480 ms in the placebo group.

Table 6: Categorical Analysis for QTcF

Treatment Group	N	Value <= 450 ms	450 ms < Value <= 480 ms	480 ms < Value <= 500 ms
Xofigo	21	16 (76.2%)	5 (23.8%)	0 (0.0%)
Placebo	8	4 (50.0%)	3 (37.5%)	1 (12.5%)

Table 7 lists the categorical analysis results for Δ QTcF. All subjects' change from baseline was below 30 ms.

Table 7: Categorical Analysis of Δ QTcF

Treatment Group	N	Value <= 30 ms
Xofigo	21	21 (100%)
Placebo	8	8 (100%)

4.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 8. The largest upper limit of the 90% CI for the HR mean difference between Xofigo and placebo is 4.6 bmp.

The outlier analysis results for HR are presented in Table 9. There is 1 (12.5%) subject who experienced HR greater than 100 ms in the placebo group.

Table 8: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group A: Xofigo x 6 days

Time	Δ HR: Xofigo			Δ HR: Placebo			$\Delta\Delta$ HR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.1	21	-1.5	0.8	8	-3.3	1.4	8	1.8	(-1.0, 4.5)
0.5	21	-3.0	0.9	8	-4.1	1.4	8	1.0	(-1.8, 3.9)
1	21	-2.3	1.2	8	-3.0	1.9	8	0.7	(-3.2, 4.6)
2	21	0.2	1.6	8	5.5	2.6	8	-5.3	(-10.5, -0.1)
3	21	-0.8	1.7	8	7.6	2.8	8	-8.4	(-14.1, -2.7)
4	21	-1.1	1.8	8	3.2	2.9	8	-4.3	(-10.1, 1.5)

Table 9: Categorical Analysis for HR

Treatment Group	N	HR < 100 ms	HR >= 100 ms
Xofigo	21	21 (100%)	0 (0.0%)
Placebo	8	7 (87.5%)	1 (12.5%)

4.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. One subject (ID: 017030) with a history of ischemic heart disease, arrhythmia and bradycardia, was removed from the data set. The sponsor removed this subject from the PR analysis as well. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper limit of the 90% CI for the PR mean difference between Xofigo and placebo is 14.5 ms.

The outlier analysis results for PR are presented in Table 11. There are 4 (20.0%) subjects in the Xofigo group and 3 (37.5%) subjects in the placebo group who experienced PR greater than 200 ms.

Table 10: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group A: Xofigo x 6 days

Time	Δ PR: Xofigo			Δ PR: Placebo			$\Delta\Delta$ PR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.1	20	0.8	1.3	8	-0.8	2.1	8	1.5	(-2.7, 5.8)
0.5	20	2.8	1.4	8	-0.3	2.2	8	3.1	(-1.4, 7.6)
1	20	4.0	1.4	8	-0.0	2.3	8	4.0	(-0.5, 8.6)
2	20	3.1	1.3	7	-2.7	2.2	7	5.8	(1.3, 10.3)
3	20	4.8	1.2	7	-5.6	2.1	7	10.3	(6.2, 14.5)
4	20	3.1	1.1	8	-1.0	1.8	8	4.1	(0.5, 7.7)

Table 11: Categorical Analysis for PR

Treatment Group	N	PR < 200 ms	PR >=200 ms
Xofigo	20	16 (80.0%)	4 (20.0%)
Placebo	8	5 (62.5%)	3 (37.5%)

4.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limit of the 90% CI for the QRS mean difference between Xofigo and placebo is 4.3 ms.

The outlier analysis results for QRS are presented in Table 13. There are 3 (14.2%) subjects in the Xofigo group and 1 (12.5%) subjects in the placebo group who experienced QRS interval greater than 110 ms.

Table 12: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group A: Xofigo x 6 days

Time	Δ QRS: Xofigo			Δ QRS: Placebo			$\Delta\Delta$ QRS		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.1	21	-1.9	0.9	8	-1.2	1.5	8	-0.8	(-3.8, 2.3)
0.5	21	-0.4	0.9	8	0.2	1.5	8	-0.6	(-3.5, 2.3)
1	21	0.1	0.9	8	-0.8	1.5	8	0.8	(-2.1, 3.8)
2	21	1.3	0.6	8	-1.1	1.0	8	2.4	(0.5, 4.3)
3	21	0.7	0.7	8	-0.3	1.1	8	1.0	(-1.3, 3.2)
4	21	0.1	1.0	8	-0.5	1.6	8	0.6	(-2.6, 3.7)

Table 13: Categorical Analysis for QRS

Treatment Group	N	QRS < 110 ms	QRS \geq 110 ms
Xofigo	21	18 (85.7%)	3 (14.3%)
Placebo	8	7 (87.5%)	1 (12.5%)

4.3 CLINICAL PHARMACOLOGY ASSESSMENTS

No pharmacokinetic concentrations were collected during study A58800. Therefore, no pharmacokinetic or exposure-response analyses could be conducted by the reviewer.

4.4 CLINICAL ASSESSMENTS

4.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

4.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. According to ECG warehouse statistics less than 0.3 % of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

4.4.3 PR and QRS Interval

Four subjects experienced postbaseline PR >200 ms, two of them at baseline i.e, subject 097013 had a baseline PR of 272 ms. No postbaseline PR were > 10% from baseline values. Three subjects had QRS > 110 ms at baseline.

5 APPENDIX

5.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Dosing regimen in currently ongoing Phase 3 study: 50 kBq/kg given 6 times at 4 week intervals
Maximum tolerated dose	<p>A human maximum tolerated dose has not been defined. Dose selection for Phase 3 study was based on biologically effective dose.</p> <p>The following single dose toxicity studies have been performed: Mice: doses of 1,250, 2,500, and 3,750 kBq/kg (0.034, 0.068, 0.101 mCi/kg) Rats: 1,027, 2,054, and 3,081 kBq/kg (0.028, 0.056, 0.083 mCi/kg) Dogs: 50, 150 and 450 kBq/kg (0, 0.0014, 0.0040 and 0.012 mCi/kg)</p> <p>In the single dose toxicity studies in mice and rats the lowest doses evaluated (above 1,000 kBq/kg [0.027 mCi/kg) were more than 20-fold higher than the individual clinical dose used in Phase 3; adverse effects were observed at the lowest dose investigated, no NOAEL (No Observable Adverse Effect Level) was established. However, a severely toxic dose to 10% of animals was established at 2,500 kBq/kg (0.068 mCi/kg) for the mouse and 2,054 kBq/kg (0.056 mCi/kg) for the rat.</p> <p>The single dose toxicity study in dogs concluded that a single intravenous injection radium-223 can be administered safely to normal dogs at doses of 50 kBq/kg and 150 kBq/kg, while dose limiting myelotoxicity was observed at the 450 kBq/kg dose.</p> <p>The following repeat dose toxicity studies have been performed: Rats: The study evaluated both single doses of 20, 80, 325, 650 or 1,300 kBq/kg (0.00054, 0.0022, 0.0088, 0.035 mCi/kg) and 4 intermittent doses of 20, 325 or 650 kBq/kg (0.00054, 0.0088, 0.018 mCi/kg) given at 4-weeks intervals. Based on the reduction observed in white blood cell count, the NOEL (No Observed Effect Level) was established to be 20 kBq/kg (0.00054 mCi/kg) in the study. Rats: 25, 50 or 100 kBq/kg (0.00068, 0.0014 or 0.0027 mCi/kg) was administered every 4 weeks for a total of 12 injections. Some non-neoplastic changes were found in bone and related tissues (depletion/fibrosis, osteocyte depletion and decreased cellularity of marrow) in a number of Alpharadin treated rats also at the low dose level 25 mg/kg. None of these pathological changes were found in the control animals. Based on these findings a NOAEL could not be established. Dogs: 50 kBq/kg once every 4 weeks for 6 treatments. This study demonstrated that Alpharadin can be safely administered to normal dogs at a repeated intermittent dose of 50 kBq/kg at monthly intervals for a total of 6 treatments without significant adverse clinical effects.</p>

Principal adverse events	<p>During the study periods, adverse events (AEs) were reported in 276 of 292 patients (95%) who received Alpharadin in the Phase 1 and 2 studies which have been reported. The doses in these studies ranged from 5 to 250 kBq as single dose and 25 to 125 kBq/kg as multiple doses up to 250 kBq/kg total dose. Overall, the system organ classes with most adverse events were the Gastrointestinal disorders, General disorders and administration site disorders, and Musculoskeletal and connective tissue disorders. This pattern is consistent across all studies including the placebo group in study BC1-02. The adverse event terms reported by most Alpharadin patients across the studies were nausea (97 patients; 33%), bone pain (89 patients; 30%), diarrhoea (77 patients; 26%), fatigue (76 patients; 26%), anaemia/decreased haemoglobin (71 patients; 24%), constipation (60 patients; 21%) and vomiting (59 patients; 20%).</p> <p>Of the 292 patients exposed to Alpharadin in the Phase 1 and 2 studies which have been reported, 135 patients received a single administration at doses ranging from 5 to 250 kBq/kg (0.00014 to 0.0068 mCi/kg). Hundred-and-fifty-seven (157) patients received multiple (up to five) administrations of Alpharadin. The multiple dose levels ranged from 25 to 125 kBq/kg (0.00068 to 0.0034 mCi/kg) and were administered once every 3, 4, or 6 weeks.</p> <p>Based on the biodistribution and route of elimination, possible target organs for radium 223 toxicity are bone marrow and the gastrointestinal tract.</p> <p>The nature and frequency of AEs or SAEs reported in the gastrointestinal disorders system organ class in the studies to date were as can be expected in these patient populations, particularly in patients taking opioid analgesics where nausea and constipation are common adverse reactions. However, data indicate that nausea, vomiting, constipation, and diarrhoea may be associated with Alpharadin.</p> <p>Myelosuppression, mainly neutropenia, in association with treatment with Alpharadin appears mild/moderate and reversible. There has been no increase in neutropenia observed upon multiple administrations, suggesting haematologic effects induced by intermittent doses of Alpharadin are not cumulative.</p> <p>Anaemia (as well as low absolute neutrophil count (ANC), thrombocytopenia and low haemoglobin/haematocrit) is a common laboratory finding in cancer patients, and is often present with bone disease involvement. Radiation, which often is given for palliation to cancer patients with bone metastases, can also cause anaemia and bone marrow suppression. However; not only would some</p>
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	patients be expected to develop low haemoglobin due to progression of disease, but also low haemoglobin can occur in patients receiving Alpharadin. As such, low haemoglobin has been observed in a number of patients in the clinical trials and should be expected. Based on data from the Phase 2 studies, in particular BC1-04, there is a suggestion that a mild dose-related anaemia may be caused by Alpharadin.	
Maximum dose tested	Single Dose	250 kBq/kg (0.0068 mCi/kg)
	Multiple Dose	80 kBq/kg (0.0022 mCi/kg) given 3 times at 6 week intervals (total dose of 240 kBq/kg) 50 kBq/kg (0.0014 mCi/kg) given 6 times at 4 week intervals (total dose of 300 kBq/kg) 125 kBq/kg (0.0034 mCi/kg) given 2 times at 6 w intervals (total dose of 250 kBq/kg)
Exposures Achieved at Maximum Tested Dose	Single Dose	Data from ATI-BC-1: 46 kBq/kg: AUC (hr*IU/g, %CV): 3,832, 7% Cmax (IU/g): 3,668, 0.9% 93 kBq/kg: AUC (hr*IU/g, %CV): 26,764, 6% Cmax (IU/g): 7,495, 0.8% 163 kBq/kg: AUC (hr*IU/g, %CV): 41,519, 7% Cmax (IU/g): 12,018, 0.8% 213 kBq/kg: AUC (hr*IU/g, %CV): 80,301, 5% Cmax (IU/g):19,854, 0.6% 250 kBq/kg: AUC (hr*IU/g, %CV): 119,130, 10% Cmax (IU/g): 20,085, 1.7%
	Multiple Dose	Data from BC1-05: 100 kBq/kg (0.0027 mCi/kg) x 2 [#] at 6 week intervals (N=6): AUC _{0-∞} (kBq*h/mL) in blood: 1.51±0.38, 25% (mean±SD, %CV) AUC _{0-∞} (kBq*h/mL) in plasma: 2.27±0.66, 24% (mean±SD, %CV) #Average of the two injections were calculated, assuming that all activity was eliminated during 6 week interval between the doses
Range of linear PK	Data available from doses ranging from 46 kBq/kg to 250 kBq/kg (ATI-BC-1) indicate that the pharmacokinetics of radioactivity was linear within this dose range.	

Accumulation at steady state	Based on the data from BC1-05 where 2 injections on 100 kBq/kg were given at 6 weeks apart, no accumulation was observed. The terminal $T_{1/2}$ of this compound is ~32 hrs. The dosage regimen used in Phase 3 study was 50 kBq/kg given every 4 weeks. Based on the $T_{1/2}$ and the frequency of dosing, accumulation is not expected at the proposed dosage regimen.	
Metabolites	There are no known pathways metabolizing radium-223.	
Absorption	Absolute/Relative Bioavailability	Not applicable (Alpharadin is only for intravenous administration)
	Tmax	Not applicable (Alpharadin is only for intravenous administration)
Distribution	Vd/F or Vd	100 kBq/kg (0.0027 mCi/kg) x 2 [#] at 6 week intervals (N=6) (BC1-05): V _d (L) in blood: 273±117, 43% (mean±SD, %CV) V _d (L) in plasma: 170±69, 41% (mean±SD, %CV) [#] Average of the two injections were calculated, assuming that all activity was eliminated during 6 week interval between the doses
	% bound	Radium-223 is not expected to bind to proteins or other components in blood
Elimination	Route	<u>Primary route:</u> The primary route of elimination is via feces; In Study BC1-05, faecal and urinary excretion was monitored up to 48 hours after injection; cumulative faecal excretion at 24 hours ranged from 0 – 13% of the injected activity. At discharge (48 hours after injection), cumulative faecal excretion was 0 – 34%. Two patients excreted no activity throughout the sampling period due to constipation. There was no evidence of hepato-biliary excretion. From the imaging data of the gastrointestinal tract, it is evident that activity passes rapidly through the small intestine wall and into the gut contents. Within 24 hours almost all of this activity appeared in the large intestine. In the majority of cases the maximum activity in the upper large intestine occurred at 24 hours and the maximum uptake in the lower large intestine occurred at 24–72 hours. <u>Other routes:</u> Urinary excretion was significantly lower than faecal excretion. Urinary excretion at 24

		hours ranged from <1% – 4% of injected activity. At discharge (48 hours after injection), cumulative urine excretion ranged from <1% – 5% and the rate of excretion was decreasing.
	Terminal t _{1/2}	<p><u>Parent:</u> The dataset seems to be adequately described by a four-exponential concentration curve in plasma and blood, with a terminal elimination phase described by very low concentrations. This last elimination phase is possible to describe due to the fact that it is radioactivity that is measured; such low concentrations are usually not possible to quantify due to limitations in bioanalytical methods. The initial half-life was not possible to estimate due to the limited number of sampling points within the initial distribution phase, but it will probably be in the range of 2 to 4 minutes.</p> <p>T_{1/2,2nd} [h] (mean±SD, %CV): blood: 0.16 ±0.04, 25% / plasma: 0.17 ±0.01, 6%</p> <p>T_{1/2,3rd} [h] (mean±SD, %CV): blood: 2.0 ±0.2, 10% / plasma: 1.7 ±0.1, 6%</p> <p>T_{1/2,4th} [h] (mean±SD, %CV): blood: 31.7 ±7.7, 24% / plasma: 28.9 ±4.8, 17%</p> <p><u>Metabolites:</u> Not applicable</p>
	CL/F or CL	<p>100 kBq/kg (0.0027 mCi/kg) x 2[#] at 6 week intervals (N=6) (BC1-05):</p> <p>CL [L/h] (mean±SD, %CV): Blood: 6.1 ±2.1, 34% Plasma: 4.1 ±1.5, 37%</p> <p>[#] Average of the two injections were calculated, assuming that all activity was eliminated during 6 week interval between the doses</p>
Intrinsic Factors	Age	Not studied
	Sex	Based on data from AT1-BC1, although the arithmetic mean values for dose normalized C _{max} and AUC are 12 and 30% higher, respectively, in females as compared to males, the range of dose normalized AUC and C _{max} values for the females is covered

		by the range of dose normalized AUC and C _{max} values seen in males. In addition, both dose normalized AUC and C _{max} are not significantly different (at significance level 5%) in terms of gender.
	Race	Not studied
	Hepatic & Renal Impairment	Not studied
Extrinsic Factors	Drug interactions	<p>No clinical interaction studies have been performed.</p> <p>A study is ongoing to evaluate the safety/tolerability in combination with docetaxel.</p> <p>A nonclinical study has been performed to investigate the pharmacokinetics and biodistribution of radium-223 in mice during treatment with zoledronic acid (Zometa) (b) (4) Study 148-013).</p> <p>A single intravenous injection of 625 kBq/kg radium-223 was injected either alone or two hours after a single intravenous injection of 100 µg/kg zoledronic acid (Zometa). No statistically significant difference in blood pharmacokinetics or tissue biodistribution was observed between radium-223 given alone or 2 hours after zoledronic acid (Zometa).</p> <p>The potential additive efficacy of administration of radium-223 with the subsequent (next day) administration of the bisphosphonate pamidronate (Aredia, a bone resorption inhibitor) has been investigated[5] in a skeletal metastasis model in nude rats. Efficacy (as percent symptom-free survival) of radium-223 in this model was not modified by subsequent administration of pamidronate indicating that no interactions occurred between these agents.</p>
	Food Effects	Not needed as the drug is given intravenously.

Expected High Clinical Exposure Scenario	Overdose is unlikely in the context of a product intravenously under direct hospital supervision. The highest single dose Alpharadin administered in clinical trials is 250 kBq/kg (0.0068 mCi/kg) (study ATI-BC-1; no dose-limiting toxicity was observed); there is no clinical experience of higher doses. It is unlikely, though, that even a single dose of 250 kBq/kg can be achieved in a human patient as it would require administration of several vials of study drug.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUSTIN C EARP
03/14/2013

KEVIN M KRUDYS
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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 7, 2013

To: Elleni Alebachew – Regulatory Project Manager
Division of Oncology Products 1 (DOP 1)
Office of Hematology Oncology Products

From: Michelle Safarik, MSPAS, PA-C – Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on draft carton/container labeling for Xofigo
(radium Ra 223 dichloride) Injection, for intravenous use (Xofigo)
NDA 203971

As requested in your consult dated December 14, 2012, OPDP has reviewed the draft carton and container labeling for Xofigo. As previously discussed, OPDP will provide comments on the draft labeling (PI) under separate cover by April 10, 2013.

OPDP's comments are based on the draft carton and container labeling sent to OPDP via e-mail (meeting request) by DOP 1 on March 7, 2013. Reference is made to the review performed by the Division of Medication Error Prevention and Analysis (DMEPA) on the draft carton and container labeling dated February 28, 2013.

We agree with DMEPA's assessment that the large alpha graphic is more prominent than the proprietary name, and detracts from the proprietary name and other important information on the principal display panel. We also agree that if there are safety concerns that should be conveyed because this product is an alpha-emitter, then the sponsor should replace the alpha graphic with a warning statement(s).

Because Xofigo is an alpha-particle emitting pharmaceutical, the alpha graphic makes a claim/representation about the product. Therefore, the sponsor should either add balancing risk information, or delete the graphic.

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/s/

MICHELLE L SAFARIK
03/07/2013

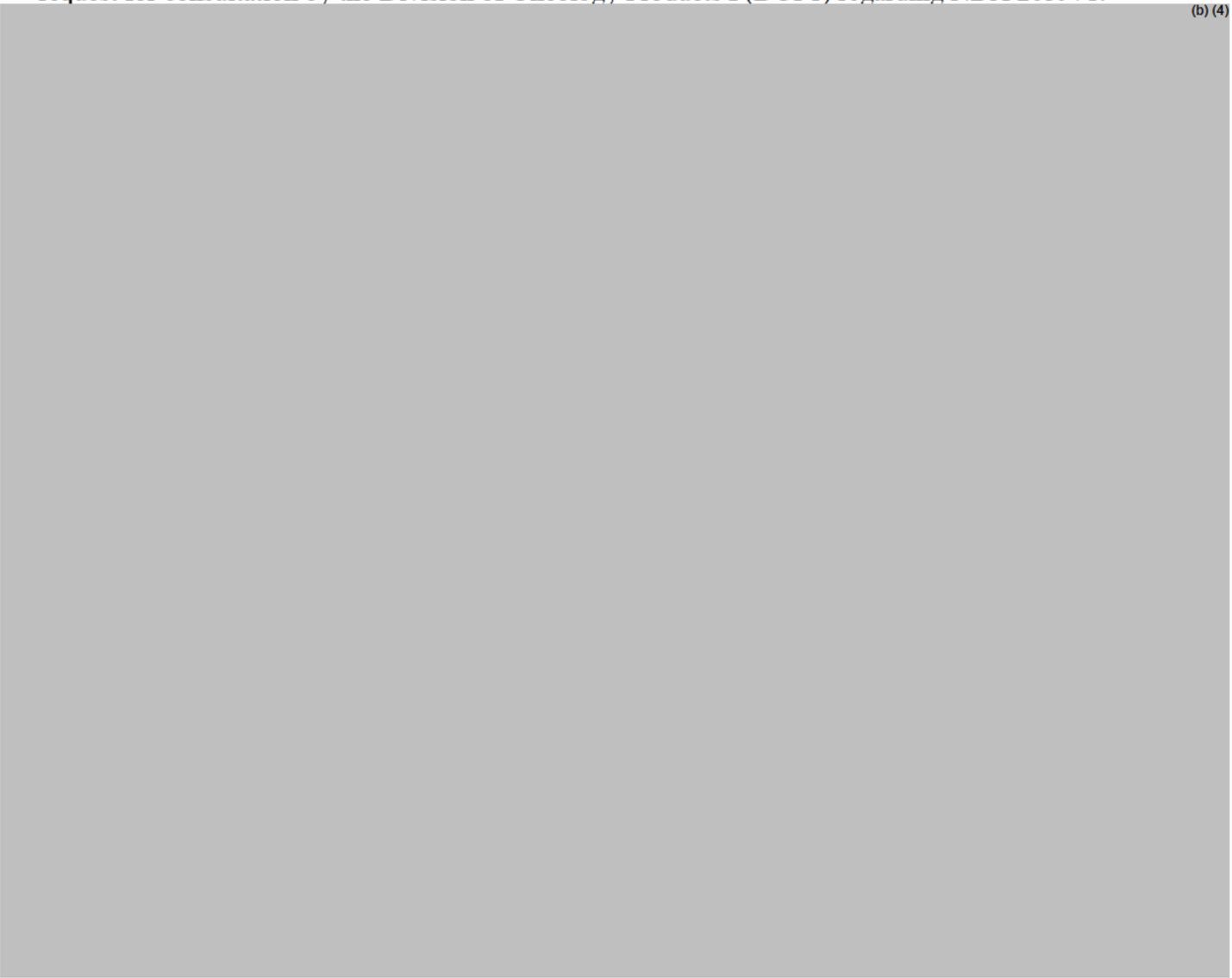
STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2013-026
APPLICATION NUMBER	NDA 203971
LETTER DATE/SUBMISSION NUMBER	
PDUFA GOAL DATE	August 14, 2013 (OHOP target action date is May 17, 2013)
DATE OF CONSULT REQUEST	February 13, 2013
REVIEW DIVISION	DOP1
MEDICAL REVIEWER	Paul Kluetz (TL: Ellen Maher)
REVIEW DIVISION PM	Elleni Alebachew
SEALD REVIEWER(S)	Jessica Voqui
REVIEW COMPLETION DATE	March 4, 2013
ESTABLISHED NAME	radium-223 dichloride
TRADE NAME	Xofigo
APPLICANT	Bayer Healthcare Pharmaceuticals
ENDPOINT(S) CONCEPT(S)	HRQL
MEASURE(S)	FACT-P; EQ-5D
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
INDICATION	Treatment of castration-resistant prostate cancer with skeletal metastases
INTENDED POPULATION(S)	Adult male patients with castration-resistant prostate cancer with skeletal metastases

A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Oncology Products I (DOP1) regarding NDA 203971.

(b) (4)



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/s/

JESSICA VOQUI
03/08/2013

LAURIE B BURKE
03/10/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, and Packaging Review

Date: February 27, 2013

Reviewer: Jibril Abdus-Samad, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Xofigo (Radium Ra 223 Dichloride) Injection
1,000 kBq/mL (0.027 mCi/mL)

Application Type/Number: NDA 203971

Applicant: Bayer HealthCare Pharmaceuticals Inc.

OSE RCM #: 2012-3011

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, lead container and insert labeling for Xofigo (Radium Ra 223 Dichloride) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Xofigo (Radium Ra 223 Dichloride) proprietary name was found conditionally acceptable in October 21, 2011 OSE Review 2011-1417 during the IND phase. The Applicant submitted the NDA on December 14, 2012. Additionally, on January 10, 2013, the Applicant submitted a request for proprietary name review for Xofigo, which will be addressed in a separate OSE Review.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 14, 2012 submission.

- Active Ingredient: Radium Ra 223 Dichloride
- Indication of Use: Therapeutic alpha particle-emitting pharmaceutical for the treatment of castration-resistant prostate cancer patients with bone metastases
- Route of Administration: Intravenous
- Dosage Form: Injection
- Strength: 1,000 kBq/mL (0.027 mCi/mL) at the reference date
- Dose and Frequency: 50 kBq (0.00135 mCi) per kg body weight every 4 weeks for 6 injections
- How Supplied: Single-Dose vials containing 6 mL of solution (1000 kBq/mL, 0.027 mCi/mL) at the reference date
- Storage: Do not store above 40°C (104°F). Store in the original container or equivalent radiation shielding.
- Container and Closure System: Glass vial

Additionally, the US Nuclear Regulatory Commission has determined Xofigo (Radium Ra 223 Dichloride) licensing under 10 CFR 35.40 “Unsealed Byproduct Material – Written Directive Required” is appropriate.¹ Thus, this product will be managed by nuclear pharmacists, authorized physician, nuclear medicine technologist, or physician authorized user. The *Written Directive* is documentation filled out by the authorized user of the nuclear pharmaceutical product whose purpose is to verify the correct patient, drug, dose, and route of administration.

¹ <http://pbadupws.nrc.gov/docs/ML1234/ML12349A275.pdf>. Last accessed February 26, 2013

2 METHODS AND MATERIALS REVIEWED

2.1 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed the proprietary name Xofigo (Radium Ra 223 Dichloride) for this product in OSE Reviews 2011-1417, dated October 21, 2011. There were no labeling concerns discussed in this review.

2.2 LITERATURE SEARCH

We searched PubMed on January 18, 2012 for medication error concerns with Radium Ra 223 Dichloride yielded no publications. We reviewed the US Nuclear Regulatory Commission's Nuclear Material Events Database Annual Report for Fiscal Year 2010, published February 2011.² There were no medication errors related to the labeling of radiopharmaceuticals.

2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis³ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted December 12, 2012 (Appendix A)
- Lead Container Labeling submitted December 12, 2012 (Appendix B)
- Decay Correction Factor Table submitted December 12, 2012 (Appendix C)

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Review of the proposed labels and labeling identified deficiencies, inconsistencies in expression of strength, and differences in units of measure as compared to other radiopharmaceutical products. The following sections describe our findings.

3.1 STRENGTH PRESENTATION

Typically, with standard injectable drug products, the strength is expressed in terms of total drug content per total volume followed by the concentration per mL in parenthesis. However, for radiopharmaceutical products, the amount of radioactivity, Becquerel (Bq) or Curie (Ci) in the vial is never constant as it decreases or decays over time, and therefore the stated radioactivity on the vial is based upon the radioactivity at the reference date. The reference date is a date printed on each vial label and lead container labeling that authorized healthcare practitioners (HCP) use for determining the amount of radioactivity in the vial. To determine the volume of Xofigo to be administered for the

² US Nuclear Regulatory Commission's Nuclear Material Events Database Annual Report for Fiscal year 2010, published February 2011

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

prescribed dose, the authorized HCP utilizes the radioactivity concentration per mL along with the decay factor.

Additionally, we found other similar radiopharmaceutical products such as Chronic 32 Phosphate, Sodium Phosphate 32, and Samarium 153 Lexidronam, which are also considered unsealed byproduct material, have a similar strength presentation consisting of the radioactivity concentration per mL (kBq/mL or mCi/mL) at the reference date. We did not identify any medication errors related to the strength presentation for these similar products. Thus, DMEPA finds the primary expression of radioactivity as concentration per mL at the reference date appropriate for this radiopharmaceutical product, rather than the total radioactivity per vial volume.

3.2 DIFFERENCE IN EXPRESSION OF UNITS FOR MEASURING RADIOACTIVITY, MEGABECQUEREL VS. KILOBECQUEREL

Typically, radiopharmaceutical strength presentations contain both International System of Units (SI) and common units expressed in becquerel and curie, respectively. Although the Applicant follows this practice, they have expressed the SI derived unit (Becquerel) as both megabecquerel (MBq) and kilobecquerel (kBq) on the label and labeling for this product. The radioactivity units should be expressed in a consistent manner throughout the label and labeling.

The majority of radiopharmaceutical products are labeled using MBq. However, if this Applicant revises the units to MBq, this changes the recommended dosage of this product from 50 kBq/kg to 0.05 MBq/kg. Changing the units of measure to MBq would require the dose to be calculated using a decimal number rather than a whole number, which may result in calculation errors. Additionally, the clinical studies submitted by the Applicant and published literature of Radium Ra 223 Dichloride provide all dosing in terms of kBq. The Applicant also uses kBq in the Decay Correction Table, which provides a reference for nuclear pharmacist to verify the correct volume of Xofigo injection. Therefore, strength presentations of *MBq* on the label and labeling should be eliminated or revised to read *kBq*. This will provide consistency with the expression of radioactivity in other areas of the label and labeling, such as the recommended dosage in the dosage and administration section (50 kBq/kg) and the radioactivity per mL strength presentation on the principal display panel of the container label.

3.3 DIFFERENCE IN EXPRESSION OF UNITS FOR MEASURING RADIOACTIVITY, MILLICURIE VS. MICROCURIE

The majority of radiopharmaceutical products use millicurie (mCi) in their labels and labeling. The Applicant also uses mCi for measuring radioactivity on the labels and labeling for this product. However, the recommended dosage of 0.00135 mCi/kg introduces a potential for calculation errors due to the preceding zeros. To eliminate the preceding zeros, the unit of measure should be changed to microcurie, which is more appropriate for Xofigo's lower strength of radioactivity. This will provide for a number that is easier to use in calculations. For example, the recommended dosage of Xofigo in the insert labeling of 0.00135 mCi/kg should be changed to 1.35 microcurie/kg. Although the majority of radiopharmaceutical products use mCi in their labels and

labeling, microcurie is also commonly used in radiopharmaceutical products with lower strengths of radioactivity such as Xofigo. We did not identify any medication errors related to confusion of millicurie and microcurie for other radiopharmaceutical products (Sodium Iodide I 123, Sodium Chromate Cr 51, and Iodinated I 125 Albumin Injection, USP) that use microcurie as the unit of measure for radioactivity in the labeling.

Additionally, many labels use the mu symbol (μ) to express microcurie (μCi). The μ symbol used for microgram (μg) has been misinterpreted as milligram (mg). Therefore, the recommended abbreviation for microgram is mcg. However, we cannot locate any instance in radiopharmaceutical labeling and literature where microcurie is expressed as mcCi. Therefore, we recommend spelling out the word microcurie in the labeling.

3.4 CONTAINER LABEL AND LEAD CONTAINER LABELING

The container label and lead container labeling contain a large alpha (α) graphic that is more prominent than the proprietary name. Although, Xofigo is an alpha particle-emitting pharmaceutical, the graphic detracts from the proprietary name and other important information on the principal display panel. The labels and labeling already contain the radioactive symbol standard on radiopharmaceuticals. However, if there are safety concerns that should be conveyed because this product is an alpha-emitter, then the Applicant should propose replacing the symbol with a warning statement.

3.5 STORAGE INFORMATION

The storage information is presented in a negative tense that is uncommon. The storage information should first provide an acceptable temperature range and then place and additional warnings afterwards.

3.6 WRONG ROUTE OF ADMINISTRATION ERRORS

There is potential for wrong route of administration errors to occur with this injectable product. If this product is administered subcutaneously or intramuscularly, there is potential for localized tissue reactions due to injection of a radioactive drug into a specific tissue location rather than in circulating in the blood. However, because this product is considered an unsealed byproduct material, a Written Directive is required per 10 CFR 35.40.⁴ This Written Directive is used to verify the correct patient, drug, dose, and route of administration, thus decreasing the likelihood of wrong route of administration errors. Additionally, the route of administration can be added to the principal display panel of the container and lead container labels to highlight the correct route.

⁴ <http://www.nrc.gov/reading-rm/doc-collections/cfr/part035/full-text.html#part035-0040> Last accessed February 26, 2013

3.7 DECAY CORRECTION FACTOR TABLE

(b) (4)



3.8 REFERENCE DATE TIME ZONE

This time zone used for the reference dates is inconsistent. The Applicant uses *12 Noon Central Standard Time (CST)* in the Decay Correction Factor Table but uses *Central European Time (CET) 12 h* on the container label and lead container labeling. The time zone for the reference data should be based on a US time zone and applied consistently across the label and labeling.

4 RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling require revisions to provide consistency in expression of radioactivity units of measure, improvement of readability, and increased prominence of important information on the labels to promote the safe use of the product. Based on this review, DMEPA provides recommendations in the following sections. We request these revisions be implemented prior to approval of this NDA.

If you have further questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

4.1 COMMENTS TO THE DIVISION

- A. ONDQA will evaluate the following concerns brought forth by DMEPA:



- B. Insert Labeling

1. Revise all the strength presentations so that they are expressed in units of kBq and microcurie rather than MBq and mCi (millicurie).
2. Dosage and Administration – section 2
 - a. Replace the abbreviation, *DK*, with the full term, *Decay*.

- b. 

- c. Revise the administration instructions by adding a separate administration section that reads as follows:

2.2 Administration

Administer Xofigo by intravenous injection over 1 minute.
Flush the intravenous access line or cannula with isotonic saline before and after injection of Xofigo.

3. Dosage Forms and Strengths – section 3
 - a. Revise to read as follows:

Xofigo (Radium Ra 223 Dichloride Injection) is supplied in single-use vials containing 6 mL of solution at a concentration of 1000 kBq/mL (27 microcurie/mL) at the reference date with a total radioactivity of 6,000 kBq/vial (162 microcurie/vial) at the reference date.
4. How Supplied Section/Storage and Handling – section 16
 - a. Revise to read as follows:

Xofigo (Radium Ra 223 Dichloride Injection) is supplied in single-use vials containing 6 mL of solution at a concentration of 1000 kBq/mL (27 microcurie/mL) at the reference date with a total radioactivity of 6,000 kBq/vial (162 microcurie/vial) at the reference date (NDC 50419-208-01).
 - b. Revise the storage information to state the recommended storage first, then any storage restrictions.

4.2 COMMENTS TO THE APPLICANT

- A. General Comment
 1. Revise all the strength presentations so that they are expressed in units of kBq and microcurie.
- B. Container Label
 1. Delete the alpha graphic as it competes with the prominence of more important information on the principal display panel. If there are specific instructions that you want to communicate regarding the alpha emitting properties, propose language to communicate this.
 2. Revise the dosage form from *INJECTION* to read *Injection*. Note the change from all CAPITAL LETTERS to Title Case.
 3. Increase the prominence of the radioactivity concentration, 1000 kBq/mL (27 microcurie/mL).
 4. Revise the total radioactivity, 6 MBq/vial (0.162 mCi/vial), to read 6,000 kBq/vial (162 microcurie/vial).
 5. Revise the time zone for the reference date to *12 Noon Central Standard Time (CST)* to be consistent with the reference time on the Decay Correction Factor Table.
 6. Relocate the route of administration, For Intravenous Administration, to the principal display panel.
 7. Add the following statement to the side panel: Single-Dose Vial: Discard Unused Portion

8. Add the total volume, 6 mL, to the principal display panel. Delete (b) (4) as this not required for a small label.

9. Delete the (b) (4).

C. Lead Container Label

1. See comments B1 through B7.

2. Add the total volume, 6 mL, to the principal display panel. Consider deleting or at a minimum relocating the word, *Sterile*, to the right-side panel to create space.

3. Revise the storage information to state the recommended storage first, then any storage restrictions.

4. Delete the (b) (4).

D. Decay Correction Factor Table



(b) (4)

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/s/

JIBRIL ABDUS-SAMAD
02/27/2013

TODD D BRIDGES
02/27/2013

CAROL A HOLQUIST
02/28/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203971

Application Type: New NDA

Name of Drug: Xofigo (radium Ra 223 dichloride) injection;

Applicant: Bayer HealthCare Pharmaceuticals Inc.

Submission Date: December 14, 2013

Receipt Date: December 14, 2013

1.0 Regulatory History and Applicant's Main Proposals

Xofigo (radium Ra 223 dichloride) injection is a therapeutic alpha particle-emitting pharmaceutical for the treatment of castration-resistant prostate cancer patients with bone metastases.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- N/A** 12. All text must be **bolded**.
Comment:
- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
Comment:
- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Selected Requirements of Prescribing Information (SRPI)

Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment: Applicant did not use the required statement stated above. Below is what the applicant included under Indications and Usage

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

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.
Comment:
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
Comment:
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE

Selected Requirements of Prescribing Information (SRPI)

2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

N/A

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES

45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

YES

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

N/A

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

N/A

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

ELLENI K ALEBACHEW
02/14/2013

ALICE KACUBA
02/14/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203971 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Xofigo Established/Proper Name: radium Ra 223 dichloride Dosage Form: Injection Strengths: 1000 kBq/mL (0.027 mCi/mL) at reference date		
Applicant: Bayer HealthCare Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: December 14, 2013 Date of Receipt: December 14, 2013 Date clock started after UN:		
PDUFA Goal Date: August 14, 2013	Action Goal Date (if different): May 17, 2013	
Filing Date: February 12, 2013	Date of Filing Meeting: January 10, 2013	
Chemical Classification: (1, 2, 3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): For castration-resistant prostate cancer patients with bone metastases		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 067521				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			<input checked="" type="checkbox"/>	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>			

<u>User Fee Status</u>		Payment for this application:			
<i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				<input checked="" type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				<input checked="" type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				<input checked="" type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?				<input checked="" type="checkbox"/>	
<i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm			<input checked="" type="checkbox"/>		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	<input checked="" type="checkbox"/>			
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5- years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input checked="" type="checkbox"/>			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?</p>	<input checked="" type="checkbox"/>			
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			<input checked="" type="checkbox"/>	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLA/BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English)</p>	<input checked="" type="checkbox"/>			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			<input checked="" type="checkbox"/>	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?		<input checked="" type="checkbox"/>		Pre-NDA meeting were held before the implementation of PDUFA V
• If yes, were all of them submitted on time?				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	<input checked="" type="checkbox"/>			
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	<input checked="" type="checkbox"/>			
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment

Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674." <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></i>	<input checked="" type="checkbox"/>			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></i>	<input checked="" type="checkbox"/>			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR) <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></i>			<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i>	<input checked="" type="checkbox"/>			NDA203971 is on the PeRC schedule for April 17, 2013.

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>			
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?			<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?	<input checked="" type="checkbox"/>			
<i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		<input checked="" type="checkbox"/>		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>			Consults sent to QT and DMIP
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): January 30, 2009	<input checked="" type="checkbox"/>			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): October 26, 2011	<input checked="" type="checkbox"/>			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 10, 2013

BLA/NDA/Supp #: NDA 203971

PROPRIETARY NAME: Xofigo

ESTABLISHED/PROPER NAME: radium Ra 223 dichloride

DOSAGE FORM/STRENGTH: Injection / 1000 kBq/mL (0.027 mCi/mL) at reference date

APPLICANT: Bayer HealthCare Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): The proposed indication is “Xofigo® (radium Ra 223 dichloride) is indicated for the treatment of castration-resistant prostate cancer patients with bone metastases.”

BACKGROUND: Xofigo® is a therapeutic alpha particle-emitting pharmaceutical with targeted anti-tumor effect on bone metastases. The active moiety of Xofigo® is the isotope radium-223 (as radium-223 dichloride) that mimics calcium and selectively targets bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in a potent and localized anti-tumor effect. The alpha particle range from radium-223 is less than 100 micrometers (less than 10 cell diameters) which minimizes damage to the surrounding normal tissue. The NDA was received on December 14, 2013.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elleni Alebachew	Y
	CPMS/TL:	Alice Kacuba	Y
Cross-Discipline Team Leader (CDTL)	V. Ellen Maher		Y
Clinical	Reviewer:	Paul Kluetz (Efficacy)	Y
	Reviewer:	William Pierce (Safety)	
	TL:	V. Ellen Maher	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	

	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		
Clinical Pharmacology	Reviewer:	Pengfei Song	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	Hui Zhang	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wei Chen	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Martin Haber (ONDQA-DMIP)	
	TL:	Eldon Leutzinger (ONDQA-DMIP)	
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Denise Miller	
	TL:		
CMC Labeling Review	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:	Mahesh Ramanadham	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	Y
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	

	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Pharmacometrics	Reviewer:	Bahru Habtemariam	N
	TL:	Nitin Mehrotra	N
Biopharm (CMC)	Reviewer:	Kareen Riviere	Y
	TL:	Angelica Dorantes	N
DMIP	Reviewer:	Cynthia Welsh	Y
	TL:	Lucie Yang	N
Other attendees	Richard Pazdur (OHOP)		Y
	Tamy Kim (OHOP)		Y
	Robert Pratt (OSE)		Y
	Deborah Mesmer (ONDQA)		Y
	Frances Fahnbulleh (OSE)		Y
	Ali H Al Hakim (ONDQA – DOP1)		Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The application showed improvement in overall survival and did not raise significant safety or efficacy issues.
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <li style="padding-left: 20px;">If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO <li style="padding-left: 20px;">If EA submitted, consulted to EA officer (OPS)? <input type="checkbox"/> YES <input type="checkbox"/> NO Comments:	<input type="checkbox"/> Not Applicable
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO Comments:	<input type="checkbox"/> Not Applicable
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO Comments:	<input type="checkbox"/> Not Applicable

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, M.D.</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): February 14, 2013</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

ELLENI K ALEBACHEW
02/12/2013

ALICE KACUBA
02/12/2013