

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203971Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203971

SUPPL #

HFD # 150

Trade Name: Xofigo®

Generic Name: radium Ra 223 dichloride

Applicant Name: Bayer HealthCare Pharmaceuticals, Inc.

Approval Date, If Known May 15, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

YES
Explain:

! NO
! Explain:

Investigation #2

!

!

YES
Explain:

! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Elleni Alebachew
Title: Regulatory Health Project Manager

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

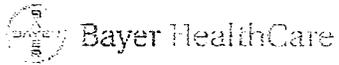
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLENI K ALEBACHEW
05/14/2013

ROBERT L JUSTICE
05/14/2013

EDR 12/14/12



NDA 203,971
BAY 88-8223/ radium-223 dichloride
1.3.3 Debarment Certification

Page: 1 of 1

Bayer HealthCare Pharmaceuticals Inc hereby certifies under FD&C Act, Section 306(k)(1) 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 New Drug Application 203,971.

Signature:

Maria C. Garrigan

Date:

November 15, 2012

Maria C. Garrigan
Director, Specialty Medicine, Oncology 1
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals Inc

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203971 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Xofigo® Established/Proper Name: radium Ra-223 dichloride Dosage Form: Injection		Applicant: Bayer HealthCare Pharmaceuticals Agent for Applicant (if applicable):
RPM: Elleni Alebachew		Division: Division of Oncology Products 1
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>August 14, 2013</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 1</p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other <u>ASCO</u>

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	<input checked="" type="checkbox"/>
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval – 5/15/13
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	5/10/13
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12/14/12
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	<input checked="" type="checkbox"/> 5/6/13;5/3/13;5/1/13;4/30/13;4/29/13;4/25/13;4/19/13;4/15/13;4/9/13;4/5/13;4/1/13;3/29/13;3/28/13;3/28/13;3/28/13;3/27/13;3/27/13;3/22/13;3/21/13;3/21/13;3/19/13;3/14/13;3/13/13;3/13/13;3/8/13;3/5/13;3/5/13;3/1/13;2/28/1;2/27/13;2/22/13;2/21/13;2/15/13;2/12/13;2/12/13;2/11/13;2/11/13;2/11/13;2/4/13;2/4/13;2/1/13;1/24/13;1/18/13;1/11/13;1/8/13;1/2/13;12/31/12;12/20/12;12/17/12
❖ Internal memoranda, telecons, etc.	1/18/13 3/20/13 4/11/13
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 10/26/11
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 01/30/09
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	Midcycle Communication teleconference : 2/28/13 Late Cycle Meeting: 4/19/13
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	N/A
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 5/14/13
Division Director Summary Review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 5/14/13
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None 4/23/13
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None 3 PMRs and 1 PMC 5/14/13
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	Co-signed 04/11/13 Primary Clinical Review
• Clinical review(s) <i>(indicate date for each review)</i>	04/11/13 Primary review 02/14/13 Filing check list
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See 04/11/13 Primary Clinical Review page 22
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None DMIP: 4/3/13 QT-IRT:3/14/13 SEALD Endpoints: 3/10/13 DEPI:5/9/13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None DRISK recommended REMS is not required for radium Ra-223 dichloride Review: 3/27/13
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested OSI letter 5/11/13 Review 4/09/13
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/02/13 Co-signed primary and secondary reviews
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/02/13
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/02/13 Primary review 2/11/13 Filing check list
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/10/13 Co-signed primary review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/10/13 Co-signed primary review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/10/13 Primary review 2/15/13 Filing check list
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/08/13
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/05/13
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/29/13 Primary review 1/11/13 Filing check list
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/11/13
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/1/13 Co-signed primary review
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None Product Quality review: 5/13/13 EES Memo 4/1/13 Primary review 12/20/12 Filing check list
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed 3/26/13 Primary review 1/8/12 Filing check list
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input type="checkbox"/> None Biopharmaceutics Review: 1/8/13 Filing check list Note: Page 4 of the filing checklist states that “no further Biopharmaceutics review is needed for this NDA”
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See ONDQA review dated 4/1/13
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁷)	Date completed: 5/13/13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested (see AP Letter) <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/s/

ELLENI K ALEBACHEW
05/15/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Maher, Virginia E.](#); [Song, Pengfei](#); [Liu, Qi \(CDER\)](#)
Subject: NDA 203971-Information Request - Post Marketing Commitment
Date: Monday, May 06, 2013 12:35:00 PM
Importance: High

Dear Dr. Jalota,

Regarding your NDA 203971, please provide your commitment to the following:

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 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.

The timetable you submitted on May 2, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/13
Study/Trial Completion: 09/18
Final Report Submission: 03/19

-
Please respond by no later than noon tomorrow, May 7, 2013.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
05/06/2013

From: Alebachew, Elleni
To: ["Deepika Jalota"](#)
Cc: [Kacuba, Alice](#)
Bcc: [Pierce, William \(CDER\)](#)
Subject: RE: NDA 203971 - Xofigo USPI - FDA comments - 02May2013
Date: Friday, May 03, 2013 10:59:00 AM
Attachments: [NDA 203971 Xofigo Draft US PI FDA Response 02May13 - Annotated \(2\).doc](#)
Importance: High

Hi Deepika,

Attached please find annotated version of the USPI with FDA comments incorporated.

Please respond by **COB Monday, May 6, 2013**.

Let me know if you have any questions.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Wednesday, May 01, 2013 4:18 PM
To: Alebachew, Elleni
Subject: RE: NDA 203971 - Xofigo USPI - Bayer response - 01May2013

Hi Elleni,

Reference is made to the FDA USPI Comments received on April 30, 2013 for NDA 203971. Attached are the clean and annotated versions of the USPI with one Bayer comment incorporated. A formal amendment to the NDA will be submitted on May 2, 2013 under eCTD sequence no. 49.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Tuesday, April 30, 2013 4:42 PM
To: Deepika Jalota
Subject: NDA 203971 - Xofigo USPI - FDA Response -4.30.13
Importance: High

Hi Deepika,

Attached please find annotated version of the USPI with FDA comments incorporated.

Please respond by **COB Wednesday, May 1, 2010**.

Let me know if you have any questions.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
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/s/

ELLENI K ALEBACHEW
05/06/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Bcc: [Song, Pengfei](#); [Liu, Qi \(CDER\)](#)
Subject: NDA 203971 - Information Request - PMC
Date: Wednesday, May 01, 2013 4:15:00 PM
Importance: High

Hi Deepika,

Please refer to your protocol design for PMC trial [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED] " submitted on April 30, 2013 under NDA203971. **Please provide a written response by 3 PM May 2, 2013** regarding the following recommendations on your [REDACTED] (b) (4) trial design:

[REDACTED] (b) (4)

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
05/02/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Bcc: [Maher, Virginia E.](#)
Subject: NDA 203971 - Xofigo USPI - FDA Response -4.30.13
Date: Tuesday, April 30, 2013 4:42:00 PM
Attachments: [NDA 203971 Xofigo Draft US PI FDA Response 30Apr13 - Annotated.doc](#)
Importance: High

Hi Deepika,

Attached please find annotated version of the USPI with FDA comments incorporated.
Please respond by **COB Wednesday, May 1, 20103**.

Let me know if you have any questions.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
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Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
04/30/2013

From: Alebachew, Elleni
To: "Deepika Jalota"
Bcc: Maher, Virginia E.
Subject: RE: NDA 203971 - PMR no. 1 to 3 - Synopses and Timelines- FDA request for Clarification
Date: Monday, April 29, 2013 12:29:00 PM
Importance: High

Hi Deepika,

Please refer to your PMR synopsis submissions received on April 25, 2013. Please respond to FDA's request for clarification (see below) as soon as possible but **no later than Wednesday, May 1.**

1. PMR #1: Please clearly state the frequency with which information will be collected concerning drug-related serious adverse events and the development of secondary malignancies.
2. PMR #2: Please clearly state that you intend to [REDACTED] (b) (4)
[REDACTED] Please discuss the feasibility of submission of your final study report in June 2018.
3. PMR #3: Please clearly state that you intend to [REDACTED] (b) (4)
[REDACTED] Please discuss the feasibility of submission of your final study report in March 2017.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

From: Deepika Jalota [mailto:deepika.jalota@bayer.com]
Sent: Wednesday, April 24, 2013 5:15 PM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: NDA 203971 - PMR no. 1 to 3 - Synopses and Timelines

Hi Elleni,

Reference is made to the Late Cycle Meeting held on April 19, 2013 for NDA 203971.

As discussed during the meeting, attached are the synopses and timelines for the following Post-Marketing Requirement studies:

1. Post-Marketing Requirement no. 1 (Non-interventional study)
2. Post-Marketing Requirement no. 2 [REDACTED] (b) (4)
3. Post-Marketing Requirement no. 3 ([REDACTED] (b) (4) - Retreatment study)

A formal amendment to the NDA will be submitted on April 25, 2013 under eCTD sequence no. 0047.

Freundliche Grüße / Best regards,

Deepika Jalota, PharmD
Global Regulatory Strategist



Bayer HealthCare

Science For A Better Life

Bayer HealthCare Pharmaceuticals Inc
Global Regulatory Affairs, Specialty Medicine
Montville, Building 100 / Office 268
Tel: 973-487-2782
Mobile: [REDACTED] (b) (6)
E-mail: deepika.jalota@bayer.com
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/s/

ELLENI K ALEBACHEW
04/29/2013

From: Alebachew, Elleni
To: ["Deepika Jalota"](#)
Cc: [Kacuba, Alice](#)
Bcc: [Maher, Virginia E.](#); [Pierce, William \(CDER\)](#)
Subject: RE: NDA 203971 - Xofigo USPI - FDA Response -4.25.13 - Request for clarification - peripheral edema and renal failure/impairment
Date: Monday, April 29, 2013 9:41:00 AM
Importance: High

Hi Deepika,

Below please find FDA's response to Bayer request for clarification received on April 25 and 26.

FDA Response: The rationale for inclusion of peripheral edema and renal failure and insufficiency in the Xofigo adverse reactions section is as follows:

1. In the randomized, controlled trial there was a small increase in each of these adverse reactions (ARs) on the Xofigo arm compared to placebo. Per the FDA Guidance for the adverse reactions section of labeling, determination of if there is a basis to believe there is a causal relationship between an adverse event and the a drug (Xofigo) are based on factors such as whether the adverse event incidence rate exceeds the placebo incidence rate in a controlled trial.
2. The data you provided has not clearly ruled out potential biologic plausibility or a possible relationship to Xofigo for either AR. With regards to renal failure and insufficiency, small increases in dehydration, adverse reactions that may affect fluid status, and this SAE on the Xofigo arm also support inclusion in labeling. The reasons for the observed increase in renal failure/insufficiency on the Xofigo arm remain unclear. The reasons for the observed increase in peripheral edema remain unclear and possible effects related to Xofigo have not been adequately ruled out.
3. The exploratory exposure adjusted incidence rates (EAIRs) provided in the referenced labeling response document are unequivocal and still result in small increases in these ARs on the Xofigo arm. We also note that this approach has not been used in oncology drug or biologic review as the primary determining factor to establish adverse reactions; even for controlled trials with much larger differences in the AE collection period across study arms.

Therefore, based primarily on the observed increase in the incidence of these ARs on the Xofigo arm of the controlled trial, and the lack of additional data that makes a relationship between these ARs and Xofigo unlikely, the FDA concludes peripheral edema and renal failure/impairment warrant inclusion in the Adverse Reactions section of the prescribing information for the indicated patient population.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1*

Office of Hematology and Oncology Products

OND/CDER/FDA

E-mail: Elleni.Alebachew@fda.hhs.gov

Phone: (301) 796-5225

Fax: (301) 796-9845

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]

Sent: Friday, April 26, 2013 11:04 AM

To: Alebachew, Elleni

Cc: Kacuba, Alice

Subject: RE: NDA 203971 - Xofigo USPI - FDA Response -4.25.13 - Request for clarification - peripheral edema and renal failure/impairment

Hi Elleni,

Bayer has an additional request for clarification on the USPI.

Reference is also made to Table 3: Adverse Reactions in the Randomized Trial. Please kindly provide the FDA's rationale for inclusion of peripheral edema in the table.

Bayer has reviewed the patient id's included as part of Clinical Safety Comment #2 within the "FDA Additional Clarifications for Labeling" for the patients with peripheral edema. Based on the marginally increased rate of edema in the Xofigo arm and the lack of a plausible pathomechanism, Bayer believes that Xofigo is not causally associated with peripheral edema as mentioned in Bayer's labeling response document.

Best regards,
Deepika

From: Deepika Jalota

Sent: Thursday, April 25, 2013 12:26 PM

To: 'Alebachew, Elleni'

Subject: RE: NDA 203971 - Xofigo USPI - FDA Response -4.25.13

Hi Elleni,

Thank you for providing the FDA comments on the USPI.

Reference is made to Table 3: Adverse Reactions in the Randomized Trial. Please kindly provide the FDA's rationale for inclusion of renal failure and impairment in the table.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]

Sent: Thursday, April 25, 2013 9:48 AM

To: Deepika Jalota

Subject: NDA 203971 - Xofigo USPI - FDA Response -4.25.13

Importance: High

Hi Deepika,

Attached please find annotated version of the USPI with FDA comments incorporated. Also

attached is additional calcification document for the label.

Please respond by **COB Monday, April 29, 2013**.

Let me know if you have any questions.

Regards,

Elleni

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Friday, April 19, 2013 6:25 PM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: Xofigo NDA - Bayer USPI Comments to FDA's Comments rec'd on April 11, 2013

Hi Elleni,

Reference is made to the FDA USPI Comments received on April 11, 2013 for NDA 203971. Attached are the clean and annotated versions of the USPI with Bayer's comments incorporated. In addition, a Labeling Response Document is provided which includes rationale for some of the proposed changes. A formal amendment to the NDA will be made early next week.

Have a great weekend!

Freundliche Grüße / Best regards,

Deepika Jalota, PharmD
Global Regulatory Strategist



Science For A Better Life

Bayer HealthCare Pharmaceuticals Inc
Global Regulatory Affairs, Specialty Medicine
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/s/

ELLENI K ALEBACHEW
04/29/2013

From: Alebachew, Elleni
To: ["Deepika Jalota"](#)
Bcc: [Maher, Virginia E.](#)
Subject: NDA 203971 - Xofigo USPI - FDA Response -4.25.13
Date: Thursday, April 25, 2013 9:47:00 AM
Attachments: [FDA Additional Clarifications for Labeling.doc](#)
[4-25-13_NDA_203971_Xofigo_Draft_US_PI_FDA_Response_-_Annotated.doc](#)
Importance: High

Hi Deepika,

Attached please find annotated version of the USPI with FDA comments incorporated. Also attached is additional calcification document for the label.

Please respond by **COB Monday, April 29, 2013**.

Let me know if you have any questions.

Regards,

Elleni

From: Deepika Jalota [mailto:deepika.jalota@bayer.com]
Sent: Friday, April 19, 2013 6:25 PM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: Xofigo NDA - Bayer USPI Comments to FDA's Comments rec'd on April 11, 2013

Hi Elleni,

Reference is made to the FDA USPI Comments received on April 11, 2013 for NDA 203971. Attached are the clean and annotated versions of the USPI with Bayer's comments incorporated. In addition, a Labeling Response Document is provided which includes rationale for some of the proposed changes. A formal amendment to the NDA will be made early next week.

Have a great weekend!

Freundliche Grüße / Best regards,

Deepika Jalota, PharmD
Global Regulatory Strategist



Science For A Better Life

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Global Regulatory Affairs, Specialty Medicine
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/s/

ELLENI K ALEBACHEW
04/25/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Bcc: [Abdus-Samad, Jibril](#)
Subject: NDA 203971 - Information Request - Carton and Container
Date: Wednesday, April 24, 2013 3:53:00 PM
Attachments: [Xofigo - 203971 DMEPA ONDOA Carton container response_04242013.doc](#)
Importance: High

Hi Deepika,

Reference is made to your April 22, 2013 submission (eCTD seq#0046).

Attached please find an information request for NDA 203971. Please respond by **April 30, 2013**.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

April 24, 2013

DMEPA and ONDQA provide recommendations for the Applicant's April 22, 2013 submission.

COMMENTS TO THE APPLICANT

A. Container Label

1. Bold the dosage form, injection, so that it is as prominent as the established name. Thus, the established name and dosage form should read as follows:

radium Ra 223 dichloride injection

2. Revise the content/reference date statement to read as follows:

6000 kBq/vial (162 microcurie/vial) at 5 AM CST (12 noon CET) on reference date:

B. Lead Container Label

1. See comment A1.
2. Revise the content/reference date statement to read as follows:
6000 kBq/vial (162 microcurie/vial) at 5 AM Central Standard Time (CST) or 12 noon Central European Time (CET) on reference date:
3. Revise statement, 950-1050 kBq radium 233, to read as follows:
950 kBq to 1050 kBq radium 223
4. Delete the trailing zeros in the pH statement. Thus, the pH statement should read as follows:

The pH is between 6 to 8.

APPENDICES

Appendix A: Container Label



Appendix B: Lead Container Labeling



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/s/

ELLENI K ALEBACHEW
04/24/2013

From: Alebachew, Elleni
To: ["Deepika Jalota"](#)
Cc: [Kacuba, Alice](#)
Bcc: [Pierce, William \(CDER\)](#)
Subject: RE: NDA 203971 - Proposed PI
Date: Friday, April 19, 2013 1:22:00 PM

Hi Deepika,

The two patients IDs are:

1. 034-004
2. 146-004

Regards,

Elleni

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Thursday, April 18, 2013 10:58 AM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Proposed PI

Hi Elleni,

Thank you for your response. We have an additional request for clarification.

In section 5.1, reference is made to the following sentence proposed by the FDA: There were two deaths due to bone marrow failure in patients treated with Xofigo.

Bayer kindly requests the patient ids for these two patients.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Wednesday, April 17, 2013 4:45 PM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Proposed PI
Importance: High

Hi Deepika,

Please find below the revised patient numbers.

This labeling statement is based on patient deaths directly attributed to hemorrhagic events or deaths that occurred with temporally associated serious hemorrhagic complications (e.g., cerebral hemorrhage, hemorrhagic CVA, multiple hemorrhages). The selected terms and grouping are based on the MedDRA HLGT level term, vascular

hemorrhagic disorders. The patient ID#s for these cases are as follows: Xofigo: #002-013, #004-001, #037-012, #170-002, #146-004, #173-008, #234-005; Placebo: #033-025. We note that patient #9050-018 could also be considered in this calculation based on the 90 day safety update narrative. Patient #034-004 (Xofigo arm) was also considered, but not included based on the case narrative.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Wednesday, April 17, 2013 2:37 PM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Proposed PI

Hi Elleni,

Thank you very much for the response.

We noticed that patient 037-012 was repeated in both the Xofigo and placebo arms. Based on our review, this patient received Xofigo treatment. Please kindly clarify.

Unfortunately, we were not able to identify patient 107-002 in the Xofigo arm. Please kindly clarify.

Thank you!

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Tuesday, April 16, 2013 12:22 PM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: FW: NDA 203971 - Proposed PI
Importance: High

Hi Deepika,

Please see below to FDA's response to your request for clarification.

This labeling statement is based on patient deaths directly attributed to hemorrhagic events or deaths that occurred with temporally associated serious hemorrhagic

complications (e.g., cerebral hemorrhage, hemorrhagic CVA, multiple hemorrhages). The selected terms and grouping are based on the MedDRA HLGT level term, vascular hemorrhagic disorders. The patient ID#s for these cases are as follows: Xofigo: #002-013, #004-001, #037-012, #107-002, #146-004, #173-008, #234-005; Placebo: #037-012. We note that patient #9050-018 could also be considered in this calculation based on the 90 day safety update narrative. Patient #034-004 (Xofigo arm) was also considered, but not included based on the case narrative.

Regards,

Elleni

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Tuesday, April 16, 2013 9:34 AM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Proposed PI

Hi Elleni,

Thank you very much for the response.

An additional point of clarification is requested below in the Warnings and Precautions section.

In Section 5.1 Bone Marrow Suppression, reference is made to the following sentence proposed by the FDA: In the randomized trial, in patients experiencing myelosuppression, there was an increase in deaths related to vascular hemorrhage in Xofigo-treated patients (1.2%) compared to patients treated with placebo (0.3%).

Please kindly clarify regarding how vascular hemorrhage is defined and how the respective vascular hemorrhage incidence rates were calculated for the Xofigo and placebo arms.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Monday, April 15, 2013 4:42 PM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Proposed PI
Importance: High

Hi Deepika,

Please find below FDA's response to your request for clarification stated in your April 12, 2013 email.

FDA Response: The A58800 AESAF dataset (July 15, 2011 cutoff) was used. The AEACNN column (i.e., drug permanently withdrawn = 3) was used to select AEs that lead to permanent drug discontinuation. AEs with the following PTN terms were included:

anemia, leukopenia, neutropenia, pancytopenia, and thrombocytopenia. Rechecking our calculations, and removing patients with multiple instances of these AE PTN terms, the recalculated incidence of patients who permanently discontinued therapy due to bone marrow suppression is 4%. If this revision is agreeable, please revise the labeling to reflect this revision in the next labeling submission.

The FDA's rationale for removing Warnings 5.2, 5.3, 5.4, and 5.5 is that these are not serious adverse events that rise to the level of a Warning. We suggest that you include this type of information in Section 14.

Regards,

Elleni

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Friday, April 12, 2013 2:53 PM
To: Alebachew, Elleni
Subject: RE: NDA 203971 - Proposed PI

Hi Elleni,

Thank you for providing the Agency's comments on the Xofigo PI.

As discussed, Bayer is currently in the process of reviewing the FDA proposed changes on the Xofigo PI. We have a few questions regarding the revised Warnings and Precautions section.

- In section 5.1, reference is made to the following sentence proposed by the FDA: On the Xofigo arm, 5% of patients permanently discontinued therapy due to bone marrow suppression. Please kindly clarify which preferred terms are grouped under bone marrow suppression since we were not able to replicate the percentage of patients that permanently discontinued therapy due to bone marrow suppression.
- For sections 5.3 Spinal Cord Compression, 5.4 Bone Fractures and 5.5 Crohn's Disease and Ulcerative Colitis, please kindly provide the Agency's rationale for deleting these Bayer proposed Warnings and Precautions.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Thursday, April 11, 2013 9:26 AM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: NDA 203971 - Proposed PI
Importance: High

Hi Deepika,

Attached please find the FDA proposed PI (with track-change). Please respond by Friday, **April 19, 2013**.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
04/22/2013

From: Alebachew, Elleni
To: ["Deepika Jalota"](#)
Cc: [Kacuba, Alice](#)
Bcc: [Maher, Virginia E.](#)
Subject: RE: NDA 203971 - Proposed PI
Date: Monday, April 15, 2013 4:42:00 PM
Importance: High

Hi Deepika,

Please find below FDA's response to your request for clarification stated in your April 12, 2013 email.

FDA Response: The A58800 AESAF dataset (July 15, 2011 cutoff) was used. The AEACNN column (i.e., drug permanently withdrawn = 3) was used to select AEs that lead to permanent drug discontinuation. AEs with the following PTN terms were included: anemia, leukopenia, neutropenia, pancytopenia, and thrombocytopenia. Rechecking our calculations, and removing patients with multiple instances of these AE PTN terms, the recalculated incidence of patients who permanently discontinued therapy due to bone marrow suppression is 4%. If this revision is agreeable, please revise the labeling to reflect this revision in the next labeling submission.

The FDA's rationale for removing Warnings 5.2, 5.3, 5.4, and 5.5 is that these are not serious adverse events that rise to the level of a Warning. We suggest that you include this type of information in Section 14.

Regards,

Elleni

From: Deepika Jalota [mailto:deepika.jalota@bayer.com]
Sent: Friday, April 12, 2013 2:53 PM
To: Alebachew, Elleni
Subject: RE: NDA 203971 - Proposed PI

Hi Elleni,

Thank you for providing the Agency's comments on the Xofigo PI.

As discussed, Bayer is currently in the process of reviewing the FDA proposed changes on the Xofigo PI. We have a few questions regarding the revised Warnings and Precautions section.

- In section 5.1, reference is made to the following sentence proposed by the FDA: On the Xofigo arm, 5% of patients permanently discontinued therapy due to bone marrow suppression. Please kindly clarify which preferred terms are grouped under bone marrow suppression since we were not able to replicate the percentage of patients that permanently discontinued therapy due to bone marrow suppression.
- For sections 5.3 Spinal Cord Compression, 5.4 Bone Fractures and 5.5 Crohn's Disease and Ulcerative Colitis, please kindly provide the Agency's rationale for deleting these Bayer

proposed Warnings and Precautions.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Thursday, April 11, 2013 9:26 AM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: NDA 203971 - Proposed PI
Importance: High

Hi Deepika,

Attached please find the FDA proposed PI (with track-change). Please respond by Friday, **April 19, 2013**.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
04/15/2013

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 11, 2013
TIME: 3:15 PM – 3:30 PM
APPLICATION: NDA 203971
APPLICANT: Bayer HealthCare Pharmaceutical
DRUG NAME: Xofigo[®] (radium Ra-223 dichloride)
TYPE OF MEETING: Teleconference
MEETING RECORDER: Elleni Alebachew

FDA ATTENDEES:

Robert L. Justice, M.D., M.S., Director, DOP1
Amna Ibrahim M.D., Deputy Director, DOP1
V. Ellen Maher, M.D., Clinical Team Leader, DOP1
Paul Kluetz, M.D., Medical Officer, DOP1
Eldon E. Leutzinger, Ph.D., CMC Lead, ONDQA
Martin T. Haber, Ph.D., Chemistry Reviewer, ONDQA
Ali Al-Hakim, Ph.D., Branch Chief, ONDQA
Todd Bridges, Pharm. D., DMEPA
Alice Kacuba, R.N., M.S.N, RAC, CPMS, DOP1
Elleni Alebachew, M.S., RAC, Regulatory Project Manager, DOP1

EXTERNAL ATTENDEES:

Bayer

Maria C. Garrigan, Director, Global Regulatory Affairs, Oncology
Deepika Jalota, Pharm.D., Deputy Director, Global Regulatory Strategist
Mike Koenig, M.S., Associate Director, CMC Regulatory Affairs
Marion Resch, Deputy Director, Global Regulatory Strategist
Audrey Anderson, M.S., Sr. Global Labeling Manager & Head - US Labeling
Gary Lunger, MSRIS, RT(R)(N)ARRT Deputy Director, Oncology Marketing
Jeffrey Bova, Director, Oncology Marketing
Mona Wahba, M.D., M.S.M. Deputy Director, U.S. Medical Affairs, Oncology

Algeta

Reidun Holtan Palm, Director, Regulatory Affairs CMC
Shaemus Gleason, Radiotherapy Specialist
Colin Biggin, Ph.D., Director, Radiation Safety Officer

BACKGROUND

On March 13, FDA requested this teleconference to discuss Bayer's April 4, 2013 response to FDA's information request, specifically, Bayer's reluctance to accept FDA's recommendations; 1) Bayer's plan to use Central European Time (CET) instead of US Central Time (CT) Zone and 2) Bayer's plan to keep the initially proposed storage information "Store at room temperature, below 40°C (104°F)".

DISCUSSION

FDA stated that since the label is intended for use in the United States and because US Nuclear pharmacists might be unfamiliar with using CET, all time zones referenced in the decay factor table and container labels should be revised to US Central Time Zone. Bayer stated that they would prefer to keep Central European Time as the bases for reference date to provide a universal calibration date for worldwide use. Bayer reiterated that the pharmacists do not need to be concerned with CET as long as the US-specific Decay Correction Factor Table is in the PI. FDA requested for Bayer to add both time zones and also show the time difference by adding "12 noon = 5 am CET". Bayer agreed to this proposal.

FDA also asked for Bayer's rationale for keeping the storage information as "Store at room temperature, below 40°C (104°F)". Bayer stated that they are keeping this storage information to have flexibility during product shipments and stated that the data supports the proposed storage condition. FDA agreed with the initial proposed storage information: "Store at room temperature, below 40°C (104°F)".

OUTCOME:

Bayer agreed to provide updated Decay Correction Factor Table in the Package Insert when they respond to FDA's proposed label by April 19, 2013.

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/s/

ELLENI K ALEBACHEW
05/13/2013

VIRGINIA E MAHER
05/13/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Maher, Virginia E.](#)
Subject: NDA 203971 - Proposed PI
Date: Thursday, April 11, 2013 9:26:00 AM
Attachments: [NDA 203971-Proposed Label \(FDA Revised\) - 4.11.13.doc](#)
Importance: High

Hi Deepika,

Attached please find the FDA proposed PI (with track-change). Please respond by Friday, **April 19, 2013**.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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

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/s/

ELLENI K ALEBACHEW
04/11/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Bridges, Todd](#)
Subject: NDA 203971 - Information Request-Decay Correction Factor Table
Date: Tuesday, April 09, 2013 8:54:00 AM
Importance: High

Hi Deepika

Reference is made to your NDA 203971 submitted on December 14, 2012. Please find the Information Request below.

Please provide your planned distribution of Decay Correction Factor Table, if it's not part of the approved PI. Please describe all methods of planned distribution of the table in detail (e.g., do you intend to include with the product, on the internet, distribute by sales force, etc.?).

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
04/10/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971 - Clinical Pharmacology Information Request
Date: Monday, April 01, 2013 4:52:00 PM
Attachments: [Xofigo_IR_NDA203971_April01_2013.pdf](#)

Hi Deepika,

Attached please find an information request for NDA 203971. Please respond by **April 3, 2013**.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

Reference is made to your NDA203971 submitted on December 14, 2012, and your submission on March 28, 2013 (for follow-up to the Mid-Cycle review status update meeting held on February 28, 2013), as well as FDA's information request regarding a combination trial proposal conveyed on March 28, 2013. Please find the Information Request below based on FDA findings analyzing the impact of ideal body weight (IBW) normalized dose on the overall survival (OS) hazard ratio in your pivotal Phase 3 trial BC1-06 (ALSYMPCA). Please provide a written response via 1) email to facilitate review and 2) by official amendment to the NDA by April 03, 2013.

INFORMATION REQUEST

Please refer to the attached FDA exploratory analyses regarding the impact of IBW-normalized dose on the overall survival. Compared to total body weight, a more clear relationship was observed between the IBW-normalized dose and the overall survival hazard ratio: the larger the IBW-normalized dose, the lower hazard ratio. Please provide a written response with the following considerations:

1. Whether you agree with our analyses;
2. Based on our analysis, we think IBW-based dosing strategy may decrease variability in the response (Figure 1) compared to total body weight based dosing. Nonetheless, we agree with you that a dose of 80 kBq/kg total body weight may be an appropriate dose for further evaluation, as this dose will likely result in lower hazard ratios for most patients (Figure 2). We recommend that you continue to conduct analyses to evaluate the impact of various body size descriptor (e.g., IBW, or TBW/IBW) on the efficacy and safety of your future trials, especially in your post-marketing dose optimization trial(s). Please comment whether you agree with this recommendation.

SUMMARY OF FDA FINDINGS

This document describes the exploratory analyses conducted by the FDA using clinical data of trial BC1-06 to explore the relationship between ideal body weight (IBW) normalized dose and overall survival (OS).

Relationship between IBW-normalized dose and OS

As radium-223 does not have significant distribution into the adipose tissue, patients with a larger TBW/IBW ratio may have a higher drug exposure in the bone, and therefore a better efficacy response. One way to look at this issue is an analysis between IBW normalized dose [using equation $(TBW \times 50 \text{ kBq/kg})/IBW$] and overall survival (OS). The analysis results indicate that higher IBW-normalized dose is related with better OS improvement (Figure 1), whereas the trend is not so clear for the total body weight.

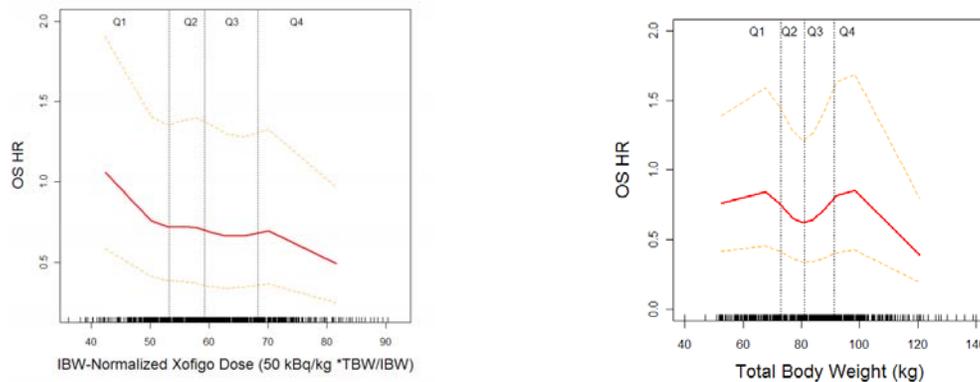
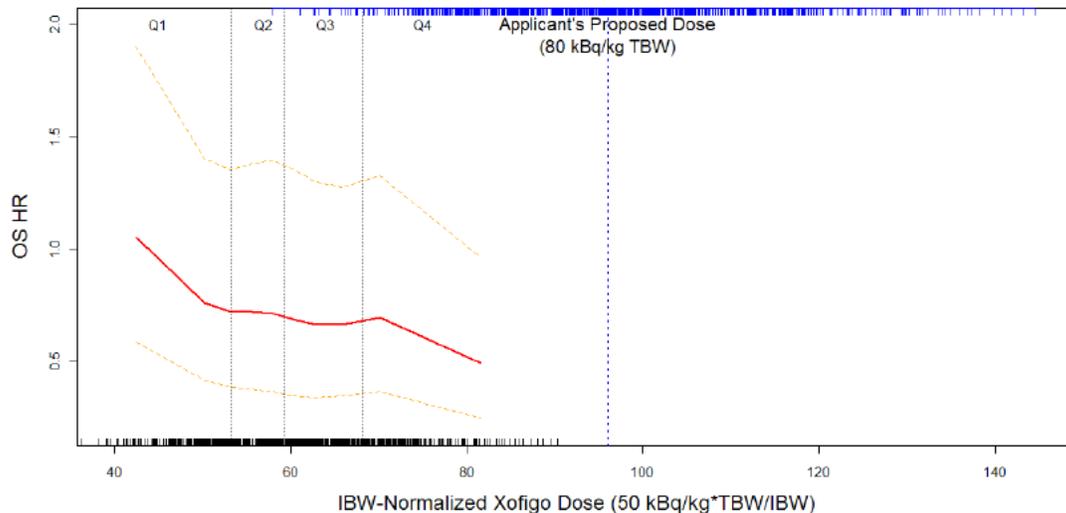


Figure 1: Left figure shows ratios of overall survival (OS) hazard at different ideal body weight (IBW) normalized Xofigo dose in Trial BC1-06. Right figure shows ratios of overall survival (OS) hazard at different total body weight (TBW). The IBW-normalized Xofigo dose was calculated for each patient using equation $(TBW \times 50 \text{ kBq/kg})/IBW$. Hazard ratio (HR) vs. the control arm for each of 10 quantiles of IBW-normalized dose was estimated using a Cox proportional hazards model stratified by the following baseline covariates: total ALP ($< 220 \text{ U/L}$ versus total ALP $\geq 220 \text{ U/L}$), concurrent use of bisphosphonates use (yes versus no), and prior use of docetaxel (yes versus no). Solid red line connected the point estimate of hazard ratio for each of 10 quantiles. Dashed orange lines connected the 95% confidence interval of the point estimates. Three dotted vertical lines separate space for four quartiles of IBW-normalized Xofigo dose. Each of the black tick above the upper x-axis represents a patient's IBW-normalized Xofigo dose. Right figure for ratios of overall survival (OS) hazard at different total body weight used the same setting for hazard ratio estimation and graph plotting.

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Acceptability of a dose of 80 kBq/kg TBW in post-marketing trial

Figure 2 demonstrated the applicant's proposed dose of 80 kBq/kg TBW will likely result in lower OS hazard ratios for most patients, and therefore may be an appropriate dose for further evaluation. However, it is also worthwhile to note that utilization of an IBW-based dosing strategy would be likely to provide better toxicity profiles by reducing the extremes on the high exposure side.



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Figure 2: Ratios of overall survival (OS) hazard at different ideal body weight (IBW) normalized Xofigo dose in Trial BC1-06. The IBW-normalized Xofigo dose was calculated for each patient using equation $(TBW \times 50kBq/kg)/IBW$. Hazard ratio (HR) vs. the control arm for each of 10 quantiles of IBW-normalized dose was estimated using a Cox proportional hazards model stratified by the following baseline covariates: total ALP (< 220 U/L versus total ALP ≥ 220 U/L), concurrent use of bisphosphonates use (yes versus no), and prior use of docetaxel (yes versus no). Solid red line connected the point estimate of hazard ratio for each of 10 quantiles. Dashed orange lines connected the 95% confidence interval of the point estimates. Three dotted vertical lines separate space for four quartiles of IBW-normalized Xofigo dose. Each of the black tick above the x-axis represents a patient's IBW-normalized Xofigo dose. The blue dotted vertical line represents the mean IBW-normalized dose of 96 kBq/kg IBW, which was calculated by multiplying the applicant's proposed dose of 80 kBq/kg TBW by 1.2 (mean ratio value of TBW/IBW in Trial BC1-06). Each of the blue tick under the upper side of the plot represents a patient's IBW-normalized Xofigo dose using a dose of 80 kBq/kg TBW.

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/s/

ELLENI K ALEBACHEW
04/01/2013

From: Alebachew, Elleni
To: ["Deepika Jalota"](#)
Cc: [Kacuba, Alice](#)
Bcc: [Maher, Virginia E.](#)
Subject: RE: NDA 203971 - Response to Information Request recd on Feb 22 (Dose calibrator information)
Date: Friday, March 08, 2013 4:28:00 PM
Importance: High

Hi Deepika,

Please refer to your submission eCTD sequence no. 0024.

We refer to Appendix 2 (Radium Ra 223 Dichloride Dose Calibrator Calibration Procedure) in your March 5, 2013 submission. Please provide information on the future use of this document. For example, do you intend to include this document with each carton?

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

From: Deepika Jalota [mailto:deepika.jalota@bayer.com]
Sent: Tuesday, March 05, 2013 5:19 PM
To: Alebachew, Elleni
Subject: RE: NDA 203971 - Response to Information Request recd on Feb 22 (Dose calibrator information)

Hi Elleni,

In follow-up to our earlier discussion, please note that the email version of response no. 1 was updated to reflect the yellow highlighted text below for the request for information referenced below. The updated response was submitted today as part of a formal amendment to the NDA (eCTD sequence no. 0024):

Request no. 1

Request:

Provide all available data regarding what dose calibrators were used with what settings and with what reference standards in the BC1-06 phase III clinical trial.

Response:

Appendix 1 presents the different dose calibrator models and dial settings used in each country that participated in the BC1-06 study. There are three main manufacturers of these instruments: Capintec, Biodex and Veenstra. Each manufacturer has several models of these instruments.

Based on the information provided in Appendix 1, the Capintec CRC-15 is the most commonly used instrument in the BC1-06 study (n = 69); dial settings ranged from 239-295. The Biodex Atomlab 100 was the second most used instrument in the BC1-06 study (n= 18); dial settings ranged from 14 to 19.5. The Veenstra VDC-405 was the third most used instrument in the BC1-06 study (n= 14); dial settings ranged from 630-653. Other models from the main three manufacturers were also used in the study and a variety of dose calibrators from smaller instrument companies.

All BC1-06 clinical study sites were able to find appropriate dial settings for their respective dose calibrators when using the NIST traceable reference source of Ra-223 supplied from the manufacturer, Institute for Energy Technology (IFE).

Thank you in advance for your understanding.

Best regards,
Deepika

From: Deepika Jalota
Sent: Tuesday, March 05, 2013 10:28 AM
To: 'Alebachew, Elleni'
Subject: RE: NDA 203971 - Response to Information Request

Hi Elleni,

I apologize for missing your call. That is correct. The formal amendment to the NDA for the response below will be submitted today.

Thank you in advance.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Tuesday, March 05, 2013 10:23 AM
To: Deepika Jalota
Subject: RE: NDA 203971 - Response to Information Request

Hi Deepika,

I wanted to follow up my voice mail with this email. I wanted to make sure the formal amendment to the NDA for the response below will be submitted today.

Elleni

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Friday, March 01, 2013 6:28 AM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Response to Information Request

Hi Elleni,

Attached is the response to the FDA Request for Information (referenced below) and associated

supportive reports and references. Appendix 1 which contains Records on instrument dial settings established during the course of Study BC1-06 will be provided as part of the formal amendment to the NDA that is planned for submission no later than March 5, 2013.

Thank you in advance for your understanding.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Friday, February 22, 2013 2:22 PM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: NDA 203971 - Information Request
Importance: High

Hi Deepika,

We have Information Request for NDA 203971. **Please reply as soon as possible but no later than February 28, 2013** by 1) email to facilitate review and 2) by official amendment to the NDA.

We are concerned that commercial U.S. nuclear pharmacies (outside of clinical trial conditions) may not be able to accurately measure the correct dose of Radium-223 using standard dose calibrators.

1. Provide all available data regarding what dose calibrators were used with what settings and with what reference standards in the BC1-06 phase III clinical trial.
2. Typically, how much gamma radiation was measured (microCuries) to verify the dose in BC1-06?
3. How do the detectors used in BC1-06 differ from the range of detectors used in standard clinical practice at U.S. nuclear pharmacies?
4. Please forward a copy of any applicable NIST reports on Radium-223 measurements.
5. What NIST traceable source (radioactive reference standards) are proposed for use at commercial U.S. nuclear pharmacies for measurements of your drug?
6. What dose calibrators and what exact setting(s) are proposed for commercial (non-clinical trial) clinical use?
7. Provide data supporting the ability of commonly used U.S. dose calibrators to verify the radiation dose of Radium-223 with respect to limit of detection, limit of quantitation and measurement variability.
8. Support your proposed plan for accurate dosing with a discussion of the appropriate physics.
9. Propose adequate labeling on this issue

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1

Office of Hematology and Oncology Products

OND/CDER/FDA

E-mail: Elleni.Alebachew@fda.hhs.gov

Phone: (301) 796-5225

Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
03/08/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Abdus-Samad, Jibril](#); [Maher, Virginia E.](#)
Subject: NDA 203971 - Information Request 3.5.13
Date: Tuesday, March 05, 2013 4:28:00 PM
Importance: High

Hi Deepika,

Please refer to your proposed labeling for Xofigo (NDA 203971). Please reply by 1) email to facilitate review and 2) by official amendment to the NDA by March 13, 2013

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)

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
03/05/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: RE: NDA 203971 - Information Request from Clinical Pharmacology
Date: Tuesday, March 05, 2013 3:13:00 PM
Importance: High

Hi Deepika,

Please refer to your responses submitted on February 27, 2013 (see below) under NDA 203971. Please submit the SAS codes that you used by March 06, 2013.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Wednesday, February 27, 2013 4:58 PM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Information Request from Clinical Pharmacology

Hi Elleni,

Attached is the Response to the FDA Request for Information referenced below. Appendix 1 and the supportive tables are also attached. A formal NDA amendment containing the associated datasets, define.pdf documents and references will be submitted today (after 4:30 PM).

Best regards,
Deepika

From: Deepika Jalota
Sent: Monday, February 18, 2013 9:24 AM
To: 'Alebachew, Elleni'
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Information Request from Clinical Pharmacology

Hi Elleni,

Based on our assessment of the request for information, Bayer will be able to provide a response by February 27, 2013. Please let me know if you have any questions.

Thank you in advance for your understanding.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Friday, February 15, 2013 10:31 AM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: NDA 203971 - Information Request from Clinical Pharmacology
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012. Please submit your written response and related datasets. Please reply by 1) email to facilitate review and 2) by official amendment to the NDA by **February 25, 2013**.

- We recommend that you conduct literature search to assess the relationship between the bone mass and various body size descriptors (such as BMI, BSA, total body weight, lean body weight, ideal body weight, adjusted body weight, fat-free mass, etc). Please share your findings with FDA.
- Please evaluate the relationship between body weight normalized doses (using total body weight, ideal body weight, lean body weight, adjusted body weight, as well as any other appropriate body size descriptor) and biomarker responses (including ALP and PSA) after the first injection across all clinical trials. Please consider conducting the analyses at 50 kBq/kg and across the dose range tested.
- Please evaluate the relationship between overall survival and body weight normalized doses (using ideal body weight, lean body weight, adjusted body weight, as well as any other appropriate body size descriptor) in the BC1-06 trial.
- Please evaluate the relationship between overall survival and cumulative dose of Xofigo, between overall survival and dose intensity (i.e. cumulative dose/time on treatment) in the BC1-06 trial.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1*

Office of Hematology and Oncology Products

OND/CDER/FDA

E-mail: Elleni.Alebachew@fda.hhs.gov

Phone: (301) 796-5225

Fax: (301) 796-9845

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For alternate languages please go to <http://bayerdisclaimer.bayerweb.com>

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/s/

ELLENI K ALEBACHEW
03/05/2013



NDA 203971

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bayer HealthCare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045

ATTENTION: Deepika Jalota, Pharm.D.
Deputy Director, Global Regulatory Affairs

Dear Dr. Jalota:

Please refer to your New Drug Application (NDA) dated and received December 14, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Radium Ra 223 Dichloride Injection, 1,000 kBq/mL (0.027 mCi/mL).

We also refer to your January 10, 2013 correspondence, received January 10, 2013, requesting review of your proposed proprietary name, Xofigo. We have completed our review of the proposed proprietary name, Xofigo and have concluded that it is acceptable.

The proposed proprietary name, Xofigo, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics as stated in your January 10, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Elleni Alebachew at (301) 796-5225.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
03/29/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Abdus-Samad, Jibril](#)
Subject: NDA 203971 - Information Request - Carton and Container
Date: Thursday, March 28, 2013 3:03:00 PM
Attachments: [203971 DMEPA ONDOA Carton container response 03282013.doc](#)

Hi Deepika,

Reference is made to your March 13 submission (eCTD seq#0028).

Attached please find an information request for NDA 203971. Please respond by **April 4, 2013**.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

March 28, 2013

DMEPA and ONDQA provide recommendations for the Applicant's March 13, 2013 submission.

COMMENTS TO THE APPLICANT

A. Container Label

1. Debold the total volume, 6 mL.
2. Delete the alpha graphic (α) as it competes with the prominence of more important information on the principal display panel. You did not propose any specific instructions to communicate regarding the alpha emitting properties.
3. Ensure the established name is at least half the size of the proprietary name per CFR 201.10(g)(2). Additionally, ensure the proprietary and established names are the most prominent information and have commensurate prominence. Currently, the established name is in a small gray font and is less prominent than the strength.
4. Debold the route of administration, For Intravenous Administration.

B. Lead Container Label

1. See comments A1 through A4.
2. Insert a space between the numeral and units of the total volume so that **6mL** appears as 6 mL.
3. Revise the storage information to read:

Store at USP controlled room temperature 20° C to 25° C
(68° F to 77° F).
4. Add the amount of sodium citrate USP, 7.2 mg, to the right-side panel.

C. Time Zone issues

US Nuclear pharmacists are unfamiliar with using Central European Time. Additionally, the times of the reference date (12 PM Central European Time = 6 AM US Central Time) and the decay factor table differ (12 pm US Central Standard Time). Although you adjust the time zone, we are unaware of radiopharmaceutical products that are labeled similarly. Therefore, we request the following:

1. Revise the all time zones to a US Central Time Zone. For example, the container labels should read 6 AM Central Time (CT) in US.
2. Adjust the Decay Factor tables accordingly such that Decay Factor on Day 0 = 1, instead of 0.98.

D. Decay Correction Factor Table

1. Authorized users can verify the radioactivity of the prepared dose prior to dispensing using a dose calibrator. (b) (4)

2. In the *Determining the Decay Factor* chart, list the physical decay factor with three digits after the decimal point.

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

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/s/

ELLENI K ALEBACHEW
03/28/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Maher, Virginia E.](#); [Pierce, William \(CDER\)](#)
Subject: NDA 203971- Clinical Information Request
Date: Thursday, March 28, 2013 2:43:00 PM
Attachments: [corrected calcium.all columns JMP](#)
Importance: High

Hi Deepika,

Reference is made to your NDA 203971 submitted on December 14, 2012. Please find the Information Request below.

Review of the laboratories found a number of patients to have hypocalcemia. Our initial thought was that this was related to the low albumin frequently seen in patients with advanced cancer. However, when we corrected the calcium for the albumin, we found 221 patients in the Radium and 114 in the placebo arm to have had a low calcium. Please perform an analysis of corrected calcium, by arm and grade, and provide your results by **April 2nd**; **April 3rd if the 2nd is not possible.**

Please see attached dataset.

Regards,

Elleni Alebachew, MS, RAC

Regulatory Health Project Manager

Division of Oncology Products 1

Office of Hematology and Oncology Products

OND/CDER/FDA

E-mail: Elleni.Alebachew@fda.hhs.gov

Phone: (301) 796-5225

Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
03/28/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971 - Information Request
Date: Thursday, March 28, 2013 12:18:00 PM
Attachments: [IR_Xofigo_NDA203971_March28_2013.pdf](#)
Importance: High

Hi Deepika,

Attached please find an information request for NDA 203971. Please respond by April 2, 2013.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

Reference is made to your NDA203971 submitted on December 14, 2012, and your responses to FDA's Information Requests (Sequence 16 on February 8, 2013; Sequence 0033 on March 21, and 0035 on March 25), as well as your Pre-Phase 3 meeting request (submitted on March 20, 2013 under IND67521) for a trial of Xofigo in (b) (4) for the treatment of patients with castration-resistant prostate cancer (CRPC) with bone metastases.

Please find the Information Request below regarding a potential pathway to optimize Xofigo dosing in the most efficient manner. Please provide a written response via 1) email to facilitate review and 2) by official amendment to the NDA by April 2, 2013.

INFORMATION REQUEST

Based on the findings we conveyed on February 1, 2013, we plan to request that you conduct a post-marketing trial is needed to evaluate the efficacy and safety of Xofigo at a higher dose.

In your response submitted on February 08, 2013, you proposed (b) (4)

We agree that 80 kBq/kg is an appropriate dose for further evaluation. Evaluation in the proposed Phase 2 trials, however, may not be the most efficient way to support a different dosing regimen recommendation in the Xofigo label as you ultimately may still need to conduct a Phase 3 trial to further evaluate the efficacy and safety of the 80 kBq/kg dose of Xofigo.

We think a more efficient approach is to conduct the Phase 3 trial of Xofigo in (b) (4)

Please consider the following points in your written response:

1. Please comment on the feasibility of our recommended approach.
2. If you decide to take our recommended approach, please provide an outline of the (b) (4) Phase 3 trial.

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/s/

ELLENI K ALEBACHEW
03/28/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika_Jalota_(deepika.jalota@bayer.com))
Cc: [Kacuba, Alice](#)
Subject: NDA 203971- Response to Information Request - Follow-up to FDA teleconference held on March 20, 2013
Date: Wednesday, March 27, 2013 5:41:00 PM
Importance: High

Hi Deepika,

Please refer to your response submitted on March 25, 2013, specifically your responses to #3. Please reply as soon as possible but no later than **March 29, 2013** by 1) email to facilitate review and 2) by official amendment to the NDA.

Please provide a statement that **prior** to implementing any changes in your current distribution model, Bayer will discuss these changes with the FDA.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Monday, March 25, 2013 8:02 PM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: RE: NDA 203971- Response to Information Request - Follow-up to FDA teleconference held on March 20, 2013

Hi Elleni,

Attached is the Response to the FDA Requests for Information received during the FDA Teleconference held on March 20, 2013.

Best regards,
Deepika

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ELLENI K ALEBACHEW
03/27/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Leutzinger, Eldon E](#); [Maher, Virginia E](#)
Subject: NDA 203971 - Information Request
Date: Wednesday, March 27, 2013 9:33:00 AM

Hi Deepika,

Please refer your submission eCTD seq# 36 received on March 25, 2013, specifically your responses to #2 and #3. Please reply as soon as possible but **no later than March 29, 2013** by 1) email to facilitate review and 2) by official amendment to the NDA.

1. FDA is concerned that the clinical site may perform radioactivity measurements with different sized vials, syringes, and geometries. Do you have data that shows the effect when using different sized syringes, different material such as glass or plastic, different thicknesses, or different geometric configurations within the dose calibrator?
2. FDA is concerned that the actual administered radioactivity be determined at the clinical site with a pre-administration measurement and a post-administration measurement. Instructions to the user should be clear enough so that a distant radiopharmacy's measurement is not considered a substitute for the individual patient measurement.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
03/27/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Maher, Virginia E.](#)
Subject: NDA 203971-Information Request
Date: Friday, March 22, 2013 9:30:00 AM
Importance: High

Hi Deepika,

Please refer to the discussions during the Mid-Cycle communication and the March 20, 2013 teleconferences between Bayer and FDA. Please provide the timelines for when you plan to submit the following information.

1. Proposed PMRs and PMC's
2. The addition of dose calibration to the proposed Package Insert
3. Statement regarding the use of a commercial radiopharmacy and any changes to your product distribution.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
03/22/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971 - Information Request
Date: Thursday, March 21, 2013 9:43:00 AM
Importance: High

Hi Deepika

Please clarify whether you have ongoing trials for hormone-sensitive prostate cancer, metastatic status of protocol [REDACTED] he
[REDACTED] (b) (4)

Please reply by 1) email to facilitate review and 2) by official amendment to the NDA by **COB today.**

Regard,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
03/21/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Pierce, William \(CDER\)](#)
Subject: NDA 203971 - Clinical Information Request
Date: Thursday, March 21, 2013 9:24:00 AM
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012. Please respond to the information request below by 1) email to facilitate review and 2) by official amendment to the NDA as soon as possible but no later than **March 26, 2013.**

1. Provide narratives and case report forms (CRFs) for the following patients or direct us to them in the submission. These are patients who have experienced malignant secondary tumors during the BC1-06 trial or a trial included in the integrated safety analysis (e.g., Table 4-1); or are BC1-06 trial patients with data that make it unclear if the tumor is a new malignant cancer or likely related to metastatic prostate cancer.

BC1-02
#BLO-506
#KLR-703
#ICK-105

BC1-04
#208

BC1-06
BC1-06-205-005
BC1-06-241-001
BC1-06-244-001
BC1-06-254-003
BC1-06-9050-012
BC1-06-004-008
BC1-06-006-048
BC1-06-050-001

BC1-06
BC1-06-006-022
BC1-06-028-007

2. Provide narratives and CRFs for any additional cases of malignant secondary tumors up to the 90-day safety cutoff date (December 1, 2012) or confirm that no additional cases have been reported.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
03/21/2013

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 20, 2013
TIME: 12:00 PM – 12:30 PM
APPLICATION: NDA 203971
APPLICANT: Bayer HealthCare Pharmaceutical
DRUG NAME: Xofigo® (radium Ra-223 dichloride)
TYPE OF MEETING: Teleconference
MEETING RECORDER: Elleni Alebachew

FDA ATTENDEES:

Robert L. Justice, M.D., M.S., Director, DOP1
Amna Ibrahim M.D., Deputy Director, DOP1
V. Ellen Maher, M.D., Clinical Team Leader, DOP1
Paul Kluetz, M.D., Medical Officer, DOP1
William Pierce, Pharm.D., Sr. Clinical Analyst, DOP1
Eldon E. Leutzinger, Ph.D., CMC Lead, ONDQA
Martin T. Haber, Ph.D., Chemistry Reviewer, ONDQA
Richard Fejka, Clinical Analyst, Nuclear Pharmacologist
Orhan Suleiman, Ph.D., Senior Science Policy Analyst
Elleni Alebachew, M.S., RAC, Regulatory Health Project Manager

EXTERNAL ATTENDEES:

Bayer

Ira Arshen, Director, Supply Chain Management
Jeffrey Bova, Director, Oncology Marketing
Lothar Everz, Ph.D., CMC Radiopharmaceutical Science
Maria C. Garrigan, Director, Global Regulatory Affairs, Oncology
Juergen Gay Ph.D., CMC Radiopharmaceutical Science
Joseph Germino, M.D., Ph.D. VP, Medical Affairs, Oncology, Hematology and Neurology
Deepika Jalota, Pharm.D., Deputy Director, Global Regulatory Strategist
Mike Koenig, M.S., Associate Director, CMC Regulatory Affairs
Gary Lunger, MSRIS, RT(R)(N)ARRT Deputy Director, Oncology Marketing
Mona Wahba, M.D., M.S.M. Deputy Director, U.S. Medical Affairs, Oncology

Algeta

Shaemus Gleason, Radiotherapy Specialist
Reidun Holtan Palm, Director, Regulatory Affairs CMC

(b) (4)

BACKGROUND

On March 13, FDA requested a clarification as to whether Bayer intends to provide the Ra-223 NIST standard to each nuclear pharmacy that will use the product or whether the standard will only be available on request. On March 15, Bayer responded by stating that the NIST traceable secondary standards will be available upon request. FDA requested this teleconference to discuss the use of a NIST standard with Bayer.

DISCUSSION

FDA stated that providing NIST traceable secondary standards only upon request is a safety concern as each radio pharmacy is expected to calibrate the dose calibrator to measure radium Ra-223 prior to administering it to patients. FDA asked Bayer to discuss how Bayer intends to address this issue. Bayer stated that in the current distribution model Bayer intends to implement they will use a central US-based commercial radio pharmacy. The US-based commercial radio pharmacy will use the NIST reference standard to verify the activity of the unit dosage prior to shipping to the administering sites. FDA asked for Bayer to provide information on the current distribution plan as well as assurance that Bayer will discuss any changes to the current distribution plan with the FDA prior to implementing these changes.

OUTCOME:

Bayer agreed to provide 1) draft labeling text for the Dosage and Administration section of the USPI to include information regarding the use of a suitable radioactivity measurement system prior to administration and the use of a NIST traceable standard; 2) Provide written confirmation regarding the current distribution model and 3) Provide assurance that if the distribution model is changed it would be discussed with the FDA prior to implementation of these changes.

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/s/

ELLENI K ALEBACHEW
03/28/2013

VIRGINIA E MAHER
03/29/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971 - Information Request
Date: Tuesday, March 19, 2013 3:07:00 PM
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012. Please provide a brief summary of all ongoing trials of Xofigo regarding the study objectives, patient populations, enrollment status, and dosing regimens. Please reply by 1) email to facilitate review and 2) by official amendment to the NDA by **March 20, 2013**.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
03/19/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Zhang, Hui](#)
Subject: NDA 203971- Statistical Information Request
Date: Thursday, March 14, 2013 4:59:00 PM
Importance: High

Hi Deepika,

Please refer to your response submitted on February 25, 2013 under NDA 203971 (eCTD sequence no. 0019, Response to FDA Request Information received 11 Feb 2013 (Part 2)). In this response, you provided a sensitivity analysis for OS adjusting for imbalance in Gleason score at diagnosis and a sensitivity analysis for OS adjusting for imbalance in baseline PSA at screening. We are unable to reproduce results of these two sensitivity analyses. Please provide variables, datasets name and sample code used for these analyses.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
03/14/2013

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705



To: Deepika Jalota, PharmD
FAX: 973-487-2016
E-mail: deepika.jalota@bayer.com
Phone: 973-487-2782
Pages, including cover sheet: 1

From: Elleni Alebachew
FAX: 301-796-9845
E-mail: elleni.alebachew@fda.hhs.gov
Phone: 301-796-5225
Date: March 13, 2013

RE: Clinical Information Request (NDA 203971)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address below by mail. Thank you.

Dear Dr. Jalota:

Please refer to your NDA 203971 submitted on December 14, 2012. Please reply by **March 15, 2013** 1) email to facilitate review and 2) by official amendment to the NDA.

We are having difficulty confirming your concomitant anti-cancer medications while on-study (Table 8 page 83 of CSR A58799). Please provide us with a summary of how the analysis was conducted including a copy of the SAS code.

Please confirm receipt.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
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DATE/TIME = MAR-13-2013 17:25
JOURNAL No. = 123
COMM. RESULT = OK
PAGE(S) = 001/001
DURATION = 00:00:21
FILE No. = 898
MODE = MEMORY TRANSMISSION
DESTINATION = 919734872016
RECEIVED ID =
RESOLUTION = STD

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- ***** -

3017969845- *****

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/s/

ELLENI K ALEBACHEW
03/13/2013

From: Alebachew, Elleni
To: "[Deepika Jalota](#)"
Cc: [Kacuba, Alice](#)
Bcc: [Leutzinger, Eldon E](#); [Maher, Virginia E](#)
Subject: RE: NDA 203971 - Response to Information Request recd on Feb 22 (Dose calibrator information)
Date: Wednesday, March 13, 2013 12:54:00 PM
Importance: High

Hi Deepika,

Please clarify whether Bayer intend to provide the Ra-223 standard to each nuclear pharmacy that will use the product or whether the standard will only be available on request? Please reply by **Friday, March 15, 2013.**

-
Regards,

Elleni

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Tuesday, March 12, 2013 1:45 PM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Response to Information Request recd on Feb 22 (Dose calibrator information)

Hi Elleni,

Reference is made to the FDA Request for Information below.

Bayer's response is provided herein:

The Radium Ra 223 Dichloride Dose Calibrator Calibration Procedure will not be provided with the commercial product. This procedure will be provided upon request by end users.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Friday, March 08, 2013 4:29 PM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Response to Information Request recd on Feb 22 (Dose calibrator information)
Importance: High

Hi Deepika,

Please refer to your submission eCTD sequence no. 0024.

We refer to Appendix 2 (Radium Ra 223 Dichloride Dose Calibrator Calibration Procedure) in your March 5, 2013 submission. Please provide information on the future use of this document. For example, do you intend to include this document with each carton?

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Tuesday, March 05, 2013 5:19 PM
To: Alebachew, Elleni
Subject: RE: NDA 203971 - Response to Information Request recd on Feb 22 (Dose calibrator information)

Hi Elleni,

In follow-up to our earlier discussion, please note that the email version of response no. 1 was updated to reflect the yellow highlighted text below for the request for information referenced below. The updated response was submitted today as part of a formal amendment to the NDA (eCTD sequence no. 0024).:

Request no. 1

Request:

Provide all available data regarding what dose calibrators were used with what settings and with what reference standards in the BC1-06 phase III clinical trial.

Response:

Appendix 1 presents the different dose calibrator models and dial settings used in each country that participated in the BC1-06 study. There are three main manufacturers of these instruments: Capintec, Biodex and Veenstra. Each manufacturer has several models of these instruments.

Based on the information provided in Appendix 1, the Capintec CRC-15 is the most commonly used instrument in the BC1-06 study (n = 69); dial settings ranged from 239-295. The Biodex Atomlab 100 was the second most used instrument in the BC1-06 study (n= 18); dial settings ranged from 14 to 19.5. The Veenstra VDC-405 was the third most used instrument in the BC1-06 study (n= 14); dial settings ranged from 630-653. Other models from the main three manufacturers were also used in the study and a variety of dose calibrators from smaller instrument companies.

All BC1-06 clinical study sites were able to find appropriate dial settings for their respective dose calibrators when using the NIST traceable reference source of Ra-223 supplied from the manufacturer, Institute for Energy Technology (IFE).

Thank you in advance for your understanding.

Best regards,
Deepika

From: Deepika Jalota
Sent: Tuesday, March 05, 2013 10:28 AM
To: 'Alebachew, Elleni'
Subject: RE: NDA 203971 - Response to Information Request

Hi Elleni,

I apologize for missing your call. That is correct. The formal amendment to the NDA for the response below will be submitted today.

Thank you in advance.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Tuesday, March 05, 2013 10:23 AM
To: Deepika Jalota
Subject: RE: NDA 203971 - Response to Information Request

Hi Deepika,

I wanted to follow up my voice mail with this email. I wanted to make sure the formal amendment to the NDA for the response below will be submitted today.

Elleni

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Friday, March 01, 2013 6:28 AM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Response to Information Request

Hi Elleni,

Attached is the response to the FDA Request for Information (referenced below) and associated supportive reports and references. Appendix 1 which contains Records on instrument dial settings established during the course of Study BC1-06 will be provided as part of the formal amendment to the NDA that is planned for submission no later than March 5, 2013.

Thank you in advance for your understanding.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Friday, February 22, 2013 2:22 PM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: NDA 203971 - Information Request
Importance: High

Hi Deepika,

We have Information Request for NDA 203971. **Please reply as soon as possible but no later than February 28, 2013** by 1) email to facilitate review and 2) by official amendment to the NDA.

We are concerned that commercial U.S. nuclear pharmacies (outside of clinical trial conditions) may not be able to accurately measure the correct dose of Radium-223 using standard dose calibrators.

1. Provide all available data regarding what dose calibrators were used with what settings and with what reference standards in the BC1-06 phase III clinical trial.
2. Typically, how much gamma radiation was measured (microCuries) to verify the dose in BC1-06?
3. How do the detectors used in BC1-06 differ from the range of detectors used in standard clinical practice at U.S. nuclear pharmacies?
4. Please forward a copy of any applicable NIST reports on Radium-223 measurements.
5. What NIST traceable source (radioactive reference standards) are proposed for use at commercial U.S. nuclear pharmacies for measurements of your drug?
6. What dose calibrators and what exact setting(s) are proposed for commercial (non-clinical trial) clinical use?
7. Provide data supporting the ability of commonly used U.S. dose calibrators to verify the radiation dose of Radium-223 with respect to limit of detection, limit of quantitation and measurement variability.
8. Support your proposed plan for accurate dosing with a discussion of the appropriate physics.
9. Propose adequate labeling on this issue

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
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ELLENI K ALEBACHEW
03/13/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Maher, Virginia E.](#)
Subject: NDA 203971 - Request for Clinical Information
Date: Monday, March 11, 2013 2:56:00 PM
Attachments: [Radium.Laboratories.doc](#)
Importance: High

Hi Deepika,

Please refer to your Response to Information Request in Amendment 19. Please submit your written response 1) email to facilitate review and 2) by official amendment to the NDA.

The method used to determine the laboratory values is included in the attached document. Please explain why this method provides values similar to those in the CSR for most labs, but markedly different values for others. Please provide detailed information on the method you used to obtain the laboratory values in the CSR. **Please reply by March 15, 2013.**

Thanks,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

Chemistries

Response to IR in Amendment 19

Used dosing dates from the exposure dataset to evaluate the date of the lab and determine whether it was on study or > 30 days after the last dose of study drug. Decided to use the analysis dataset, LAB.xpt. This is an analysis dataset for A58800 with data cutoff July 14, 2011 (not the analysis dataset in A58800 Raw Datasets).

1. SAF = 1
2. Remove LABDAY = negative number, 1
3. Used LDOSDTN - LBDTN to determine labs done on study or within 30 days of last dose, kept labs where LDOSDTN _ LBDTN = blank (these resulted from no date of last dose)
4. Used LVALSTD and LBTOXGR to grade the labs
5. Most of the laboratory values were similar to the CSR. However, some (AKP, ANC, lymphs, etc.) are markedly different.

	Radium 223 N = 600		Placebo N = 301	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
ALT (%)	92 (15)	6 (1)	42 (14)	3 (1)
AST (%)	185 (31)	10 (2)	130 (43)	8 (3)
AKP (%)	340 (57)	51 (9)	246 (82)	84 (28)
Bilirubin (%)	18 (3)	1 (0.2)	15 (5)	0
Creatinine (%)	110 (18)	1 (0.2)	64 (21)	0
Hypercalcemia (%)	30 (5)	1 (0.2)	14 (5)	0
Hypocalcemia (%)	176 (29)	3 (0.5)	112 (37)	3 (1)
Hypermagnesemia (%)	74 (12)	1 (0.2)	57 (19)	2 (0.7)
Hypomagnesemia (%)	71 (12)	0	19 (6)	0
Hyperkalemia (%)	77 (13)	1 (0.2)	51 (17)	1 (0.3)
Hypokalemia (%)	83 (14)	4 (0.7)	25 (8)	2 (0.7)
Hypernatremia (%)	40 (7)	0	15 (5)	0
Hyponatremia (%)	129 (22)	13 (2)	72 (24)	9 (3)
Hyperphosphatemia (%)	0	0	0	0
Hypophosphatemia (%)	102 (17)	31 (5)	43 (14)	12 (4)

Gr 3-4 ALT

BC1-06-017-033

BC1-06-025-022

BC1-06-039-016

BC1-06-039-016

BC1-06-048-010

BC1-06-060-010

BC1-06-150-002

Gr 2-4 Bilirubin

BC1-06-017-032

BC1-06-020-005

BC1-06-060-010

BC1-06-209-003

Gr 3 Creatinine

BC1-06-028-003

	Radium 223 N = 600		Placebo N = 301	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
WBC (%)	211 (35)	19 (3)	31 (10)	1 (0.3)
ANC (%)	65 (11)	5 (0.8)	7 (2)	0
Lymphocytopenia (%)	256 (43)	76 (13)	79 (26)	8 (3)
Anemia (%)	555 (93)	33 (6)	264 (88)	17 (6)
Thrombocytopenia (%)	184 (31)	16 (3)	65 (22)	6 (2)

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/s/

ELLENI K ALEBACHEW
03/11/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kluetz, Paul](#)
Subject: NDA 203971 - clinical/statistical Information Request
Date: Friday, March 01, 2013 4:27:00 PM
Importance: High

Hi Deepika,

Please find the following information request from the clinical/statistical reviewers. Please reply by **COB Wednesday March 6, 2013**:

1. We note the PSA response results from BC1-06 are not as robust as the ALP findings and likely reflect the bone-targeted nature of your therapy. Recognizing the limitations with the use of bone scan to determine anti-tumor activity, please provide bone scan results for any trial of Radium-223 which obtained baseline and routine follow up bone scan data. Please provide a brief summary of your interpretation of any bone scan findings.
2. In your response 1 to FDA request for information dated February 11, 2013, you provided the following analyses results.
 - a. time from initiation of hormonal therapy to failure of hormonal therapy
 - b. time from initiation of hormonal therapy after diagnosis of bone mets to failure of hormonal therapy

Please provide datasets, variables and sample code used for this analysis.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
03/01/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971 - Clinical Pharmacology Information Request
Date: Thursday, February 28, 2013 10:14:00 AM
Importance: High

Hi Deepika,

Please refer to your response submitted on February 27, 2013 under NDA 203971. Please provide the following references you cited by 1) email to facilitate review and 2) by official amendment to the NDA.

- Edelstein and Barrett-Connor 1993
- Glauber et al. 1995
- Orwoll et al. 2000
- Ensrud et al. 2006

Thanks,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
02/28/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [John, Christy](#)
Subject: NDA 203971 - Clinical Pharmacology Information Request
Date: Wednesday, February 27, 2013 4:37:00 PM
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012. Please submit your written response **by March 7, 2013**. 1) email to facilitate review and 2) by official amendment to the NDA.

- 1) Please provide separate graphs for Injection 1 and 2 for fraction of injected activity in the **normal bone** as a function of time after injection for all six patients in study BC1-05
- 2) Please provide separate graphs for Injection 1 and 2 for fraction of injected activity in the **plasma** as a function of time after injection for all six patients in study BC1-05

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
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Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
02/27/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Maher, Virginia E.](#); [Kluetz, Paul](#)
Subject: NDA 203971 - Information Request
Date: Friday, February 22, 2013 2:21:00 PM
Importance: High

Hi Deepika,

We have Information Request for NDA 203971. **Please reply as soon as possible but no later than February 28, 2013** by 1) email to facilitate review and 2) by official amendment to the NDA.

We are concerned that commercial U.S. nuclear pharmacies (outside of clinical trial conditions) may not be able to accurately measure the correct dose of Radium-223 using standard dose calibrators.

1. Provide all available data regarding what dose calibrators were used with what settings and with what reference standards in the BC1-06 phase III clinical trial.
2. Typically, how much gamma radiation was measured (microCuries) to verify the dose in BC1-06?
3. How do the detectors used in BC1-06 differ from the range of detectors used in standard clinical practice at U.S. nuclear pharmacies?
4. Please forward a copy of any applicable NIST reports on Radium-223 measurements.
5. What NIST traceable source (radioactive reference standards) are proposed for use at commercial U.S. nuclear pharmacies for measurements of your drug?
6. What dose calibrators and what exact setting(s) are proposed for commercial (non-clinical trial) clinical use?
7. Provide data supporting the ability of commonly used U.S. dose calibrators to verify the radiation dose of Radium-223 with respect to limit of detection, limit of quantitation and measurement variability.
8. Support your proposed plan for accurate dosing with a discussion of the appropriate physics.
9. Propose adequate labeling on this issue

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
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/s/

ELLENI K ALEBACHEW
02/22/2013

From: Alebachew, Elleni
To: ["Deepika Jalota"](#)
Cc: [Kacuba, Alice](#)
Bcc: [Maher, Virginia E.](#)
Subject: RE: NDA 203971 - 90 day safety update alternative proposal
Date: Thursday, February 21, 2013 11:50:00 AM
Importance: High

Hi Deepika,

Please find below FDA's response to your proposal regarding 90 day safety update.

We note that the safety data you have supplied has a database lock date of July 15, 2011, 19 months prior to this date.

1. Narratives and CRFs should be included for all deaths due to an adverse event within 30 days of study drug, discontinuations due to an adverse event, and serious adverse events.
2. CIOMS reports containing case narratives are acceptable. Line listings are not acceptable for events that occurred in your Phase 3 study, BC1-06. Line listings are acceptable for other ongoing studies, but narratives should be available on request.
3. An updated adverse event dataset should be provided for your Phase 3 study, BC1-06.
4. Please provide a written summary including a discussion of any safety findings considered to be substantially different from the conclusions in the original NDA.
5. Please clarify whether all data has been "cleaned" up to the December 1, 2012 cutoff or whether this represents a data snapshot.

Regards,

Elleni

From: Deepika Jalota [mailto:deepika.jalota@bayer.com]
Sent: Wednesday, February 20, 2013 12:21 PM
To: Alebachew, Elleni
Subject: NDA 203971 - 90 day safety update alternative proposal

Hi Elleni,

Reference is made to the Applicant Orientation meeting (Datasets overview session) held on January 4, 2013. For the 90 day safety update, Bayer has evaluated the feasibility of providing updated AE datasets, CRFs and narratives (deaths during treatment or within 30 days after last administration of study drug, SAEs, patients discontinued from treatment due to an AE, and patients withdrawn from the study due to an AE) for the March 14, 2013 target submission date.

Based on our evaluation, we would like to obtain the Agency's agreement on an alternative proposal as noted below:

1. Updated CRFs and narratives for AEs leading to treatment discontinuation or study withdrawal:

Please note that the proposed safety update will only include tables of AEs leading to treatment discontinuation. For SAEs resulting in the discontinuation of treatment, CIOMS-I case narratives

will be provided in lieu of standard CSR narratives. It would be difficult to provide standard Clinical Study Report (CSR) narratives for all these events in these ongoing studies. CRFs would be available upon request.

2. Updated CRFs and narratives for deaths and SAEs:

Please note that the proposed safety update will include SAEs and deaths with CIOMS-II line listings and CIOMS-I case narratives in lieu of standard narratives. Updated CRFs would be available upon request.

3. Updated safety datasets:

Please note that consistent with the approach taken for the safety update to the Regorafenib CRC NDA 203,085, updated safety datasets are not planned for inclusion in the safety update for the Xofigo NDA 203,971. The safety update will focus on an assessment of safety data that may potentially impact on the overall benefit-risk assessment or safety information in the proposed labeling. This includes SAEs, deaths during treatment or within 30 days after last administration of study drug, and adverse events leading to permanent discontinuation of study drug or withdrawal from the study. Updated AE safety datasets for Study BC1-06 would be available upon request.

In summary, Bayer proposes to provide the following as part of the 90 day safety update targeted for submission March 14, 2013:

- Written summary including a discussion of any safety findings considered to be substantially different from conclusions in the original NDA.
- Data review focusing on the following compared to the original NDA
 - Data cut-off: December 1, 2012
 - SAEs and treatment-emergent deaths within 30 days after last administration of study drug from all ongoing radium-223 dichloride studies
 - CIOMS-II line listings
 - CIOMS-I case narratives
 - Adverse events leading to discontinuation or study treatment withdrawal from all ongoing radium-223 dichloride studies
 - Listings

Freundliche Grüße / Best regards,

Deepika Jalota, PharmD
Global Regulatory Strategist



Science For A Better Life

Bayer HealthCare Pharmaceuticals Inc
Global Regulatory Affairs, Specialty Medicine
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ELLENI K ALEBACHEW
02/21/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971 - Information Request from Clinical Pharmacology
Date: Friday, February 15, 2013 10:30:00 AM
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012. Please submit your written response and related datasets. Please reply by 1) email to facilitate review and 2) by official amendment to the NDA by **February 25, 2013**.

- We recommend that you conduct literature search to assess the relationship between the bone mass and various body size descriptors (such as BMI, BSA, total body weight, lean body weight, ideal body weight, adjusted body weight, fat-free mass, etc). Please share your findings with FDA.
- Please evaluate the relationship between body weight normalized doses (using total body weight, ideal body weight, lean body weight, adjusted body weight, as well as any other appropriate body size descriptor) and biomarker responses (including ALP and PSA) after the first injection across all clinical trials. Please consider conducting the analyses at 50 kBq/kg and across the dose range tested.
- Please evaluate the relationship between overall survival and body weight normalized doses (using ideal body weight, lean body weight, adjusted body weight, as well as any other appropriate body size descriptor) in the BC1-06 trial.
- Please evaluate the relationship between overall survival and cumulative dose of Xofigo, between overall survival and dose intensity (i.e. cumulative dose/time on treatment) in the BC1-06 trial.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
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/s/

ELLENI K ALEBACHEW
02/15/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Subject: RE: NDA 203971 - Request for Clinical Information
Date: Tuesday, February 12, 2013 4:55:00 PM

Hi Deepika,

In response to your phone request to provide responses in parts to the IR below:

Please provide the responses in two parts. The first part to be submitted on Friday, February 15, 2013. And the second part to be submitted next Thursday, February 21, 2013.

Regards,
Elleni

From: Alebachew, Elleni
Sent: Monday, February 11, 2013 4:55 PM
To: Deepika Jalota (deepika.jalota@bayer.com)
Cc: Kacuba, Alice
Subject: NDA 203971 - Request for Clinical Information
Importance: High

Hi Deepika,

We have Clinical Information Request for NDA 203971. Please reply by **February 15, 2013** by 1) email to facilitate review and 2) by official amendment to the NDA.

Please note the information request below is also attached as word document.

-

Clinical Efficacy:

1. We have concern regarding imbalances in your baseline demographic data for multiple prognostic factors. It appears that the placebo arm had higher grade disease at diagnosis, higher incidence of metastases at diagnosis (M1) and shorter times to disease progression events (time from diagnosis to randomization, time from confirmed hormone resistance to randomization). We also note the placebo group did not reach as low a PSA nadir in their previous LHRH agonist treatment and had a higher PSA at study enrollment. Please provide analyses to confirm that the overall survival benefit demonstrated in BC1-06 is not the result of an imbalance in disease characteristics with a more rapidly progressive prostate cancer phenotype more prevalent in the placebo arm.

Include in your response the following analyses for both the primary (interim analysis) dataset and the updated overall survival dataset:

- Time to castration resistance: Compare the time from initiation of castrate levels

of testosterone to failure of hormonal therapy and ensure they are equal between arms.

- Provide a sensitivity analysis for overall survival defining overall survival as time from initiation of hormonal therapy to death from any cause.
- Provide a sensitivity analysis for overall survival defining overall survival as time from castration resistance to death from any cause.
- Provide a sensitivity analysis for OS adjusting for imbalances in M stage and Gleason score at diagnosis.
- Provide a sensitivity analysis for OS adjusting for imbalance in baseline PSA at screening.

2. We note in your study report and in analysis of the raw dataset [CMRPT] and analysis dataset [PRTRTYN] that not all patients are recorded as having received prior castration with orchiectomy (approximately 15% of patients) or LHRH agonist (approximately 30%). While we note that 98% of patients had castrate testosterone on enrollment, please clarify why all patients have not had prior LHRH or Orchiectomy listed as prior cancer therapy in the CSR and datasets.

3. Approximately 25% of patients received "other" prior prostate cancer therapy. Please provide a table listing these other therapies per arm to ensure these were also well-balanced.

Clinical Safety:

1. Provide updated exposure (e.g., A58800-EX; ISS-ADEX) datasets that includes each patient's cumulative exposure in kBq/kg and in total kBq for the BC1-06 and 50 kBq/kg (n=703) patient populations (July 15, 2011 cutoff date).

2. Provide a dose response analysis of adverse events (AEs) based on cumulative exposure using both the total kBq/kg dose and the total kBq doses. Provide an updated AE analysis dataset to support for the BC1-06 trial (e.g., A58800-AESAF+ kBq/kg and kBq dose columns) (July 15, 2011 cutoff date).

3. Verify or provide complete case report forms (CRFs) and narratives for the following patients. These patients were treated with radium-223 and experienced non-prostate cancer-related deaths associated with AEs per the Death Reports in the CRF. These AE events were not captured in the Adverse Event (AE) datasets as a G5 AE or in the previous analyses of AEs with an outcome of death. Please discuss why these deaths associated with AEs were not included in the original analysis of AEs with an outcome of death.

BC1-06-001-013

BC1-06-001-020

BC1-06-002-005
BC1-06-002-011
BC1-06-005-001
BC1-06-006-019
BC1-06-006-032
BC1-06-006-034
BC1-06-006-035
BC1-06-010-004
BC1-06-023-001
BC1-06-028-001
BC1-06-033-001
BC1-06-033-010
BC1-06-034-008
BC1-06-044-005
BC1-06-045-012
BC1-06-059-001
BC1-06-060-009
BC1-06-086-002
BC1-06-103-006
BC1-06-106-002
BC1-06-139-002
BC1-06-139-009
BC1-06-141-005
BC1-06-148-010
BC1-06-157-002
BC1-06-170-002
BC1-06-170-006
BC1-06-171-001
BC1-06-181-008

4. Verify or provide complete case report forms (CRFs) and narratives for the following patients. These patients were treated with radium-223 and experienced non-prostate cancer-related deaths within 84 days of treatment with the last dose of therapy.

BC1-06-133-012
BC1-06-017-018
BC1-06-075-001
BC1-06-033-023
BC1-06-035-027
BC1-06-041-008
BC1-06-033-005
BC1-06-006-008

BC1-06-006-005
BC1-06-233-005
BC1-06-181-005
BC1-06-093-002
BC1-06-173-008
BC1-06-060-002
BC1-06-002-013
BC1-06-141-005
BC1-06-037-012
BC1-06-179-006

5. Verify or provide CRFs and narratives for the patients who experienced osteonecrosis AEs (BC1-06, safety cutoff 7/15/2011).
6. Verify or provide CRFs for patients who experienced Grade 3 or 4 pancytopenia AEs (BC1-06, safety cutoff 7/15/2011).
7. Please provide a detailed summary of the duration and number of patients followed for secondary malignancies in the BC1-06 trial using the July 15, 2011 safety cutoff date. Include a discussion of the expected duration of follow up for patients in the BC1-06 trial [e.g., until death, until the 3 year follow up period, and follow up beyond three years (if reconsented)].
8. In Text Table 29 from study report for A58800 (cutoff 7-15-2011), you provide the nadir hematology values by patient and grade. Using the laboratory dataset included with A58800, we are unable to reproduce these values. We have used the tabulation dataset lb.xpt, removing LBBLFL flag = Y, Visit = Screen, W0 Baseline, Follow Up.
 - a. Please provide a detailed step-by-step method to derive laboratory values from this dataset.
 - b. In this dataset, we note that neutrophils and lymphocytes can be expressed as a percentage or as an absolute value. Please provide a dataset in which the neutrophils and lymphocytes are converted into absolute values.
 - c. Laboratories are expressed as LBORRES and then all converted into the same units using LBSTRESN. However, not all values have been converted to the same units. Many of the LBORRES are expressed as < 0.5 or > 500 and these are difficult to convert. However, others are presented as a specific value (0.2, 12, etc.) and are not converted. Please provide a dataset in which laboratories with a specific value are converted to LBSTRESN.
 - d. LB.xpt contains a variable LBDY. This seems to be derived from the laboratory date and the date of informed consent. Please provide a column which provides the days from the first dose of study drug to that laboratory value
 - e. Please provide a flag in the revised laboratory dataset for patients who received cytotoxic chemotherapy during follow up. Please provide a flag in the revised

laboratory dataset for patients who received cytotoxic chemotherapy or radiation therapy prior to study entry.

Statistical:

1. In Text Table 15 from study report for A58799 (cutoff 10-14-2010), you provide the analysis results for maximum percentage decrease from baseline up to Week 12. In attachment 6 of response to IR dated 18 January 2013, you provide the variables and sample code for PSA/ALP secondary efficacy endpoint analysis. We are unable to reproduce the analysis results for maximum percentage decrease from baseline up to Week 12 using variable ALPMXR12. In addition, in Text Table 16 from this study report, we are unable to reproduce the analysis results for maximum percentage decrease from baseline during the 24-week treatment period using variable ALPMXR24.

Please provide variables and sample code used for these analyses.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
02/12/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971 - Request for Clinical Pharmacology Information
Date: Tuesday, February 12, 2013 10:48:00 AM
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012. Please submit your written response **by February 13, 2013**. 1) email to facilitate review and 2) by official amendment to the NDA.

Please clarify whether you had the calculated absorbed doses to bone in trial BCI-08 as you did in Trials BCI-05. If yes, please combine the data from these two trials to evaluate the relationship between body weight and the calculated absorbed doses to bone.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
02/12/2013



NDA 203971

FILING COMMUNICATION

Bayer HealthCare Pharmaceuticals
Attention: Deepika Jalota, Pharm.D.
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Dr. Jalota:

Please refer to your New Drug Application (NDA) dated December 14, 2012, received December 14, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xofigo (radium Ra 223 dichloride) Injection, 1000 kBq/mL (0.027 mCi/mL) at reference date.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. This application is also subject to the provisions of "The Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is August 14, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 12, 2013. In addition, the planned date for our internal mid-cycle review meeting is February 14, 2013. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing and Controls

1. The NDA states that limited information is available regarding radium compounds in the literature because there are no stable radium isotopes. However, radium chemistry has been studied for over a century and the half-life of radium-226 is 1600 years. Please provide a concise summary of the pharmaceutically relevant general properties (e.g., water solubility) of radium salts such as radium chloride, radium citrate and other radium chelates based on the chemical literature.
2. Add an assay method and limits for (b) (4)
[Redacted]
3. Discuss the chemical basis for (b) (4)
[Redacted]
4. Regarding the specifications, what are the dose calibrator instrument settings for assay of radium-223 in drug substance and product? In addition, how will radium-223 be accurately measured by dose calibrators at clinical sites? NIST standardization and certification for radium-223 radioactivity assay was established before the IND submission. Where is this information located in the NDA? What is the current status regarding the NEI/NIST measurement assurance program?
5. Regarding determination of the radionuclidic identity of radium-223 in the drug substance specifications, include appropriate additional tests and limits for alpha and beta emissions. Provide appropriate characterization data for the drug substance solution, containing radium-223 and its daughters, that includes determination of alpha and beta particle emissions.
6. Provide measurement data (e.g., by ICP-MS) on the individual trace metal content (e.g., for Hg, Pb, Cd, As, Th, Ac, Ra, Po, Rn, Bi, Ca, Sr, etc.) in the drug product.
7. In the specification, (b) (4)
[Redacted]
8. Describe the closure used for the drug substance container.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

There is no white space before each major heading in the Highlight (HL) section.

We request that you resubmit labeling that addresses this issue by February 26, 2013. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Elleni Alebachew, Regulatory Project Manager, at (301) 796 5225.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
02/11/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971/Xofigo/ Clinical Pharmacology Information Request
Date: Monday, February 04, 2013 4:51:00 PM
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012, and your response submitted on February 01, 2013 to the FDA request regarding the unit conversion of clearance. Please reply by 1) email to facilitate review and 2) by official amendment to the NDA by COB of February 05, 2013.

Please clarify whether two "IU"s in the CL unit of IU/hr*IU/g can be canceled out and what the unit of "g" stands for. If "g" stands for the mass of the blood, can "g" be converted to the volume unit of "mL"? In addition, please clarify the definition for "standard sample". If clearance in the unit of L/Hr can be calculated for the whole blood in all three Phase 1 trials, please continue to address issues in the previous IR conveyed on January 28, 2013.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
02/04/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Miller, Denise](#)
Subject: NDA 203971/Xofigo/ Quality Information Request
Date: Monday, February 04, 2013 4:43:00 PM
Importance: High

Hi Deepika,

We have an Information Request from Quality for NDA 203971. Please reply by **February 28, 2013** by 1) email to facilitate review and 2) by official amendment to the NDA.

- 1) Document P.3.5.01-01 is a summary of the (b) (4) validation in which the use of self-contained biological indicator ampoules is described. Information on the incubation parameters for the ampoules or the positive controls was not provided.
 - a. What are the incubation parameters for the self-contained biological indicator ampoules?
 - b. Describe the positive control.
- 2) How often is the (b) (4) load configuration re-qualified?
- 3) Is reprocessing of the drug product allowed?
- 4) The information provided for the container closure integrity (CCI) testing in Document P.2.5.01-01 included the statement that the limit of detection was based on a reference sample with a known level of (b) (4); however this limit of detection was not provided. Provide the limit of detection for the CCI testing and a rationale of how it correlates to microbial ingress.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
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Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
02/04/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971 - Information Request from Clinical Pharmacology
Date: Friday, February 01, 2013 12:56:00 PM
Attachments: [Information Request Xofigo NDA203971.pdf](#)
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012. Attached please find information request from clinical pharmacology reviewer. Please respond by **February 8, 2013**.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
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Reference is made to your NDA203971 submitted on December 14, 2012. Please find the Information Request below based on FDA findings regarding the impact of body weight on the efficacy and safety of Xofigo in your pivotal Phase 3 trial BC1-06 (ALSYMPCA). Please provide a written response via 1) email to facilitate review and 2) by official amendment to the NDA by February 8, 2013.

INFORMATION REQUEST

Given the finding that higher body weight (i.e., higher total Xofigo dose) is related with better OS improvement and no changes in Grade 3 or worse adverse events (as shown below and your results in Tables 3-8, 3-9 of 2.7.2 Summary of Clinical Pharmacology Studies), please provide a written response regarding possible reasons for this finding and whether this can be linked to exposures. Also comment on the feasibility of optimizing the dose of Xofigo (by increasing dose per body weight and/or injection numbers, or other strategies such as flat dosing or ideal body weight-based dosing) by February 8, 2013.

Please consider the following points in your written response:

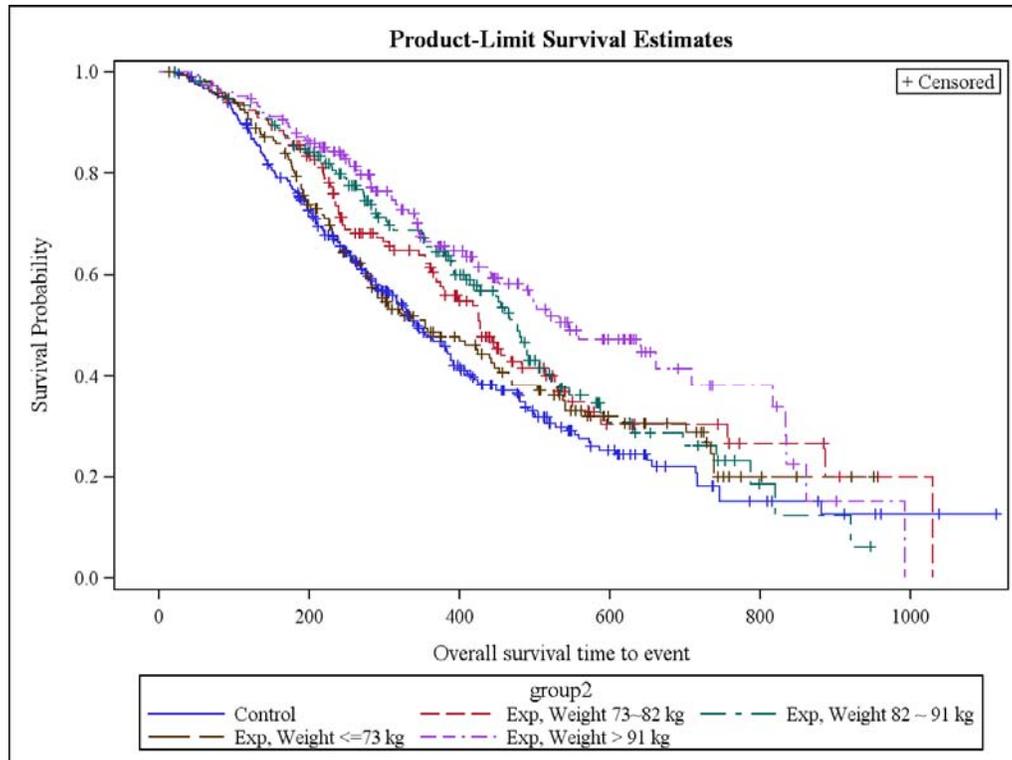
1. Whether there is a room for a higher dose or extended treatment duration (more than 6 injections) of Xofigo to gain better OS improvement in a subpopulation (such as patients with low body weight) or in the overall patient population
2. Whether a non-body weight based flat dosing can be used, based on your evaluation on the relationship between the body weight and clearance, as well as the impact of body weight on the OS and safety
3. Whether an ideal-body-weight-based dosing of Xofigo may be an appropriate dosing strategy

SUMMARY OF FDA FINDINGS

This document describes the analyses conducted by the FDA using data of trial BC1-06. to explore the relationship between body weight and overall survival (OS) and between body weight and Grade 3 or worse AEs.

Relationship between body weight and overall survival (OS)

The body weight-OS analysis results indicate that higher body weight is related with better OS improvement as shown in Figure 1.



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Figure 1. Kaplan-Meier curve of overall survival (OS) for the Xofigo arm (N=614) divided by quartiles of body weight (≤ 73 , 73-82, 82-91 and > 91 kg) and for the control arm (N=307) of the study BC1-06 (ALSYMPCA).

Subgroup OS analyses comparing the two treatment arms were performed according to quartiles of body weight (≤ 73 , 73-82, 82-91 and > 91 kg). Hazard ratio (HR) for each body weight quartile subgroup was estimated using a Cox proportional hazards model adjusted by the following baseline covariates: total ALP (< 220 U/L versus ≥ 220 U/L), current use of bisphosphonates (yes versus no), any prior use of docetaxel (yes versus no) and ECOG performance status (< 2 versus ≥ 2) (Table 1).

Table 1. Hazard ratio (HR) for each quartile of body weight was estimated using a Cox proportional hazards model adjusted by the following baseline covariates: total ALP (< 220 U/L versus \geq 220 U/L), current use of bisphosphonates (yes versus no), any prior use of docetaxel (yes versus no) and ECOG performance status (< 2 versus \geq 2).

Body Weight Quartiles	HRs (95% CI) (Xofigo vs. Control)
Q1 (\leq 73 kg)	0.90 (0.63, 1.28)
Q2 (73-82 kg)	0.58 (0.40, 0.82)
Q3 (82-91 kg)	0.70 (0.47, 1.04)
Q4 (>91 kg)	0.59 (0.40, 0.88)

Relationship between body weight and Grade 3 or worse adverse events

Similar incidences of Grade 3 or worse (Grade 3+) adverse events (AEs) were observed across body weight quartile. Compared to the control arm, Xofigo treatment arm has slightly lower incidence of Grade 3+ AEs across body weight quartiles.

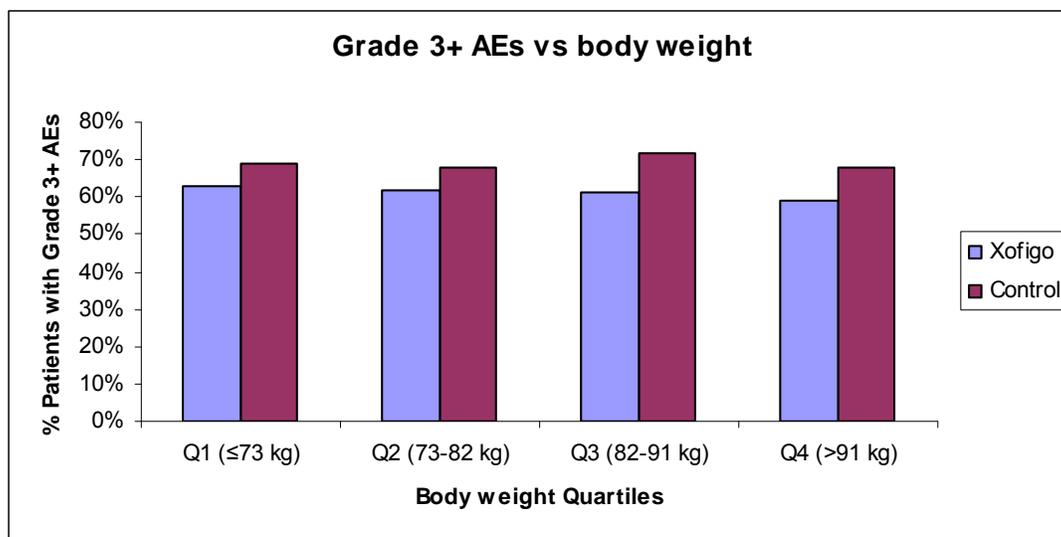


Figure 2. Bar graph represents the incidence of Grade 3 or worse AEs in 921 patients in the pivotal Phase 3 trial BC1-06 (ALSYMPCA).

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/s/

ELLENI K ALEBACHEW
02/01/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: RE: NDA 203971 - Additional Information Request from Clinical Pharmacology
Date: Monday, January 28, 2013 2:05:00 PM
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012. Please reply by 1) email to facilitate review and 2) by official amendment to the NDA.

Please submit your written response and related datasets as SAS transport files (*.xpt) for the following items **by February 1, 2013**.

1. Please clarify whether the CL unit of $\text{IU/hr} \cdot \text{IU/g}$ in table 2-1 can be converted to L/hr as in Table 2-4 (2.7.2 Summary of Clinical Pharmacology Studies) . If yes, please submit the PK parameters calculated using noncompartmental analysis (NCA) for three Phase 1 trial (ATI-BC1, BC1-05, BC1-08).
2. Please evaluate the dose proportionality of Radium-223 using a power model over the range of 46 to 250 kBq/kg after single doses.
3. Please clarify whether you collect the PK data for patients who took multiple doses in Phase 1 trials. If yes, please evaluate the time dependence of Radium-223 after multiple doses.
4. Please evaluate the effect of body-weight on the clearance (using non-bodyweight adjusted values) of Radium-223.

Regards,

Elleni

From: Alebachew, Elleni
Sent: Thursday, January 24, 2013 10:07 AM
To: Deepika Jalota (deepika.jalota@bayer.com)
Cc: Kacuba, Alice
Subject: NDA 203971 - Information Request from Clinical Pharmacology
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012. Please reply by 1) email to facilitate review and 2) by official amendment to the NDA.

1. Please submit the datasets as SAS transport files (*.xpt) you used for study report PH-36915 **by January 28, 2013**. A description of each data item should be provided in a Define.pdf file. Also please explain how you derived the Estimated Creatinine Clearance Rate (eCCr) at baseline, and provide your rationale for categorizing the body weight using cutoff values of 80 kg and 100 kg.
2. Please evaluate whether various degrees of hepatic impairment at baseline have impact on the

efficacy and safety using NCI organ dysfunction working group (NCI-ODWG) criteria. Please submit your written response and related datasets as SAS transport files (*.xpt) and a Define.pdf file by **January 31, 2013**.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
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/s/

ELLENI K ALEBACHEW
01/28/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971 - Information Request from Clinical Pharmacology
Date: Thursday, January 24, 2013 10:06:00 AM
Importance: High

Hi Deepika,

Please refer to your NDA 203971 submitted on December 14, 2012. Please reply by 1) email to facilitate review and 2) by official amendment to the NDA.

1. Please submit the datasets as SAS transport files (*.xpt) you used for study report PH-36915 **by January 28, 2013**. A description of each data item should be provided in a Define.pdf file. Also please explain how you derived the Estimated Creatinine Clearance Rate (eCCr) at baseline, and provide your rationale for categorizing the body weight using cutoff values of 80 kg and 100 kg.
2. Please evaluate whether various degrees of hepatic impairment at baseline have impact on the efficacy and safety using NCI organ dysfunction working group (NCI-ODWG) criteria. Please submit your written response and related datasets as SAS transport files (*.xpt) and a Define.pdf file by **January 31, 2013**.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
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E-mail: Elleni.Alebachew@fda.hhs.gov
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/s/

ELLENI K ALEBACHEW
01/24/2013



NDA 203971

NDA ACKNOWLEDGMENT

Bayer HealthCare Pharmaceuticals
Attention: Deepika Jalota, Pharm.D.
Deputy Director, Global Regulatory Affairs
P.O.Box 1000
Montville, NJ 07045

Dear Dr. Jalota:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Xofigo[®], (radium Ra 223 dichloride, alpharadin) Injection

Date of Application: December 14, 2012

Date of Receipt: December 14, 2012

Our Reference Number: NDA 203971

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 12, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (301) 796-5225.

Sincerely,

{See appended electronic signature page}

Elleni Alebachew, M.S., RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ELLENI K ALEBACHEW
01/23/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Kluetz, Paul](#)
Subject: RE: NDA 203971/Xofigo/ Clinical Information Request
Date: Friday, January 18, 2013 4:07:00 PM
Importance: High

Hi Deepika,

Thank you for taking the time to participate in the teleconference today. As we discussed, we have a few additional requests and would ask that you provide responses as soon as possible.

1. Provide the program/algorithm used to derive OSVDTN (OS date of event) in [SURV] for the interim analysis data cutoff 10/14/2010. Please also provide the algorithm to derive OSVDTN for the 2011 data cutoff dataset if it is different.
2. The variable OSVINCMP in [SURV] was set to "1" if a patient was lost to follow-up or withdrew and did not consent to be followed for survival. There are 15 patients in the interim analysis dataset with OSVINCMP=1 (10 Radium and 5 Placebo). In your slides from our 1-18-2012 tcon, slide 14 states that the number of patients lost to follow up for the interim analysis was 0. We interpret this as the 15 patients withdrew and did not consent to be followed for survival. Please confirm this is accurate.
3. Please provide CRFs for the following patients:

BC1-06-001-034
BC1-06-002-001
BC1-06-002-009
BC1-06-003-004
BC1-06-003-007
BC1-06-003-018
BC1-06-005-008
BC1-06-006-007
BC1-06-006-015
BC1-06-006-035
BC1-06-008-015
BC1-06-011-004
BC1-06-011-008
BC1-06-017-025
BC1-06-017-026
BC1-06-017-028
BC1-06-020-007
BC1-06-021-004
BC1-06-022-001
BC1-06-024-004
BC1-06-024-025
BC1-06-024-026
BC1-06-025-007
BC1-06-025-010
BC1-06-026-013
BC1-06-034-001
BC1-06-035-001
BC1-06-035-007
BC1-06-035-019
BC1-06-035-031

BC1-06-035-035
BC1-06-036-002
BC1-06-037-011
BC1-06-039-028
BC1-06-042-035
BC1-06-043-008
BC1-06-043-015
BC1-06-043-016
BC1-06-044-004
BC1-06-044-008
BC1-06-046-004
BC1-06-046-006
BC1-06-047-003
BC1-06-048-006
BC1-06-049-004
BC1-06-049-005
BC1-06-050-018
BC1-06-051-016
BC1-06-051-019
BC1-06-053-003
BC1-06-060-001
BC1-06-060-011
BC1-06-063-002
BC1-06-065-001
BC1-06-066-002
BC1-06-066-003
BC1-06-075-003
BC1-06-128-002
BC1-06-128-009
BC1-06-133-001
BC1-06-133-027
BC1-06-135-005
BC1-06-137-009
BC1-06-137-010
BC1-06-154-004
BC1-06-173-006
BC1-06-173-007
BC1-06-174-004
BC1-06-181-030
BC1-06-181-051
BC1-06-191-006
BC1-06-200-001
BC1-06-203-006
BC1-06-230-005
BC1-06-233-007

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov

Phone: (301) 796-5225

Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
01/18/2013

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 18, 2013
TIME: 12:00 PM – 1:00 PM
APPLICATION: NDA 203971
APPLICANT: Bayer HealthCare Pharmaceutical
DRUG NAME: Xofigo® (radium Ra-223 dichloride)
TYPE OF MEETING: Teleconference
MEETING RECORDER: Eleni Alebachew

FDA ATTENDEES:

Richard Pazdur, M.D., Director, OHOP
Robert L. Justice, M.D., M.S., Director, DOP1
Amna Ibrahim M.D., Deputy Director, DOP1
V. Ellen Maher, M.D., Clinical Team Leader, DOP1
Paul Kluetz, M.D., Medical Officer, DOP1
Shenghui Tang, Ph.D., Biostatistics Team Leader, DBV
Hui Zang, Ph.D., Biostatistics Reviewer
Eleni Alebachew, M.S., RAC, Regulatory Health Project Manager

EXTERNAL ATTENDEES:

Bayer

Gerhard Schlueter, Regulatory Affairs
Maria Garrigan, Regulatory Affairs
Deepika Jalota, Regulatory Affairs
Marion Resch, Regulatory Affairs
David Weinreich, Clinical Development
Dimitris Voliotis, Clinical Development
Jose Garcia-Vargas, Clinical Development
Jeanne Lewis, Clinical Development
Minghua Shan, Statistics
Fang Fang, Statistics
Claire Blanchette, Project Management
Andy Hargreaves, Good Clinical Practice - Quality Assurance
Lisa Rogers, Good Clinical Practice - Quality Assurance

Algeta

Gillies O'Bryan-Tear, Clinical Development
Irene Skjørestad, Clinical Development
Inger M Torgersen, Regulatory Affairs

BACKGROUND

FDA requested this teleconference on January 11, 2013 to discuss Bayer's Quality Verification Program for BC1-06. FDA express concerned regarding the accuracy of CRF data and asked Bayer to discuss the accuracy of the following data in the CRF:

1. Targeted Eligibility Criteria including:
 - a) The use of a GnRH analog and a castrate testosterone level at baseline; and
 - b) The absence of visceral metastases and the presence of at least 2 metastatic bone lesions at baseline.
2. Audit findings concerning source verification of the date of death
3. Audit findings concerning source verification of the date of the skeletal related events and the type of skeletal related event.

DISCUSSION

Bayer provided their assurance to the FDA concerning the small number of adverse events that were found to be unreported when they audited selected sites. Bayer also stated that they had provided extensive training to the CRAs after this finding. Finally, Bayer assured the FDA that death dates, in this survival study, were 100% source verified.

OUTCOME

FDA requested additional case report forms so that they could be verified against the datasets.

FDA stated that an information request regarding the program/algorithm used to derive OS date of event in [SURV] for the interim analysis data cutoff 10/14/2010 and the number of patients lost to follow up for the interim analysis will be sent after the teleconference.

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/s/

ELLENI K ALEBACHEW
04/01/2013

VIRGINIA E MAHER
04/02/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203971

MEETING DENIED

Bayer HealthCare Pharmaceuticals
Attention: Deepika Jalota, Pharm.D.
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Dr. Jalota:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xofigo (radium Ra 223 dichloride) Injection.

We also refer to your February 7, 2013, correspondence requesting a type C meeting to discuss Bayer's proposed plan to [REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) (4) We recommend that Bayer discusses the details of the [REDACTED] (b) (4) directly with the NRC or applicable Agreement State agencies.

If you have any questions, call Elleni Alebachew, Regulatory Project Manager, at (301) 796-5225.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
02/11/2013

From: Alebachew, Elleni
To: ["Deepika Jalota"](#)
Subject: RE: FDA Request for Information - Applicant Orientation Meeting - BC1-06 Amendments with summary of changes and rationale
Date: Tuesday, January 15, 2013 3:00:00 PM

Hi Deepika,

You are correct, we did not request for references for sample size calculation in the dataset review session but the stat reviewers are requesting for it now.

Please provide the references for both alpha calculation and sample size calculation.

Thank you,

Elleni

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Tuesday, January 15, 2013 2:32 PM
To: Alebachew, Elleni
Subject: RE: FDA Request for Information - Applicant Orientation Meeting - BC1-06 Amendments with summary of changes and rationale

Hi Elleni,

Regarding item number 3, Bayer's understanding from the Dataset Review Session was that references were needed for the interim alpha boundary calculation, not for the sample size calculation. Please kindly confirm if our understanding is correct.

We plan to provide the requested information via email by EOB Thursday, Jan 17th. A formal amendment to the NDA will be submitted early next week.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Tuesday, January 15, 2013 10:49 AM
To: Deepika Jalota
Subject: RE: FDA Request for Information - Applicant Orientation Meeting - BC1-06 Amendments with summary of changes and rationale

Hi Deepika,

I wanted to follow up with you regarding the additional information requests discussed during the Dataset Review Session on Jan 04, 2013.

1. Provide SAP amendments and rational
2. Provide R program used for the sample size calculation
3. Provide references for sample size calculation.

Please let me know when you plan to provide the information listed above.

Thanks,

Elleni

From: Deepika Jalota [<mailto:deepika.jalota@bayer.com>]
Sent: Monday, January 07, 2013 1:50 AM
To: Alebachew, Elleni
Subject: FDA Request for Information - Applicant Orientation Meeting - BC1-06 Amendments with summary of changes and rationale

Hi Elleni,

Thank you again for the opportunity to provide an overview of NDA 203971 during the Xofigo Applicant Orientation Meeting (AOM) held on January 4, 2013. It was a pleasure meeting you.

Bayer is in the process of compiling the responses to the FDA Requests for Information that were received during the AOM. I will send the information via email as the responses become available. It is planned to formally submit all of these responses related to the AOM collectively under 1 amendment to the NDA.

As requested during the AOM, attached are the Study BC1-06 protocol amendments 1 through 6 with the summary of changes and rationale.

Freundliche Grüße / Best regards,

Deepika Jalota, PharmD
Global Regulatory Strategist



Science For A Better Life

Bayer HealthCare Pharmaceuticals Inc
Global Regulatory Affairs, Specialty Medicine
Montville, Building 100 / Office 268
Tel: 973-487-2782
Mobile: (b) (6)
E-mail: deep_ka.jalota@bayer.com
Web: <http://www.bayerhealthcare.com>

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/s/

ELLENI K ALEBACHEW
01/15/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Miller, Denise](#)
Subject: NDA 203971/Xofigo/ Quality Information Request
Date: Friday, January 11, 2013 12:01:00 PM
Importance: High

Hi Deepika,

We have an Information Request from Quality for NDA 203971. Please reply by **Jan 25, 2013** by 1) email to facilitate review and 2) by official amendment to the NDA.

- DMF (b) (4) is referenced for (b) (4) to be used for NDA 203-971. (b) (4)
Clarify which (b) (4) are to be used.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
01/11/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:deepika.jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Song, Pengfei](#)
Subject: NDA 203971 - Information Request from Clinical Pharmacology
Date: Tuesday, January 08, 2013 8:36:00 AM
Importance: High

Hi Deepika,

We have an Information Request from Clinical Pharmacology for NDA 203971. Please reply by **January 23, 2013** by 1) email to facilitate review and 2) by official amendment to the NDA.

1. Evaluate whether patients experiencing constipation have higher incidence of AEs
2. Evaluate whether baseline creatinine clearance is associated with increased incidence of renal failure or other adverse events
3. Comment on whether calcium (or divalent cation-selective TRP) channel blockers can interfere with the transport of Radium-223
4. Provide a subgroup analysis for OS and SRE for those patients taking concurrent calcium channel blockers for hypertension

Please confirm receipt.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
01/08/2013

From: Alebachew, Elleni
To: [Deepika Jalota \(deepika.jalota@bayer.com\)](mailto:Deepika.Jalota@bayer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Kluetz, Paul](#)
Subject: NDA 203971/Xofigo/ Clinical Information Request
Date: Wednesday, January 02, 2013 12:23:00 PM
Importance: High

Hi Deepika,

We have an Information Request from Clinical for NDA 203971. Please reply by **noon, 12:00PM Jan 4, 2013** by 1) email to facilitate review and 2) by official amendment to the NDA.

1. Where is the study master file and all necessary records located and maintained? Are they all with Bayer or are a portion with Algeta?
2. We note in section 8.2 of the study report that 7 sites were closed (209, 28, 170, 173, 181 155 and 71). Were these closures reported to the FDA under the alpharadin IND?

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ELLENI K ALEBACHEW
01/02/2013

Kacuba, Alice

From: Kacuba, Alice
Sent: Monday, December 31, 2012 6:19 PM
To: Deepika Jalota
Cc: Alebachew, Elleni
Subject: Information Request from Clin Pharm for NDA 203971
Importance: High

Hi,

We have an Information Request from Clin Pharm for NDA 203971. Please reply by Jan 9, 2013 by 1) email to facilitate review and 2) by official amendment to the NDA.

1. Radioactivity counting method validation report
2. Bioanalytical reports for the radioactive sample analysis (including the details on the acceptance of each batch run, the storage time of the samples from blood collection to analysis, and incurred sample reanalysis)
3. A sample calculation of conversion of raw CPM to activity in mCi. Please comment on counting efficiency and contribution of alpha and beta emissions to total radioactivity.
4. Details on accuracy of measurement of dose before patient administration (microCurie/kg) using a Capintech dose calibrator or any other pertinent measurement method.

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC
 Chief, Project Management Staff
 Division of Oncology Products 1 (new name for DDOP)
 Office of Hematology and Oncology Products
 OND/CDER/FDA
 301-796-1381
 (f) 301-796-9845
 alice.kacuba@fda.hhs.gov

*Consider setting your email font setting to at least 12 font.

From: Deepika Jalota [mailto:deepika.jalota@bayer.com]
Sent: Saturday, December 29, 2012 3:03 PM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Application Orientation Presentation meeting - Updated Meeting Attendees List and Foreign Visitor Data Request Form
Importance: High

Hi Elleni,

I received confirmation that Lothar Everz will be attending as the CMC expert for the NDA 203971 Applicant Orientation Meeting. The attendee list is updated below.

Attached is Lothar's Foreign Visitor Data Request Form. The Request form is being sent less than 11 days before the meeting, however would it be possible to have the security clearance performed in time for the meeting?

Thank you in advance for your understanding!

Best regards,
Deepika

From: Deepika Jalota

Sent: Wednesday, December 26, 2012 3:11 PM

To: 'Alebachew, Elleni'

Subject: RE: NDA 203971 - Application Orientation Presentation meeting - Meeting Attendees

Hi Elleni,

Below is a list of attendees for the Applicant Orientation Meeting. Regarding the CMC expert, please note that we are awaiting confirmation regarding which representative will be attending.:

Applicant Orientation Meeting (Pivotal Information Presentation)	
Meeting Attendee	Function
1. Deepika Jalota	Regulatory Affairs
2. Maria Garrigan	Regulatory Affairs
3. Dimitris Voliotis	Clinical Development
4. Jose Garcia-Vargas	Clinical Development
5. David Weinreich	Clinical Development
6. Fang Fang	Statistics
7. Christian Zurth	Clinical Pharmacology
8. Gerhard Reike	Pharmacovigilance
9. Pamela Gilles	Toxicology
10. Lothar Everz	CMC
11. Andy Hargreaves	GCP -QA
12. Gillies O'Bryan-Tear	Algeta

Applicant Orientation Meeting (Dataset review session)	
1. Jeremy Gratt	Statistics (Dataset Review)
2. Fang Fang	Statistics
3. Deepika Jalota	Regulatory Affairs
4. Jose Garcia-Vargas	Statistics (Dataset Review)

Best regards,
Deepika

From: Alebachew, Elleni [mailto:Elleni.Alebachew@fda.hhs.gov]

Sent: Wednesday, December 26, 2012 1:57 PM

To: Deepika Jalota

Subject: RE: NDA 203971 - Application Orientation Presentation meeting - Foreign Visitor Data Request Forms

Thanks.

Could you also send me the list of attendees.

Thanks,

Elleni

From: Deepika Jalota [mailto:deepika.jalota@bayer.com]
Sent: Wednesday, December 26, 2012 1:47 PM
To: Alebachew, Elleni
Subject: RE: NDA 203971 - Application Orientation Presentation meeting - Foreign Visitor Data Request Forms

Dear Elleni,

Attached are the completed foreign visitor data request forms for the following individuals for the NDA 203971 Applicant Orientation Meeting on January 4th, 2013:

Bayer
Dimitris Voliotis
Christian Zurth
Gerhard Reike
Jose Garcia-Vargas

Algeta
Gillies O'Bryan-Tear
Inger Margrethe Torgersen

Best regards,
Deepika

From: Alebachew, Elleni [mailto:Elleni.Alebachew@fda.hhs.gov]
Sent: Wednesday, December 26, 2012 9:23 AM
To: Deepika Jalota
Subject: RE: NDA 203971 - Application Orientation Presentation meeting

Hi Deepika,

Please see attached an updated Foreign visitor data request form.

Thanks,

Elleni

From: Deepika Jalota [mailto:deepika.jalota@bayer.com]
Sent: Saturday, December 22, 2012 2:34 PM
To: Alebachew, Elleni
Cc: Kacuba, Alice
Subject: RE: NDA 203971 - Application Orientation Presentation meeting

Hi Elleni,

Thank you for the invitation. Bayer accepts the FDA's invitation to provide an Application Orientation Presentation for NDA 203971 on January 4, 2013.

Please kindly confirm that the final slide deck can be provided to you via email by 11 PM on January 3rd.

Best regards,
Deepika

From: Alebachew, Elleni [<mailto:Elleni.Alebachew@fda.hhs.gov>]
Sent: Friday, December 21, 2012 4:29 PM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: NDA 203971 - Application Orientation Presentation meeting
Importance: High

Hi Deepika,

DOP1 invites you to an Application Orientation Presentation meeting to present the pivotal information that you think supports your NDA. The audience will be the review team and any interested reviewers from the Office of Hematology and Oncology Products.

Available date =Friday, January 4, 2013

Time:	Pivotal Information Presentation	1:30 PM to 2:30PM
	Dataset review session	2:40 PM to 3:40 PM

See attached instructions to facilitate your preparation.

In addition, attached please find the Foreign Visitor Data request form. If any of the attendees to our meeting are non-US citizens, you will need to fill out the attached form for each person. Please e-mail the completed form(s) to me no later than 10 days before the scheduled meeting. Security may not allow the individual(s) in the building if the forms are not sent in time. The non-US citizens will need to show their Passport or other national identity source document (i.e. a document which allowed the immigration into the US) as identification when entering the building at FDA.

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845

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/s/

ALICE KACUBA
12/31/2012



NDA 203971

NDA ACKNOWLEDGMENT

Bayer HealthCare Pharmaceuticals
Attention: Deepika Jalota, Pharm.D.
Deputy Director, Global Regulatory Affairs
340 Changebridge Rd.
Pine Brook, NJ 07058

Dear Dr. Jalota:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Xofigo®, (radium Ra 223 dichloride, alpharadin) Injection

Date of Application: December 14, 2012

Date of Receipt: December 14, 2012

Our Reference Number: NDA 203971

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 12, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call me, at (301) 796-5225.

Sincerely,

{See appended electronic signature page}

Elleni Alebachew, M.S., RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ELLENI K ALEBACHEW
12/20/2012

From: [Deepika Jalota](#)
To: [Alebachew, Elleni](#)
Cc: [Kacuba, Alice](#)
Subject: RE: Information Request: NDA 203971/radium 223 dichloride injection/
Date: Monday, December 17, 2012 12:41:50 PM

Hi Elleni,

Thank you for your email. Bayer acknowledges receipt. We are in the process of reviewing the FDA Request for Information and plan to respond by Dec 20, 2012 as requested.

Best regards,
Deepika

From: Alebachew, Elleni [mailto:Elleni.Alebachew@fda.hhs.gov]
Sent: Monday, December 17, 2012 12:14 PM
To: Deepika Jalota
Cc: Kacuba, Alice
Subject: Information Request: NDA 203971/radium 223 dichloride injection/

Hi Deepika:

We reference your NDA submission 203971 submitted 12/14/2012 for radium 223 dichloride injection. We have the following information request. **Please reply by 12-20-2012.**

1. Describe in adequate detail the challenges/difficulties that led to the delay in the filing of this application. If this is already included in the application, please direct the review team to its location.
2. Describe the procedure for ensuring the activity of the radium-223 dose given to each patient. From review of the protocol, it does not appear that direct measurement of radioactivity using a radio assay system before and after patient dosing was performed at the clinical sites.

Please confirm receipt of this email.

Regards,

*Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
E-mail: Elleni.Alebachew@fda.hhs.gov
Phone: (301) 796-5225
Fax: (301) 796-9845*

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/s/

ELLENI K ALEBACHEW
12/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE - DMEPA		FROM: Elleni Alebchew, RPM DOP1 DOP1/ (301) 796 5225		
DATE 12/14/12	IND NO.	NDA NO. 203971	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 12/14/12
NAME OF DRUG Xofigo (radium-223 dichloride)		PRIORITY CONSIDERATION Priority Review (EXPEDITED REVIEW)	CLASSIFICATION OF DRUG Oncology	DESIRED COMPLETION DATE 04/01/13
NAME OF FIRM: Bayer Healthcare Pharmaceuticals				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Original NDA				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: The purpose of this consult is to request review of a FPI and Carton and Container for Xofigo. This is a new NDA. PDUFA date is August 14, 2013 – OHOP’s target action date is May 17, 2013. Link to submission = \\cdsesub1\evsprod\NDA203971\0000\m1\us\114-labeling\draft-labeling MO= Paul Kluetz (efficacy) and Bill Pierce (safety) CDTL = V. Ellen Mahar PM= Elleni Alebachew Filing Meeting: Thursday, January 10, 2013 From: 3 – 4 PM Room: Bld 22 / Rm 5270 Mid-Cycle Meeting: TBD Late Cycle Meetings: TBD Wrap-Up Meeting: TBD				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

ELLENI K ALEBACHEW
12/19/2012



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

EDR 12/14/12

NDA 203971

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 26, 2011; 1:00PM-2:30PM
Meeting Location: White Oak Building #22; Conf. Room 1309

Application Number: 067521
Product Name: Radium-223 chloride solution for injection (Alpharadin)
Indication: **Castration-resistant (hormone refractory) prostate cancer in patients with bone metastases.**

Sponsor/Applicant Name: Bayer Healthcare Pharmaceuticals
Meeting Request Date: August 19, 2011
Meeting BGP date: September 26, 2011

Meeting Chair: V. Ellen Maher, M.D.
Meeting Recorder: Kim J. Robertson

FDA ATTENDEES

Robert Justice, M.D., M.S., Director DOP 1
Anthony Murgio, M.D., M.S., FACP, Associate Director OODP IO, Acting Deputy Director, DOP 1
V. Ellen Maher, M.D., Lead Medical Officer, DOP 1
John R. Johnson, M.D., Lead Medical Officer, DOP 2
Paul G. Kluetz, M.D., Medical Officer, DOP 1
Y. Max Ning, M.D., Ph.D., Medical Officer, DOP 1
Gerald Sokol, M.D., M.S., F.C.P., Medical Officer, DOP 1
Robert J. Yaes, M.D., DMIP
Milagros Salazar-Drive, Ph.D., CMC, ONDQA, DNDQA I
Eldon Leutzinger, Ph.D., ONDQA, DNDQA I
Robert Mello, Ph.D., NDMS
Dhananjay Chhatre, OBI/DRRS
Sarah J. Schrieber, PharmD, Clinical Pharmacology Reviewer, DCP5
Anne Pillaro, Ph.D., Supervisory Pharmacologist, DOP 1
Mary-Jane Masson-Hinrichs, Ph.D., Pharmacologist, DOP 1
Shenghui Tang, Ph.D, Team Leader, DB 5

Meeting Minutes
[Insert Meeting Type]
DATE

[Insert Office/Division]

Chia-Wen (Kiki) Ko, Ph.D., Mathematical Statistician, DB 5
Kim J. Robertson, Regulatory Health Project Manager, DOP 1

BAYER HEALTHCARE PHARMACEUTICALS ATTENDEES

Puneet (Michael) Badlani, Head of statistical programming – North America
Wenny Du, Global Project Leader, Radium-223 chloride
Lothar Everz, Ph.D., Head of Radiopharmaceutical Science, Global CMC
Radiopharmaceutical Development
Fang Fang Ph.D., Project Statistician, Oncology
Margaret Foley, US Regulatory Strategist, Global Regulatory Affairs
Jose Garcia-Vargas, M.D. DMRT, Senior Director, Global Clinical Leader
Maria C. Garrigan, Director, Global Regulatory Affairs, Oncology
Joseph Germino, M.D., US Medical Affairs Expert
Pamela Gilles, Ph.D., Senior Toxicologist, Toxicology
Andy Hargreaves, Head, GCP Study Audit Management
Mike Koenig, Deputy Director, Global Regulatory Affairs, CMC
Marion Resch, Ph.D., Deputy Director, Global Regulatory Strategist, Global Regulatory
Affairs
Anita Shah, Ph.D., Senior Director, Clinical Pharmacokinetics
Minghua Shan, Ph.D., Senior Director, Expert Statistician, Oncology
Mukesh Verma MD, Global Safety Leader, TA Oncology, Global Pharmacovigilance
Dimitris Voliotis, M.D., Vice President, Global Clinical Development Oncology

Algeta

Ragnhild Løberg, MSc.Pharm., Senior Vice President, Quality and Regulatory Affairs
Kari Grønås Dyvik, MSc.Pharm., Senior Vice President, Operations
Vigdis Reinton, MSc.Pharm., Senior Director Regulatory Affairs
Anne-Kirsti Aksnes, Ph.D., Vice President, Clinical Research

1.0 BACKGROUND

Alpharadin is a radiopharmaceutical product which targets areas of increased bone turnover by forming a complex with hydroxyapatite. The active moiety, Radium-223 chloride, is an alpha-emitting nuclide with half life of 11.4 days. Following several pre-IND and type C meetings conducted from June 2004 through July 2007, IND 67,521 was submitted in December of 2007 by Algeta. The development of alpharadin has been initially focused on prostate cancer patients with bone metastases. The pivotal phase III study, ALYMPCA, was stopped early based on an interim analysis revealing a significant improvement in overall survival. Bayer HealthCare Pharmaceuticals, Inc. accepted sponsorship and responsibility of the IND on 5-27-2011.

The ALSYMPCA trial is a double-blind, randomized, phase III, multicenter study comparing Alpharadin plus best standard of care versus placebo plus best standard of care in the treatment of patients with symptomatic hormone-refractory prostate cancer with skeletal metastases. The primary efficacy endpoint was overall survival (OS). The investigational study treatment consists of 6 intravenous administrations of alpharadin each separated by 4 weeks. Enrollment in the trial was completed in February of 2011 with 922 patients randomized. A pre-planned interim analysis was carried out on 6-3-2011 with 50% of the specified number of total events (314). The study was reported to meet its primary objective with the radium-223 arm showing a statistically significant improvement in OS (two-sided p-value = 0.00185, HR = 0.695). Median OS was 14.0 months for alpharadin and 11.2 months for placebo. The independent data monitoring committee recommended the study be stopped and that patients in the placebo arm be offered alpharadin.

Based on the reported positive results from the pivotal phase III trial, this pre-NDA meeting is being held to discuss Bayer's plans on submitting a New Drug Application in April, 2012 for radium-223 chloride for the treatment of castration-resistant (hormone refractory) prostate cancer in patients with bone metastases. The primary purpose of the meeting is to discuss the presentation of the required information.

2.0 DISCUSSION

Questions on Chemical, Pharmaceutical and Biological Development

Question 1

Bayer proposes to include real-time stability data

(b) (4)

(b) (4)

(b) (4) Does the Agency agree that this approach is acceptable?

FDA Response (October 19, 2011):

No. Stability data for 3 lots manufactured by the commercial line process and packaged in the commercial container/closure system will be considered the primary stability data for submission at the time of NDA filing. Product made by the clinical line process may be used as supporting stability data.

Bayer's Comments (October 25, 2011):

Bayer Comments: Bayer acknowledges the FDA's position that the three primary stability batches must be from the commercial production line in the commercial container/closure system. Bayer plans to include full shelf-life stability data from the commercial line in the NDA, however not all the data will be available for the initial NDA submission. Bayer proposes to include the following data in the initial NDA submission:



Agency agree that this is acceptable?

Meeting Discussion: No. The Agency would prefer to see complete stability data for 3 batches submitted at the time of the NDA submission. In addition, we would like to have a statement of the readiness of inspection.

Question 2

A written and approved validation plan for the commercial manufacturing process will be available at the time of the NDA submission. The final validation however, will be completed after the submission. Depending on the timing of the pre-approval inspection, the results from the validation might not be available at the time of inspection, but will be completed prior to commercial distribution in the US. Does the Agency agree that this approach is acceptable?

FDA Response (October 19, 2011):

Yes. You should have the written and approved protocol for the commercial manufacturing scale process and the sterilization process validation on the commercial line completed with documentation available at the time of NDA submission. Also, a statement of process validation completion prior to manufacturing and releasing any batch for commercial use should be included in the NDA submission.

At the time of NDA submission, you will need to submit complete (b) (4) validation, methods qualification for the sterility and pyrogen test, and container-closure integrity test. As the non-sterile drug substance is to be held for up to (b) (4) we will need to see bioburden data from the drug substance prior to pooling from at least 3 commercial scale lots.

Bayer's Comments (October 25, 2011):

Bayer plans to submit complete (b) (4) validation, methods qualification for the sterility and pyrogen test, and container-closure integrity test.

Regarding the bioburden data, Bayer proposes bioburden data from three non-radioactive technical batches produced on the commercial line be used to satisfy the Agency's requirement. Generating this data on non-radioactive batches presents a worst-case scenario for bioburden, since the radioactivity exhibits a significant antimicrobial effect. Bayer plans to include a justification for the anti-microbial effect of the radioactive drug substance in the NDA. The bioburden test requires a large amount of sample, and testing on radioactive material exposes personnel to a high amount of radioactivity. Therefore for radioprotection reasons, it is advantageous to perform the test using non-radioactive batches. Does the Agency agree that this is acceptable?

Meeting Discussion: Yes; this is acceptable, assuming that the commercial production equipment and the composition of the drug without the radioactive component are the same as that which will be used in routine production. In addition, we recommend the duration extend beyond the longest holding time you anticipate occurring during routine production.

Question 3

Radium-223 chloride solution for injection clinical supply is released before the sterility test is concluded, in accordance with established procedures for radiopharmaceuticals where the time required to gather results for sterility testing constitute a significant proportion of the half life of the radioactive nuclide and thus the shelf-life of the product. Agreement to this procedure was obtained from the Office of New Drug Quality Assessment on April 27 2009. Bayer wishes to confirm that this practice continues to be acceptable for future clinical supplies and commercial product under the assumption of adequate sterility assurance documentation.

FDA Response (October 19, 2011):

Yes.

Bayer's Comments (October 25, 2011): Bayer Comments: Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Question 4

Due to the nature of this product (Ra^{2+} , not bound to any other molecule), radiochemical purity testing is not a quality indicating parameter of the product in the release testing. For this reason Bayer does not intend to perform radiochemical purity testing on either the drug substance or drug product. Does the Agency agree that this approach is acceptable?

FDA Response (October 19, 2011):

The approach may be acceptable however, you need to include in the NDA a detailed rationale along with evidence such as, all the radiochemical purity co-precipitation testing data done during drug development, indicative that no other radiochemical forms exist (e.g., $^{223}\text{Ra}^{+2}$ citrate), or if they do exist are at negligible levels and hence preclude the necessity for radiochemical purity as a quality indicating attribute for inclusion in the product release testing. This will be a review issue in the forthcoming NDA and will ultimately be evaluated for acceptability during review of the NDA.

Bayer's Comments (October 25, 2011): Bayer Comments: Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Question 5

The drug substance and drug product release specifications were amended according to comments from the Office of New Drug Quality Assessment at the End-of-Phase 2 meeting 30 January 2009. The final specifications proposed for commercial manufacture are presented in the briefing package. Does the Agency have any comments to the proposed parameters or acceptance criteria?

FDA Response (October 19, 2011):

No, the following revisions and comments on release specifications are recommended:

For Drug Substance

A. Test and acceptance limits for (b) (4) should be established.

Bayer's Response (October 25, 2011): A trace amount of (b) (4)

(b) (4)

Meeting Discussion: Please provide alternative information regarding the testing of
(b) (4)

For Drug Product

B. Radionuclidic identity should include half-life measurement (test and acceptance limits) in addition to gamma spectrometry.

Bayer's Response (October 25, 2011): The gamma spectroscopy method used for radionuclidic identification analyzes (b) (4) lines, and is more specific to ^{223}Ra than half-life measurement. Implementation of half-life measurement will represent additional radioactive exposure of analysts without any quality benefit. On this basis, Bayer suggests not to include half-life measurement for radionuclidic identity.

Meeting Discussion: Please provide a rationale and supportive data regarding this issue and it will be reviewed during the time of NDA submission.

C. The radiochemical identity proposed via gamma spectroscopy is not a chemical test. Therefore, radiochemical identity should include a test based on the chemical nature of $^{223}\text{Ra}^{+2}$ species including the use of a reference material. In these regards, we recommend that you develop an appropriate chromatographic method, e.g., ion chromatography (IC), that can be used to compare $^{223}\text{Ra}^{+2}$ with a suitable reference material. The suitability and validity of the radiochemical identity test will be a review issue in the forthcoming NDA, and its acceptability will be evaluated during review of the NDA.

Bayer Comments (October 25, 2011): The justification for not including the radiochemical purity test, (to be provided in the NDA to address question 4), is also a valid justification for not including a radiochemical identity test. Bayer agrees that the gamma spectroscopy method is only specific for the radionuclide and not for the radiochemical form. Based on the fact that radium-223 only can exist in one oxidation state (2+) in the drug substance and drug product and that radium-223 is not covalently bound to a carrier, different chemical substances containing radium-223 cannot be present in the drug substance or drug product. The radiochemical form has been confirmed by the co-precipitation test used during development for radiochemical purity, and data will be provided in the NDA.

An alternative chromatographic method is not feasible as no suitable references are available. Due to radioprotection reasons Ra-226 is not suitable, and Ra-223 is not suitable due to the short half-life.

Based on the above argumentation Bayer proposes to remove the radiochemical identity test from the specification as Bayer believes the gamma spectroscopy test is highly specific and provides assurance of the correct radiochemical species.

Meeting Discussion: Please provide rationale and data in support of the radiochemical identity for the drug product. This will be considered during the review of the submitted NDA.

Question 6

Bayer has the following question regarding labeling clinical supplies for studies to be conducted under IND 67,521, Alpharadin, Radium-223 chloride.

Since Alpharadin is a radioactive product, special considerations must be taken to minimize the handling and radiation exposure of the workers during production. During ongoing development, as clinical supply production is scaled, Bayer would like to limit the amount of text on the drug product vial so that the same vials can be used in worldwide clinical trials. This is done for safety reasons, to minimize the amount of manual handling steps, and therefore the amount of radiation exposure of the workers in the production environment. Each vial will be supplied with an outer shield, and it is Bayer's intent to include complete information on the label affixed to the outer shield. The attached document contains proposed example text for the vial label, and the outer shield label. Does the agency agree that this approach is acceptable?

Glass Vial Label:



(b) (4)



FDA Response (October 19, 2011):

The following revisions to the immediate container labels are recommended:

For the vial, include the vial number and the comments on the name of the drug, strength and route of administration below.

For the lead container, please replace with the following:

Name of drug/ Strength/ Route of Administration:

**“Alpharadin® (Radium Chloride Ra 223) Injection, 1000 kBq/mL,
6.0 MBq/vial Cal :{DD/MM/YYYY} (12 h CET) intravenous use”**

Other additional information:

**“Composition per mL: 950-1050 kBq of radium-223, 6.3 mg of sodium
chloride, 7.2 mg sodium citrate. The pH is between 6.0 - 8.0”**

“Radioactive half-life of Ra-223 is 11.4 days”

Bayer Comments (October 25, 2011): Bayer will consider the Agency’s comments and provide a revised proposal in the future.

Meeting Discussion: No further discussions were necessary.

Questions on Nonclinical Development

Question 7

Does the Agency concur that the nonclinical studies of the pharmacokinetics (PK), biodistribution, and excretion of single injections of radium-223 chloride in mice, with determination of radiation in blood and organs over 14 days (ca. 1.3 half-lives) or 56 days (ca. 5 half-lives) and single- and repeated-dose biodistribution and excretion studies in Beagle dogs, sufficiently describe the nonclinical pharmacokinetics profile necessary for marketing application of radium-223 chloride for use in castration-resistant (hormone refractory) prostate cancer patients with bone metastases on a dosing regimen of an injection every 4 weeks for 6 cycles (i.e. 6 q4w cycles)?

FDA Response (October 19, 2011):

Based on the summary information provided in the meeting briefing package, the nonclinical PK studies with radium-223 chloride appear appropriate to support a marketing application; however, the adequacy of the resulting nonclinical data will be a review issue at the time of the NDA submission.

Bayer Comments (October 25, 2011): Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Question 8

Does the Agency concur that the conducted Good Laboratory Practices (GLP) safety pharmacology studies of radium-223 chloride in rats (CNS and respiratory function) and in conscious telemetered dogs (cardiovascular function and ECG) after a single intravenous bolus injection sufficiently satisfy the requirements of ICH S7A and S7B for marketing application of radium-223 chloride for use in castration-resistant (hormone refractory) prostate cancer patients with bone metastases on a dosing regimen of an injection every 4 weeks for 6 cycles (i.e. 6 q4w cycles)?

FDA Response (October 19, 2011):

Based on the summary information provided, the nonclinical GLP safety pharmacology studies with radium-223 chloride appear appropriate to support a marketing application; however, the adequacy of the resulting nonclinical data will be a review issue at the time of the NDA submission.

Bayer Comments (October 25, 2011): Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Question 9

Does the Agency concur that a GLP systemic toxicology program (dog studies were non-GLP with the exception of histology) consisting of the administration of bolus intravenous injections of radium-223 chloride as a single dose to mice, rats and dogs and as repeated doses, 4 weeks apart, for 4 and 12 months to rats and for 6 months in Beagle dogs sufficiently meets the regulatory requirements for marketing application of radium-223 chloride for use in castration-resistant (hormone refractory) prostate cancer patients with bone metastases on a dosing regimen of an injection every 4 weeks for 6 cycles (i.e. 6 q4w cycles)?

FDA Response (October 19, 2011):

Based on the summary information provided in the meeting briefing package, the nonclinical 4- and 12-month rat and 6-month repeat-dose dog GLP toxicology studies with radium-223 chloride appear appropriate to support a marketing application; however, the adequacy of the resulting nonclinical data will be a review issue at the time of the NDA submission.

Bayer Comments (October 25, 2011): Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Question 10

Does the Agency concur that nonclinical studies of fertility in male and female animals and of reproductive and developmental toxicity in female animals are not necessary for marketing application of radium-223 chloride for use in castration-resistant (hormone refractory) prostate cancer patients with bone metastases on a dosing regimen of an injection every 4 weeks for 6 cycles (i.e. 6 q4w cycles)?

FDA Response (October 19, 2011):

Yes, FDA agrees that nonclinical fertility and embryo-fetal toxicity studies are not necessary to support a marketing application for radium-223 chloride intended for use in castration-resistant prostate cancer patients with an overall life expectancy of less than 5 years.

Bayer Comments (October 25, 2011): Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Question 11

Does the Agency concur that studies of the genotoxic effects of radium-22 chloride *in vitro* and/or *in vivo* and lifetime studies of the tumorigenic potential of radium-223 chloride are not necessary for marketing application for the use of radium-223 chloride in castrate-resistant (hormone refractory) prostate cancer patients with bone metastases on a dosing regimen of an injection every 4 weeks for 6 cycles (i.e. 6 q4w cycles)?

FDA Response (October 19, 2011):

Yes, FDA agrees that genotoxicity and carcinogenicity studies are not required to support a marketing application for radium-223 chloride based on the known mechanism of action and the proposed patient population, as per ICH S9 guidance pertaining to the nonclinical evaluation for anticancer pharmaceuticals.

Bayer Comments (October 25, 2011): Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Questions on Clinical Development

Question 12

Does the Agency agree that the results from the registrational Phase III study BC1-06 (ALSYMPCA), together with the Phase I and Phase II study results that were conducted with radium-223 chloride solution for injection, provide sufficient information for evaluation of the efficacy and safety of the product in order to support the following indication: “radium-223 chloride is indicated for the treatment of castration-resistant (hormone refractory) prostate cancer in patients with bone metastases.”

FDA Response (October 19, 2011):

The adequacy of the clinical data to support the proposed indication will be a review issue at the time of the NDA submission.

Bayer Comments (October 25, 2011): Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Question 13

Does the Division agree with the proposal regarding the scope, format, and documentation of the electronic datasets to be submitted as described in the briefing book?

FDA Response (October 19, 2011):

Your proposal appears to be acceptable. In addition, please account for the preferences and issues contained in the CDER Data Standards Common Issues Document that can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Please also reference the Study Data Specifications found at:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>

Technical questions regarding datasets and data standards can be directed to the CDER eDATA team at: edata@fda.hhs.gov.

Since you are submitting CDISC/SDTM tabulation data, are the analysis datasets to be submitted according to the CDISC/ADaM IG? If not, are the analysis datasets being derived from the CDISC/SDTM tabulation data? Please indicate what your source data are for the analysis datasets, keeping in mind that analysis datasets need to be traced back to the "raw" data provided.

Bayer Comments (October 25, 2011): All of the studies in this submission are in a legacy data structure therefore Bayer is not planning to submit the analysis datasets according to the

CDISC/ADaM IG. The complete description of the structure and contents of each analysis dataset will be described in the corresponding define.pdf documentation that will be provided in the submission. This approach is in accordance with the Study Data Specifications document referred to in your response.

SDTM datasets will be provided only for the pivotal study ALSYMPCA BC01-06. The SDTM datasets are being derived for submission purposes only after the finalization of the analysis datasets. The analysis datasets are derived from raw datasets which contain data as it was collected in the CRF. These raw datasets, which serve as the source for the analysis datasets, can also be provided in the submission for BC1-06 if requested.

Meeting Discussion: The sponsor's plan is acceptable.

For your efficacy dataset, please include a variable describing a patient's docetaxel use (Received, Refused, Not Fit or Other). If collected please include information describing the "Other" reason for each patient who did not receive docetaxel.

Bayer Comments (October 25, 2011): Data on prior use of docetaxel (Yes vs. No) was collected. A flag for prior docetaxel use (Yes vs. No) will be provided in the database for the phase 3 study. Reasons for not receiving prior docetaxel treatment were not collected (non-protocol driven - investigator decision).

Meeting Discussion: The sponsor's plan is acceptable.

We will also be interested in an analysis of the number of cycles of prior docetaxel. Information regarding the reason for docetaxel discontinuation would be helpful if available.

Bayer Comments (October 25, 2011): Number of cycles of prior docetaxel and reason for docetaxel discontinuation were not collected. However, the start date and the stop date of each treatment of prior docetaxel treatment were collected.

Meeting Discussion: The sponsor agreed to provide information on the duration of docetaxel use (less than, greater than or equal to 12 weeks). This may include multiple cycles, or multiple courses of docetaxel.

***Comment added after the meeting: Within the adverse events dataset and within the dataset that provides the information for the analysis of overall survival, please also provide a flag which distinguishes patients who received ≥ 24 weeks of docetaxel from those who received < 24 weeks of docetaxel.**

Please also include a flag for patients who were symptomatic on enrollment.

Bayer Comments (October 25, 2011): The flag will be included.

Meeting Discussion: The sponsor agreed that they will be able to provide the flag.

We would also like a flag for any patients who may have experienced visceral or soft tissue progression while on study, if collected.

Bayer Comments (October 25, 2011): We can not provide a flag for visceral or soft tissue progression. Post-baseline tumor assessment was not scheduled in study BC1-06 (ALSYMPCA). Clinical progression was reported as ECOG PS progression or new skeletal related events. Visceral or soft tissue progressions may have been collected as adverse events during the study. The disease progression was also recorded as a reason for study drug discontinuation. However, discontinuation of a patient with disease progression was according to the investigator's judgment, not mandatory.

Meeting Discussion: The Agency understands that this information was not systematically collected and a flag will not be provided.

In your safety datasets, please include a flag for prior docetaxel use and prior radiation therapy.

Bayer Comments (October 25, 2011): A flag for prior docetaxel use (Yes vs. No) will be provided.

We collected history of prior radiation therapies including external radiotherapy and brachytherapy to the prostate, external beam radiation to bone and systemic radiation (with radionuclides). Bayer can provide a flag for each type of radiation therapy. Is this acceptable?

Meeting Discussion: The sponsor agreed to provide a flag for each type of radiation therapy received and can also provide the time period of use.

Question 14

Since the pivotal support of the submission will be based on one single Phase III study, does the Agency concur with the proposal that a pooled analysis for efficacy will not be performed?

FDA Response (October 19, 2011):

Yes, however please provide separate efficacy datasets for the phase 2 studies and your efficacy analyses for each of these trials in your NDA submission.

Bayer Comments (October 25, 2011): Bayer plans to include separate efficacy datasets for the phase 2 studies. Of note only BC1-02 was placebo controlled.

Meeting Discussion: No further discussions were necessary.

Question 15

Does the Agency agree with the proposal on how data will be discussed in the ISS?

FDA Response (October 19, 2011):

Yes, however this will be a review issue. In your safety analyses, please include an analysis for secondary malignancies and for ophthalmologic toxicity.

Bayer Comments (October 25, 2011): Yes, we will include an analysis for secondary malignancies and for ophthalmologic toxicity.

Meeting Discussion: No further discussions were necessary.

Please provide one AE dataset for the ALSYMPCA safety analysis (n=762) and a second integrated AE dataset for all clinical studies with a variable identifying which study the patient was treated on.

Bayer Comments (October 25, 2011): The datasets requested will be provided.

Meeting Discussion: No further discussions were necessary.

Question 16

In accordance with FDA guidances, Bayer will be submitting an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in Module 5.3.5.3 of the eCTD.

In the FDA “Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Documents” (April 2009), it is described that if the narrative portion of the ISE or ISS is suitable for use in section 2.7.3 or 2.7.4, the narrative portion should be submitted only once and referenced in both Module 2, section 2.7.3 or 2.7.4 and Module 5, section 5.3.5.3 (i.e., provide leaf elements in both locations).

In view of the small number of studies included in the dossier, does the Agency agree with Bayer’s plans to include the textual parts of efficacy / safety analyses in 2.7.3/2.7.4, and to include pertinent cross-references in 5.3.5.3 for ISE/ISS?

FDA Response (October 19, 2011):

Yes.

Bayer Comments (October 25, 2011): Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Question 17

Bayer is intending to submit CRF’s in electronic format only, in accordance with FDA guidance on electronic submissions, and to include CRF’s and patient narratives for only those patients who died during treatment or within 30 days after last administration of study drug, who experienced an adverse event meeting the definition of serious adverse event or who experienced

an adverse event and discontinued from the treatment phase of the study as a result of the adverse event. All other case report forms will be available upon request. Does the Agency agree with this approach?

FDA Response (October 19, 2011):

This appears reasonable. Please clarify that you will include CRFs and narratives for patients who meet the above criteria from all phase 1, 2 and 3 clinical trials.

Bayer Comments (October 25, 2011): Bayer plans to include CRFs and narratives for patients who meet the above criteria for all Phase 1, 2 and 3 clinical trials.

Meeting Discussion: No further discussions were necessary.

Question 18:

For the Phase III ALSYMPCA BC1-06 study included in the NDA submission, two databases are planned to be included:

- Data up to 14 October 2010 (interim analysis database) will provide definitive efficacy results which had been used by the IDMC for its recommendation to stop the trial early.
- Data up to 15 July 2011 (prior to offering placebo patients radium-223 treatment). will provide updated descriptive efficacy and safety results.

For studies ongoing and/or in follow-up period, Bayer will provide SAE listings from the Global Safety Database up to the cut-off off date of December 31, 2011.

Does the Agency agree?

FDA Response (October 19, 2011):

This appears reasonable. However, please clarify whether you are intending to submit the second dataset (data up to 15 July 2011) in the safety update or as an addendum in the original submission. Please keep efficacy data out of the safety update.

Bayer Comments (October 25, 2011): Bayer intends to submit both databases in the original NDA submission.

The database with a cut off date of 14 October 2010 is used to prepare the original clinical study report (CSR). Analysis datasets will be submitted for this database.

The secondary database with a cut off date of 15 July 2011 is an aggregate database containing the 14 October 2010 data. A CSR addendum will be included in the original NDA submission to provide the updated descriptive efficacy and safety analyses based on this database. Similar to the October data, analysis datasets for the July database will be submitted. In addition, SDTM datasets will also be provided for this July database.

Meeting Discussion: The sponsor's proposal is acceptable.

Question 19

Does FDA have any comments about the Quality activities undertaken for BC1-06 or require any additional information prior to review of the NDA submission?

FDA Response (October 19, 2011):

Please clarify whether you have monitored all study sites for source data verification and clarify what percentage of patient records was monitored. We would like a list of the study

sites that were chosen for your quality verification program. Please also provide a list of the 32 sites that were identified as needing increased quality oversight.

You have stated that your review found that adverse events were under-reported. Please provide examples of the type of AEs that were under-reported, information on the magnitude of this problem, and detailed information on the way in which you have addressed this at audited and unaudited sites.

In addition, we would like you to provide us with a table similar to the one below containing information for patients on each arm. Please include the address and contact information for each site in an appendix to the table:

Site #	Number of Patients Enrolled		Number of Adverse Events Reported		Number of Protocol Violations		Median Overall Survival		PSA Response rate	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B

Bayer Comments (October 25, 2011):

In accordance with the monitoring plan for study BC1-06, source data verification was performed globally throughout study for all subjects at all study sites.

The Quality Verification Program referred to in the question is conducted over and above the routine monitoring, and was initiated in order to fully investigate trends identified with respect to complete reporting of adverse events, confirmation of eligibility of subjects and Clinical Research Associate (CRA) access to source data, in particular electronic source data.

The Quality Verification program was initiated in January 2011 .The program was executed with the aim of assuring adequate data quality before closing of the database for the planned interim analysis (IA).

The following table provides an overview of the Quality Verification program.

	67 selected sites*
Total number of subjects at the sites	726*
Total number of subjects reviewed for AEs/SAEs	594 (73%**)
Total number of subjects reviewed	92

	67 selected sites*
for SDV	

** Percentage of the total number of randomized subjects (809 subjects) up to the data lock point for the interim analysis of 14 Oct 2010

Totally 67 sites (52% of the 128 sites having included subjects up to the data lock point for the interim analysis, 14 October 2010) were included in the Quality Verification Action Plan.

At these 67 sites, 594 subjects were reviewed for complete AE/SAE reporting. A subset of 92 subjects' records (11% of all subjects randomized in the study up to the data lock point for the interim analysis) were selected for broader source data verification activities. The 67 study sites selected were as follows:

Country	Site number	Principal Investigator Name
Australia	200	Dalley
	203	Brown
	207	Jackson
	208	Harrup
Belgium	028	Billiet
	029	Duck
Brazil	170	Damiao
	173	Murad
	179	Koff
	181	Dall'Oglio
Canada	127	Reid
	128	Klotz
	129	Patel
	130	Leung
Czech Republic	017	Chodacki
Germany	148	Wedel
	149	Boehmer
	152	Strauss
	155	Schrader
Hong Kong	103	Yau Tsz Kok
	106	Leung
Israel	085	Mermershtain
Italy	078	Amadori
	081	Slavo
Netherlands	053	Verhagen
	055	Vergunst
Norway	001	Fosså

Country	Site number	Principal Investigator Name
	002	Johannessen
	003	Solberg
	006	Helle
	007	Klepp
	008	Kasti
Poland	133	Demkow
	137	Jarzab
	139	Klijer
Singapore	191	Tay
Slovakia	097	Kliment
Spain	059	Arbizu
	060	Mellado
	062	Estorch
	063	Lopez
	066	Saenz-Cusi
Sweden	071	Donas
	020	Franzen
	022	Falkmer
	024	Seke
	025	Widmark
UK	026	Nilsson
	033	Parker
	034	Pascoe
	035	O'Sullivan
	036	Staffurth
	037	Vasanthan
	039	Hoskin
	040	Bahl
	041	Coleman
	042	Logue
	043	James
	044	Heath
	045	Stockdale
	047	Graham
	048	Ramchandra
049	Chakraborti	
050	Bottomley	
051	Syndikus	

Country	Site number	Principal Investigator Name
	233	Dixit
USA	240	Sartor

The following 31 sites were furthermore identified for further quality oversight (program currently ongoing). The number of sites was reported in the Briefing Document referred in error to 32, not 31 sites:

Country	Site number	Principal Investigator Name
Brazil	181	Dall'Oglio
Canada	129	Patel
	128	Leung
Czech Republic	010	Zachoval
	012	Schraml
France	110	Pecking
	111	Toubeau
	113	Priou
	117	Rudenko
Hong Kong	106	Leung
Norway	001	Fosså
	003	Solberg
	006	Helle
	007	Klepp
	008	Kasti
Spain	059	Arbizu
	062	Estorch
	063	Lopez
	071	Donas
Sweden	020	Franzen
	022	Falkmer
	025	Widmark
UK	033	Parker
	035	O'Sullivan
	039	Hoskin
	042	Logue
	043	James
	233	Dixit
USA	240	Sartor
	241	Vogelzang
	254	Tomblyn

There were no adverse events found during the Quality verification activities, which were not observed in the set of adverse events already reported for radium-223 chloride. Examples of the types of adverse events which were found during the Quality verification activities are: anemia, anorexia, bone pain, constipation, decreased appetite, diarrhea, edema in legs, fatigue, fever, increased or intermittent pain, nausea, vomiting, pain (hip, knee, femur, no specification), skin reaction/thin skin/skin spots, topic allergy, weight loss. The quality verification program showed an underreporting of safety events of 0.9 events per subject re-monitored.

At the sites included in the Quality Verification program, the findings have been discussed with the sites during the additional monitoring visits, and relevant site personnel have been re-trained as necessary. In addition monitoring frequency has been increased together with an increase in the duration of the visits.

Globally, the issue of adverse event reporting has been a focus area for training of all CRAs. The monitoring visit report template has been revised to specifically require information on source data access, to ensure all source data are available for monitoring. In addition, global re-training of regular CRAs on key outcomes and expectations following the Quality Verification activity has been undertaken as web based training sessions in February 2011, and global face-to-face training in April 2011.

The additional tabulated information requested will be provided as an IND information amendment.

Meeting Discussion: The sponsor's explanation was helpful. The sponsor agreed to provide the requested table, with the October 2010 cut-off, in the NDA.

Question 20

The effect of age will be derived only from BC1-06 ALSYMPCA trial by subgroup analysis, as other Phase I and II clinical studies were small in size and also included different dosage regimens than the dose and regimen intended for the NDA submission. Does the Agency agree?

FDA Response (October 19, 2011):

Yes, but all data may be reviewed.

Bayer Comments (October 25, 2011): Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Question 21

The clinical pharmacology/clinical studies and analysis that are planned to be included in the clinical pharmacology section of the NDA are described in Section 10.3.3 of the briefing document. Does the Agency consider this clinical pharmacology package acceptable for submission?

FDA Response (October 19, 2011):

Your proposed clinical pharmacology package appears acceptable. Please also submit the QTc prolongation evaluation with the NDA.

Bayer Comments (October 25, 2011): Thank you for your response, no further comments at this time.

Meeting Discussion: No further discussions were necessary.

Question 22

Throughout the development of radium-223 chloride, the sponsor has worked with recognized scientific experts to develop methods for dosimetry calculations for an alpha-emitter. The biodistribution data and dosimetry calculations from study BC1-05 are provided in the briefing document section. Does the Agency agree with the proposed methodology for dosimetry calculations?

FDA Response (October 19, 2011) :

Your dosimetry submission appears reasonable, however we await physics review and dosimetric analysis will be a review issue.

Bayer Comments (October 25, 2011): Based on your response, we understand that the dosimetry section from the briefing document was forwarded for a physics review. Can we expect comments from the Physics review prior to NDA submission?

Meeting Discussion: This will be reviewed at the time of the NDA submission. The Agency requested that organ doses be specified in rem or Sieverts, as well as in rad or Grey, using an RBE factor that is justified by referenced literature.

Please state your rationale for using standard organ masses, rather than patient-specific estimates.

Bayer Comments (October 25, 2011):

Whole organ uptake was not visible in imaging studies for most organs because of the rapid clearance and low retention of radium-223 chloride (except for bone and GI). For bone and GI patient-specific mass determination is not feasible to assess from the imaging. The cumulated activity (CA) estimates for normal organs were obtained from plasma and blood concentration based on standard reference plasma and blood volumes in each organ of interest. Reference values had to be used because patient-specific measurement of such parameters are generally not feasible. Since reference values were used to derive cumulative activities (CAs) for dosimetry, a

corresponding reference of standard organ masses had to be used to avoid inconsistency for dose calculations and used to calculate CAs. The absorbed dose estimates were not close to tolerance

for organs therefore we believe that patient-specific mass calculations would have not made a difference even if that was possible to calculate.

Meeting Discussion: The sponsor will include their rationale in the NDA.

Multidisciplinary Questions

Question 23

Does the Agency anticipate requesting an Applicant Orientation meeting for the radium-223 chloride NDA or that the NDA will be subject to a Oncologic Drugs Advisory Committee meeting?

FDA Response (October 19, 2011):

Yes; please plan on an Applicant Orientation Meeting. With regard to your ODAC query, we will not be able to definitively answer this question until we are in receipt of the NDA and the review process has begun.

Bayer Comments (October 25, 2011): Thank you for your response.

Meeting Discussion: No further discussions were necessary.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

4.0 ACTION ITEMS

N/A

5.0 ATTACHMENTS AND HANDOUTS

N/A

Minutes Preparer:

{See appended electronic signature page}

Kim J. Robertson
Project Manager

Meeting Chair:

{See appended electronic signature page}

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

Meeting Adjourned:

2:22PM

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

/s/

KIM J ROBERTSON
10/27/2011

VIRGINIA E MAHER
10/28/2011

MID-CYCLE COMMUNICATION
DOCUMENTS



NDA 203971

MEETING MINUTES

Bayer HealthCare Pharmaceuticals
Attention: Deepika Jalota, Pharm.D.
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Dr. Jalota:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xofigo® (radium Ra-223 dichloride) Injection, 1000 kBq/mL (0.027 mCi/mL) at reference date.

We also refer to the Late-Cycle Meeting (LCM) briefing package sent to you on April 5, 2013 and the LCM teleconference between representatives of your firm and the FDA on April 19, 2013. The purpose of a Late-Cycle meeting (LCM) was to share information and to discuss any substantive review issues and the objectives for the remainder of the review.

We acknowledge your response to the LCM briefing package received on April 19, 2013.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Elleni Alebachew, Regulatory Project Manager, at (301) 796-5225.

Sincerely,

{See appended electronic signature page}

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Products
Center for Drug Evaluation and Research

V. Ellen Maher, M.D.
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Category: Late-Cycle Meeting

Meeting Date and Time: April 19, 2013 11:00 AM to 12:00 PM
Meeting Location: Teleconference

Application Number: NDA 203971
Product Name: Xofigo[®] (radium Ra 223 dichloride) Injection
Indication: For the treatment of castration-resistant prostate cancer patients with bone metastases

Applicant Name: Bayer HealthCare Pharmaceuticals, Inc.

Meeting Chair: V. Ellen Maher, M.D., Clinical Team Leader, DOP1
Meeting Recorder: Elleni Alebachew, M.S., RAC, Regulatory Project Manager, DOP1

FDA ATTENDEES

John Jenkins, M.D., Director, OND
Richard Pazdur, M.D., Director, OHOP
Robert L. Justice, M.D., M.S., Director, DOP1
Amna Ibrahim M.D., Deputy Director, DOP1
V. Ellen Maher, M.D., Clinical Team Leader, DOP1
Paul Kluetz, M.D., Medical Officer, DOP1
William Pierce, Pharm.D., Sr. Clinical Analyst, DOP1
Katherine Fedenko, M.S., CRNP, Deputy Director for Safety, DOP1
Cynthia Welsh, M.D., Medical Officer, DMIP
Shenghui Tang, Ph.D., Biostatistics Team Leader, DBV
Hui Zang, Ph.D., Biostatistics Reviewer, DBV
Todd Palmby, Ph.D., Acting Pharm/Tox Supervisor, DHOT
Wei Chen, Ph.D., Pharm/Tox Reviewer, DHOT
Nam Atiqur Rahman, Ph.D., Director, DCP5
Brian Booth, Ph.D., Deputy Director, DCP5
Pengfei Song, Ph.D., Clinical Pharmacology Reviewer, DCP5
Eldon E. Leutzinger, Ph.D., CMC Lead, ONDQA
Ali Al-Hakim, Ph.D., Branch Chief, ONDQA
Tamy Kim, Pharm. D., Associate Director of Regulatory Affairs, OHOP
Erik Laughner, Regulatory Scientist, OHOP
Kimberly Taylor, Operations Research Analyst, OPI
Lauren Iacono-Connors, Ph.D., Office of Scientific Investigations

Peter E. Waldron, M.D., Medical Officer, DPV-II, OSE
Min Chu Chen, M.S., R.Ph., Acting Director, DPV, OSE
Tracy M. Salaam, Pharm.D., Safety Evaluator Team Leader, DPV-II, OSE
Katherine M. Coyle, Pharm.D., BCOP, Evaluator, DPV-II, OSE
Kate Gelperin, M.D., M.P.H, DEPI-I, OSE
Frances Fahnbulleh, Pharm.D., Safety Regulatory Project Manager, OSE
Susan Jenney, M.S., Safety Regulatory Health Project Manager, DOP1
Alice Kacuba, R.N., M.S.N, RAC, CPMS, DOP1
Elleni Alebachew, M.S., RAC, Regulatory Health Project Manager, DOP1

(b) (4)

SPONSOR ATTENDEES

Bayer

Joseph Scheeren, Pharm.D., Senior VP, Head of Global Regulatory Affairs
Gerhard Schlueter, Ph.D., Vice President, Global Regulatory Affairs, Specialty Medicine
Max Wegner, Ph.D., Vice President, US Regulatory Affairs Interim Head
Maria C. Garrigan, Director, Global Regulatory Affairs, Oncology
Deepika Jalota, Pharm.D., Deputy Director, Global Regulatory Strategist
Marion Resch, Deputy Director, Global Regulatory Strategist
Mike Koenig, M.S., Associate Director, CMC Regulatory Affairs
Lothar Everz, Diplom/Pharmacist, Radiopharmaceutical Science
David Weinreich, M.D., M.B.A., VP, Head, Global Clinical Development, TA Oncology
Dimitris Voliotis, M.D., Vice President, Global Clinical Development, TA Oncology
Jose Garcia-Vargas, M.D., Senior Director, Global Clinical Leader
Julie Rosenberg, Director, Global Clinical Leader, Oncology
Minghua Shan, Ph.D., Senior Director, Expert Statistician, Oncology
Fang Fang, Ph.D., Project Statistician, Oncology
Claire Blanchette, Global Project Leader
Pamela Gilles, Ph.D., Senior Toxicologist, Toxicology
Christian Zurth, Ph.D., Senior Pharmacokinetics Expert, Clinical Pharmacology Leader
Gerhard Reike, M.D., Global Pharmacovigilance, TA Oncology Head
Nils Opitz, M.D., Global Safety Leader
Joseph Germino, M.D., Ph.D. VP, Medical Affairs, Oncology, Hematology and Neurology
Mona Wahba, M.D., M.S.M. Deputy Director, U.S. Medical Affairs, Oncology
Jeffrey Bova, Director, Oncology Marketing
Justin Daniels, Ph.D., Director, Global Medical Affairs Oncology
Svetlana Kobina, M.D., VP, Global Medical Affairs, Oncology

Algeta

Gillies O'Bryan-Tear MB MRCP, Chief Medical Officer
Inger Margrethe Torgersen, Director, Regulatory Affairs

BACKGROUND

This NDA was submitted December 14, 2012 for Xofigo[®] (radium Ra 223 dichloride) and is currently under an expedited review clock. This teleconference (LCM) was held to discuss the status of NDA 203971 for radium Ra 223 dichloride.

DISCUSSION OF SUBSTANTIVE REVIEW ISSUES

1. Post-Marketing Commitment: We plan to request that you conduct a PMC trial to evaluate the efficacy and safety of Xofigo at a higher dose. Please evaluate the different options and provide a plan to address this PMC

Meeting Discussion:

- In the April 19, 2013 response to FDA, Bayer proposed to conduct a phase 2 trial to evaluate the efficacy and safety of Xofigo at a dose higher than 50 kBq/kg (e.g., 80 kBq/kg given over 6 cycles) (b) (4)
 - FDA asked Bayer to provide criteria that would be used to move to a phase 3 trial after completion of the proposed phase 2 studies, and asked Bayer to clarify why Bayer did not choose to investigate higher doses of treatment in Phase 3 trials at this time.
 - Bayer stated that the current data to support phase 3 trials is not sufficient for higher doses of Xofigo therapy. Bayer has not developed criteria to initiate phase 3 trials after completion of the proposed phase 2 trials. Bayer stated that they plan to discuss the next step with FDA after the conclusion of the phase 2 trials.
 - Bayer expressed concern regarding a direct-to-Phase-3 approach due to the possibility of late toxicity and the risk of exceeding a threshold (“cliff”) exposure level that could result in irreversible toxicities in some patients.
 - Bayer stated that they plan to evaluate higher doses (b) (4) of Xofigo while minimizing potential late toxicities at higher Xofigo exposure levels.
 - FDA recommended that Bayer to incorporate the Option C comments regarding the Phase 2 trial designed as conveyed in LCM briefing package. Bayer stated that they may not fully incorporate comment 3 (b) (4) (b) (4) FDA stated that it is Bayer’s decision to determine how the trial will be designed as this is a PMC trial. Bayer will submit protocol synopsis of the proposed Phase 2 trial in late April or early May, 2013.
2. Post-Marketing Requirement 1: You plan to conduct an observational study (N = 1200) to assess the long-term safety of radium-223 50 kBq/kg every 4 weeks for 6 doses in patients with castration-resistant prostate cancer with bone metastases. (b) (4)

Meeting Discussion:

- An agreement was made between FDA and Bayer that since this study is observational and non-interventional, scheduled laboratory monitoring post treatment will not be required. Reporting laboratory data based on local practice appears to be acceptable based on the non-interventional trial design.
 - An agreement was made between FDA and Bayer to provide an interim safety analysis approximately three years after study initiation. This interim analysis will include a comprehensive assessment of any potential safety issues based on data available in the Xofigo safety database at the time of the interim report.
3. Post-Marketing Requirement 2: The duration of follow up dictated by the life expectancy of the patients with advanced prostate cancer enrolled in your observational trial may be inadequate to fully assess the development of secondary malignancies. Provide long-term follow up for secondary malignancies in your proposed trial (b) (4)

Meeting Discussion:

- Bayer agreed to provide long-term follow up for secondary malignancies and hematologic toxicities in the planned Phase 3 trial treating prostate cancer patients with Xofigo (b) (4)
 - An agreement was made between FDA and Bayer to provide a study synopsis that will include scheduled laboratory monitoring after discontinuation of Xofigo treatment.
 - An agreement was made between FDA and Bayer that patients treated with cytotoxic chemotherapy after study treatments would be actively monitored and assessments would include laboratory and safety assessments for febrile neutropenia and hemorrhage.
4. Post-Marketing Requirement 3: You plan to conduct a trial of re-treatment with radium-223. To fully assess the safety of re-treatment (b) (4)

Meeting Discussion:

- An agreement was made between FDA and Bayer to provide a revised study synopsis that will include scheduled laboratory monitoring after discontinuation of Xofigo treatment.
- Bayer agreed to provide long-term follow up for secondary malignancies and hematologic toxicities in the planned retreatment trial.

DISCUSSION OF UPCOMING ADVISORY COMMITTEE MEETING

FDA stated that an Advisory Committee meeting is not planned.

CURRENT ASSESSMENT OF THE NEED FOR REMS OR OTHER RISK MANAGEMENT ACTIONS

FDA stated that the Agency does not think that a Risk Evaluation and Mitigation Strategy will be necessary.

MAJOR LABELING ISSUES

FDA stated that FDA has revised the indication statement for Xofigo and proposed to discuss the revised indication during label negotiations. Bayer agreed.

WRAP UP AND ACTION ITEMS

Bayer agreed to provide updated protocol synopsis for the PMC and PMRs discussed above. The protocol synopsis for the PMC will not be provided until the beginning of May 2013. FDA reviewed the remainder of the review cycle with Bayer and advised Bayer to respond to any future information request expeditiously.



NDA 203971

LATE CYCLE MEETING BACKGROUND

Bayer HealthCare Pharmaceuticals
Attention: Deepika Jalota, Pharm.D.
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Dr. Jalota:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xofigo® (radium Ra-223 dichloride) Injection, 1000 kBq/mL (0.027 mCi/mL) at reference date.

We also refer to the Late-Cycle meeting (LCM) scheduled for April 19, 2013. Attached is our briefing package, including our agenda for this meeting.

If you have any questions, call Elleni Alebachew, Regulatory Project Manager, at (301) 796-5225.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Briefing Package

LATE-CYCLE MEETING BRIEFING PACKAGE

Meeting Date and Time: April 19, 2013, from 11:00 AM to 12:00 PM
Meeting Location: WO Building 22, Room 1311

Application Number: NDA 203971
Product Name: Xofigo[®] (radium Ra-223 dichloride)
Indication: For the treatment of castration-resistant prostate cancer patients with bone metastases
Applicant Name: Bayer HealthCare Pharmaceuticals

INTRODUCTION

The purpose of a Late-Cycle meeting (LCM) is to share information and to discuss any substantive review issues, Advisory Committee (AC) meeting plans (if scheduled), and the objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues, whether it will be reviewed by the Agency in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. If you submit any new information in response to the issues identified in this briefing package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

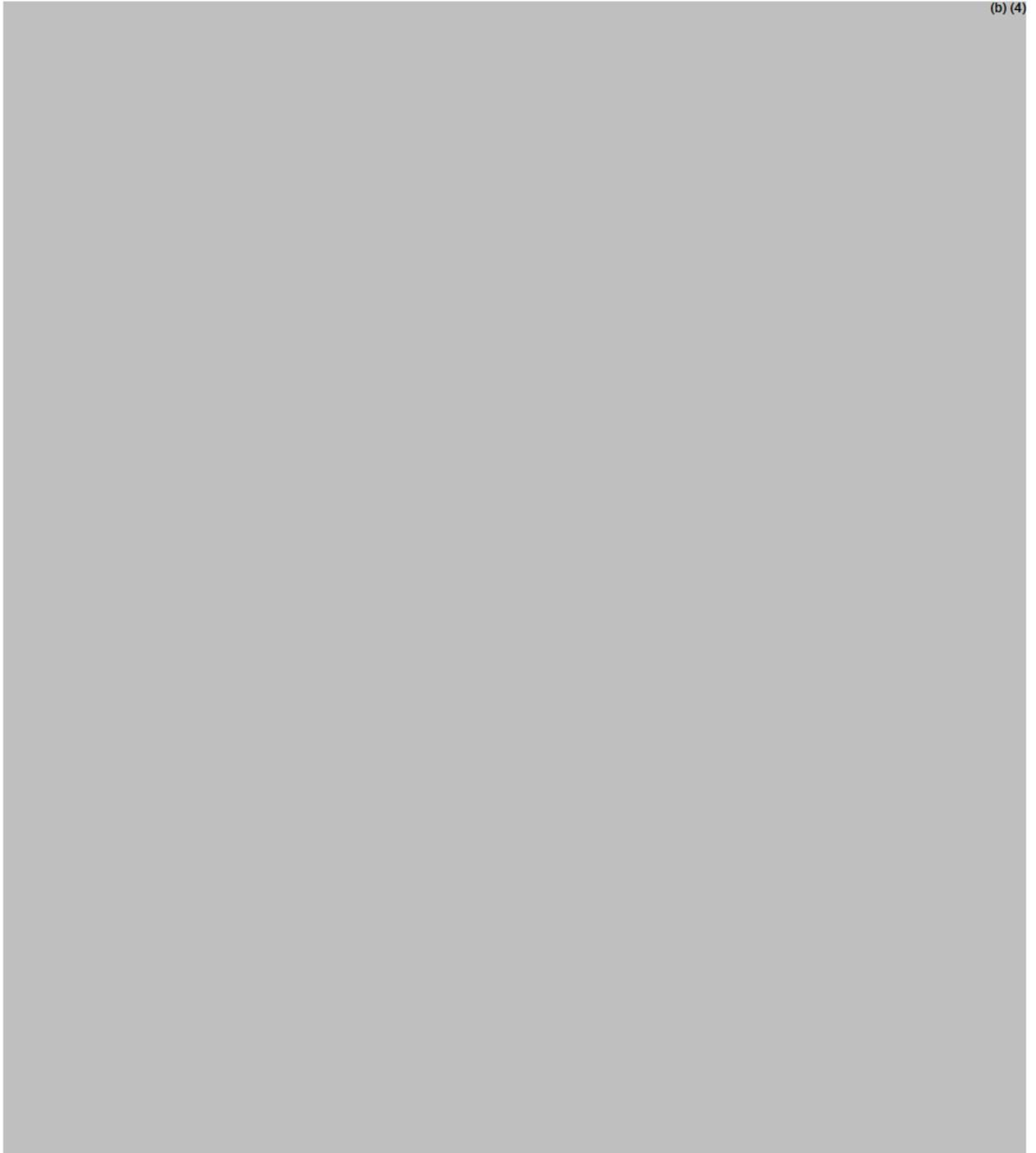
OVERVIEW OF ISSUES IDENTIFIED TO DATE:

The current substantive review issues are as follows:

1. Chemistry, Manufacturing, and Control:
 - a. There are no current substantive review issues.
 - b. Facilities inspections have been completed and the results are pending.
2. Nonclinical: There are no current substantive review issues.

3. Clinical Pharmacology:

Based on the findings we conveyed to you on February 1, 2013, we plan to request that you conduct a Post-Marketing Commitment (PMC) trial to evaluate the efficacy and safety of Xofigo at a higher dose. There are different options for you to consider for this PMC:





- d. Once agreement is reached on the trial design, please provide timelines (final protocol submission, trial completion, final report submission with submission of any necessary labeling) for the conduct of this trial.

4. Clinical:

- a. Post-Marketing Requirement 1: We refer to your March 28, 2013, submission outlining your plan to conduct an observational study (N = 1200) to assess the long-term safety of radium-223 in patients with castration-resistant prostate cancer with bone metastases.

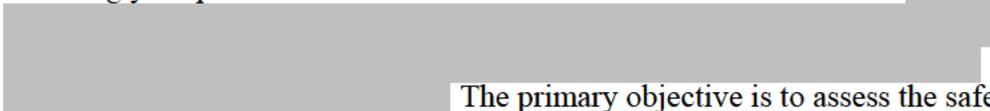


i.



ii.

- iii. We are concerned that it will take many years to finalize the results of this study. Develop a plan to provide an interim analysis of the safety findings to the Agency. Provide timelines (final protocol submission, study completion, interim report submission, and final report submission with submission of any necessary labeling) for the conduct of this trial.
 - b. Post-Marketing Requirement 2: The median overall survival in the radium-223 arm of your Phase 3 trial, BC1-06 was 14.9 months (95% CI: 13.9, 16.1). The duration of follow up dictated by the life expectancy of patients with advanced prostate cancer may be inadequate to fully assess the development of secondary malignancies. In addition to your proposed study, provide long-term follow up for secondary malignancies in your proposed trial of radium-223 (b) (4)

 - i. State the power of this study to estimate the incidence of secondary malignancies.
 - ii.  (b) (4)
 - iii.
 - iv. We are concerned that it will take many years to finalize the results of this study. Develop a plan to provide an interim analysis of the safety findings to the Agency. Provide timelines (final protocol submission, trial completion, interim report submission, final report submission with submission of any necessary labeling) for the conduct of this trial.
 - c. Post-Marketing Requirement 3: We refer to your March 28, 2013, submission outlining your plan to conduct a trial of re-treatment with radium-223. (b) (4)


The primary objective is to assess the safety of re-treatment, but the safety parameters that will be collected are not further defined.

 - i. We are concerned that patients with castration-resistant prostate cancer will be exposed to the unknown risk of re-treatment when there are other options available (i.e., abiraterone, enzalutamide). We recommend that you modify your protocol to include only patients who have evidence of radiographic progression (per PCWG2) or definitive evidence of clinical progression.

- ii. To fully assess the safety of re-treatment, [REDACTED] (b) (4) and for the development of related serious adverse events.
 - iii. Provide timelines (final protocol submission, trial completion, final report submission with submission of any necessary labeling) for the conduct of this trial.
- d. The Office of Scientific Investigations has completed their inspections and the results are pending at this time.

5. Labeling:

- a. We have revised the indication statement as follows.
 - i. Bayer provided the following indication statement [REDACTED] (b) (4)
 - ii. The FDA revised indication states, "Xofigo is a radioactive therapeutic agent indicated for the treatment of symptomatic castration-resistant prostate cancer patients with bone metastases and no evidence of visceral metastatic disease."
 - iii. The indication statement has been revised to reflect the population enrolled in your Phase 3 trial, BC1-06.
- b. Labeling is tentatively scheduled to be provided to the applicant on Wednesday, April 10, 2013. Please state when you will be able to return the package insert to the Agency.

ADVISORY COMMITTEE MEETING:

An Advisory Committee meeting is not planned.

CURRENT ASSESSMENT OF THE NEED FOR REMS OR OTHER RISK MANAGEMENT ACTIONS:

The Agency does not think that a Risk Evaluation and Mitigation Strategy will be necessary.

AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issue(s) – 45 minutes

Each issue will be introduced by FDA and followed by a discussion.

- Post-Marketing Commitment: We plan to request that you conduct a PMC trial to evaluate the efficacy and safety of Xofigo at a higher dose. Please evaluate the different options and provide a plan to address this PMC
- Post-Marketing Requirement 1: You plan to conduct an observational study (N = 1200) to assess the long-term safety of radium-223 50 kBq/kg every 4 weeks for 6 doses in patients with castration-resistant prostate cancer with bone metastases. (b) (4)
[REDACTED]
- Post-Marketing Requirement 2: The duration of follow up dictated by the life expectancy of the patients with advanced prostate cancer enrolled in your observational trial may be inadequate to fully assess the development of secondary malignancies. Provide long-term follow up for secondary malignancies in your proposed trial of radium-223 (b) (4).
- Post-Marketing Requirement 3: You plan to conduct a trial of re-treatment with radium-223. To fully assess the safety of re-treatment please include (b) (4)
[REDACTED] and for the development of related serious adverse events.

3. Discussion of Upcoming Advisory Committee Meeting – N/A

4. Current Assessment of the need for REMS or other risk management actions – N/A

5. Major labeling issues – 5 minutes

- The FDA has revised indication statement to, “Xofigo is a radioactive therapeutic agent indicated for the treatment of symptomatic castration-resistant prostate cancer patients with bone metastases and no evidence of visceral metastatic disease.” This has been revised to reflect the population enrolled in your Phase 3 trial, BC1-06.
- Tentatively, labeling will be provided to the applicant on Wednesday, April 10, 2013.

6. Wrap up and Action Items – 5 minutes

- Timeline for submission of revised protocol synopses for post-marketing requirements and post-marketing commitments.
- Timeline for submission of revised labeling to the FDA.

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/s/

ROBERT L JUSTICE
04/05/2013



NDA 203971

MID-CYCLE COMMUNICATION

Bayer HealthCare Pharmaceuticals
Attention: Deepika Jalota, Pharm.D.
Deputy Director, Global Regulatory Affairs
P.O.Box 1000
Montville, NJ 07045

Dear Dr. Jalota:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xofigo™ (radium-223 dichloride) Injection.

We also refer to the teleconference between representatives of your firm and the FDA on February 28, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application following our Mid-Cycle meeting.

A record of the teleconference is enclosed for your information.

If you have any questions, call Elleni Alebachew, Regulatory Project Manager, at (301) 796-5225.

Sincerely,

{See appended electronic signature page}

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

V. Ellen Maher, M.D.
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center of Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

MID-CYCLE COMMUNICATION

Meeting Date and Time: February 28, 2013 12:00 PM to 12:30 PM

Application Number: NDA 203971

Product Name: Xofigo™ (radium-223 dichloride) Injection

Indication: For the treatment of castration-resistant prostate cancer patients with bone metastases

Applicant Name: Bayer HealthCare Pharmaceuticals, Inc.

Meeting Chair: V. Ellen Maher, M.D., Clinical Team Leader, DOP1

Meeting Recorder: Elleni Alebachew, M.S., RAC, Regulatory Project Manager, DOP1

FDA ATTENDEES

Amna Ibrahim M.D., Deputy Director, DOP1
V. Ellen Maher, M.D., Clinical Team Leader, DOP1
Tamy Kim, Pharm. D., Associate Director of Regulatory Affairs, OHOP
Patrick Frey, Director, Office of Planning and Analysis
Kimberly Taylor, Operations Research Analyst, Office of Planning and Analysis
Alice Kacuba, R.N., M.S.N, RAC, CPMS, DOP1
Elleni Alebachew, M.S., RAC, RPM, DOP1

(b) (4)

APPLICANT ATTENDEES

Bayer

Gerhard Schlueter, Ph.D., Vice President, Global Regulatory Affairs, Specialty Medicine
Maria C. Garrigan, Director, Global Regulatory Affairs, Oncology
Deepika Jalota, Pharm.D., Deputy Director, Global Regulatory Strategist
Marion Resch, Ph.D., Deputy Director, Global Regulatory Strategist
Max Wegner, Ph.D., VP, US Regulatory Affairs Interim Head and Head of General Medicine Head
Mike Koenig, M.S., Associate Director, CMC Regulatory Affairs
David Weinreich, M.D., M.B.A., VP, Head, Global Clinical Development, TA Oncology
Dimitris Voliotis, M.D., VP, Global Clinical Development, TA Oncology
Jose Garcia-Vargas, M.D., Senior Director, Global Clinical Leader
Minghua Shan, Ph.D., Senior Director, Expert Statistician, Oncology
Fang Fang, Ph.D., Project Statistician, Oncology
Jeremy Gratt, Ph.D. Candidate, Lead Statistical Analyst
Claire Blanchette, Global Project Leader
Andy Hargreaves, B.S., Senior Director, GCP Study Audit Management US CAN LA
Pamela Gilles, Ph.D., Senior Toxicologist, Toxicology
Lothar Everz, Ph.D., CMC Radiopharmaceutical Science
Christian Zurth, Ph.D., Sr. Pharmacokinetics Expert, Clinical Pharmacology Leader, Clinical Sciences
Nils Opitz, M.D., Global Safety Leader

Algeta

Gillies O'Bryan-Tear MB MRCP, Chief Medical Officer
Reidun Holtan Palm, Director, Regulatory Affairs CMC
Inger Margrethe Torgersen, Director, Regulatory Affairs

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

1. Long-term evaluation of the risk of secondary malignancy is likely to be a post-marketing requirement.
2. A plan for optimization of the dose or schedule of Radium-223 is likely to be a post-marketing commitment.
3. On February 22, 2013, the Agency sent an information request for data on the ability of commonly used U.S. dose calibrators to verify the radiation dose of Radium-223. The results of the review of this data will be of key importance during labeling.

3.0 INFORMATION REQUESTS

Any further new information requests will be sent separately.

3.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, the Agency does not think that a Risk Evaluation and Mitigation Strategy will be necessary.

5.0 ADVISORY COMMITTEE MEETING

As communicated to you on in the Filing Communication Letter dated February 12, 2012, no Advisory Committee Meeting is planned at this time.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

PMR/PMC and Labeling	April 12, 2013
Late-Cycle Meeting	April 19, 2013
PDUFA Action Date	August 14, 2013

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
03/07/2013

VIRGINIA E MAHER
03/11/2013