CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203971Orig1s000

<u>CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)</u>

Clinical Pharmacology Review

NDA	203971
Submission Date	December 14, 2012
Brand Name	XOFIGO
Generic Name	Radium-223 Dichloride Injection
Dosage Form / Strength	Single-use vial containing 6000 kBq/6 mL (27 µCi/6 mL)
Related IND	67521
Applicant	Bayer, Inc.
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OCP Division	Division of Clinical Pharmacology 5
ORM Division	Division of Oncology Products 1 (DOP1)
Submission Type; Code	Original NDA 000; 505 (b) (1); New Molecular Entity
Dosing Regimen	50 kBq (1.35 µCi) per kg body weight, given at 4-week intervals for 6 injections
Indication	Castration-resistant prostate cancer with bone metastases

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1 EXECUTIVE SUMMARY

Xofigo (radium-223 dichloride) is an alpha particle-emitting radioactive therapeutic agent. The applicant seeks the approval of Xofigo for the treatment of castration-resistant prostate cancer (CRPC) with bone metastases. The proposed dosing regimen is 50 kBq (1.35 µCi) per kg total body weight, given at 4-week intervals for 6 intravenous injections. The efficacy and safety of treatment beyond 6 injections have not been studied.

A randomized Phase 3 trial BC1-06 (ALSYMPCA) in CRPC patients with bone metastases demonstrated a significantly improved overall survival (OS) in the Xofigo arm (median:14.9 months) compared to the placebo control arm (median:11.3 months), with a hazard ratio of 0.70 (95% CI: 0.58, 0.83). Most common adverse reactions (> 10%) of Xofigo treatment were diarrhea, nausea, vomiting, and thrombocytopenia.

Xofigo demonstrated linear pharmacokinetics in blood in terms of dose proportionality and time independence in a dose range of 46-250 kBq/kg total body weight. After intravenous injection, Radium-223 is rapidly cleared from blood and distributed to bone and intestine. At 10 minutes post injection, radioactivity was observed in bone and intestine. The fraction of the injected radioactivity remained in blood, bone, and intestine was 4 ±1%, 61 ± 10%, and 49 ±16%, respectively, at 4 hours post injection. Approximately 63% of administered radioactivity was excreted from the body within 7 days, primarily via fecal route. Dosimetry data suggested that bone, red marrow, and intestine wall received the highest absorbed radiation doses. Radium-223 is not metabolized, and there was no evidence of hepato-biliary excretion based on imaging data.

Exploratory analyses suggested that the proposed dosing regimen may not be optimal. In the pivotal trial BC1-06, the separation of OS Kaplan-Meier curves stratified by body weight quartiles suggested that higher body weight was related with better overall survival in the Xofigo arm but not in the placebo control arm. Patients whose body weight ≤ 73 kg did not have improved OS from the Xofigo treatment compared to the control arm. The incidence of Grade 3 or worse (Grade 3+) adverse events (AEs) is similar across body weight range, with slightly lower incidence of Grade 3+ AEs in Xofigo arm. Furthermore, a trend was observed for ideal body weight (IBW)-normalized dose: the larger the IBW-normalized dose, the lower OS hazard ratio.

Furthermore, Xofigo has a favorable safety profile, and no maximum tolerated dose (MTD) was determined at a cumulative dose up to 250 kBq/kg. Therefore, a dose higher than 50 kBq/kg may improve the OS in the subpopulation especially with body weight lower than 73 kg (25% of the overall population), or even in the overall patient population. A post-marketing clinical trial will be recommended to evaluate the safety and efficacy of Xofigo at a higher dose.

Based on subgroup analyses of the trial BC1-06, no dose adjustment is needed for patients with mild hepatic impairment, or patients with mild/moderate renal impairment. No dose adjustments can be recommended for patients with moderate/severe hepatic impairment, or severe renal impairment due to limited data available. Furthermore, subgroup analyses suggested that the concurrent use of calcium channel blockers or bisphosphonates did not affect the OS and safety in the trial BC1-06. No large changes in mean QTc intervals (i.e., > 20 ms) were detected at up to 4 hours post-injection at the proposed dose.

1.1 RECOMMENDATIONS

This NDA is approvable from the clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the post-marketing commitment and labeling language.

1.2 POST-MARKETING COMMITMENTS

(The following post-marketing trial is under negotiation. The final post-marketing commitment will be documented in an review addendum once the mutual agreement is reached between the Agency and the Applicant.)

1. Conduct a randomized 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.

(b) (4)

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1.3   SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Xofigo (radium-223 dichloride) is an alpha particle-emitting radioactive therapeutic agent. The applicant seeks the approval of Xofigo for the treatment of castration-resistant prostate cancer (CRPC) with bone metastases. The proposed dosing regimen is 50 kBq (1.35 µCi) per kg total body weight, given at 4-week intervals for 6 intravenous injections. The efficacy and safety of treatment beyond 6 injections have not been studied.

Randomized Phase 3 trial BC1-06 (ALSYMPCA) in CRPC patients with bone metastases demonstrated a significantly improved overall survival (OS) in the Xofigo arm (median: 14.9 months) compared to the placebo control arm (median:11.3 months), with a hazard ratio of 0.70 (95% CI: 0.58, 0.83). Most common adverse reactions (> 10%) of Xofigo treatment were diarrhea, nausea, vomiting, and thrombocytopenia.

Radium-223 is an isotope which decays and is not metabolized. Xofigo demonstrated linear pharmacokinetics in blood in terms of dose proportionality and time independence in a dose range of 46-250 kBq/kg body weight. After injection, radioactivity is rapidly cleared from blood, and is distributed to bone and intestine. The fraction of injected radioactivity remained in the body was 99 ±7% (range: 84-100%) 24 hours after injection. The fraction of the injected radioactivity remained in blood was 20 ± 8%, 4 ± 1%, and 0.4 ± 0.2%, respectively, at 15 minutes, 4 hours, and 72 hours post injection. At 10 minutes post injection, radioactivity was observed in bone and intestine. The fraction of the injected radioactivity in bone and intestine was 61 ± 10% and 49 ±16%, respectively, at 4 hours post injection. Approximately 63% of the injected radioactivity was excreted from the body within 7 days post injection. Fecal excretion is the major route of elimination from the body. Cumulative fecal and urinary excretion within 48 hours post injection was 13 ± 12% (range 0-34%) and 2 ± 2% (range 1- 5%), respectively. The rate of elimination of radium-223 dichloride from the gastrointestinal tract is influenced by the high variability in intestinal transit rates across the population.

Dosimetry data suggested that bone, red marrow, and lower large intestine wall received the highest absorbed radiation doses, corresponding to 1.15, 0.14, and 0.05 Gy/MBq (or 4262.6, 513.5, and 171.9 rads/mCi), respectively. The calculated absorbed radiation doses to other organs including liver, kidney and heart were low. There was no evidence of hepato-biliary excretion based on imaging data.

The impact of body weight on the clearance of radium-223 in blood is inconclusive due to limited data available. Furthermore, as radium-223 is rapidly cleared from the blood and distributed to bone and intestine, the pharmacokinetics in blood may not be an appropriate indicator for exposure-response analyses. Though the calculated radiation doses of Xofigo in bone were available in six CRPC patients with bone metastases, the sample size is too small to conclude the relationship between total dose and calculated radiation doses.

Exploratory analyses suggested that the proposed dosing regimen (50 kBq/kg body weight every 4 weeks for 6 injections) may not be optimal. Since no pharmacokinetic data were collected in the pivotal trial, relationship of total body weight (measure of total Xofigo dose) or ideal body weight (IBW) normalized dose with overall survival was explored. The separation of Kaplan-Meier OS curves stratified by body weight quartiles indicated that higher body weight was related with better overall survival in the Xofigo arm but not in the control arm, which suggested that the effect of body weight on OS in the Xofigo arm is drug related. This finding

was verified by conducting a multivariate Cox-proportional hazard analysis adjusting for confounding baseline risk factors which also indicated that higher body weight was related to better overall survival. Patients whose body weight ≤ 73 kg (approximately 25% of the overall population) did not have improved OS from the Xofigo treatment compared to the control arm. The incidence of Grade 3+ AEs was similar across body weight range, with slightly lower incidence in the Xofigo arm. Moreover, no maximum tolerated dose was determined in the Phase 1 dose escalation trial at a cumulative dose up to 250 kBq/kg body weight (either as a single dose of 250 kBq/kg, or divided into 125 kBq/kg for two injections with a 6-week interval, or 50 kBq/kg for five injections with 3-week intervals). Logistic regression analysis found that body weight has no significant impact on the incidence of thrombocytopenia. Furthermore, a trend was observed for ideal body weight (IBW)-normalized dose: the larger the IBW-normalized dose, the lower OS hazard ratio.

Given the above findings, a dose higher than 50 kBq/kg body weight may improve OS in the subpopulation with body weight ≤ 73 kg, or even in the overall patient population. Based on the relationship between IBW-normalized dose and OS, the applicant's proposed dose of 80 kBq/kg body weight for a post-marketing trial would result in lower OS hazard ratios for most patients, and therefore may be an appropriate dose for further evaluation. However, it is 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.

No dedicated organ dysfunction trials have been conducted. Based on the subgroup analyses of the clinical data of the pivotal trial, no dose adjustment is needed for mild hepatic impairment, mild or moderate renal impairment. No dose adjustments can be recommended for patients with moderate (N = 1) or severe (N = 0) hepatic impairment, or with severe renal impairment (N = 2) due to limited data available.

Subgroup analyses of the pivotal trial suggested that the concurrent use of calcium channel blockers or bisphosphonates did not affect the OS and safety (Grade 3+ AEs) of Xofigo. Subgroup analyses also suggested that constipation did not affect the OS in the pivotal trial. Compared to the incidences of Grade 3+ AEs observed in patients with and without constipation in the control arm (73.1% vs 67.8%), a larger difference in the incidences of Grade 3+ AEs was observed in patients with and without constipation in the Xofigo arm (75.4% vs 57.8%).

The effect of Ra-223 of a single dose of 50 kBq/kg body weight on QTc interval was evaluated in a subgroup of 29 patients (21 received Xofigo and 8 received placebo) in the randomized clinical trial BC1-06. No large changes in the mean QT interval (i.e., greater than 20 ms) were detected up to 4 hours post-dose. The potential for delayed effects on the QT interval after 4 hours was not evaluated.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Radium-223, is an isotope of element radium. Radium-223 chloride drug substance is presented as a solution of divalent cations ($^{223}Ra^{2+}$). The drug product, Xofigo, is supplied in single use vials containing 6 mL of solution (1000 kBq/mL, 27 µCi /mL at the reference date).

Radium-223 has a physical half-life of 11.43 days via six-stage-decay from Ra-223 to Pb-207 (Figure 1). The fractions of energy emitted from radium-223 and its daughters as alpha-particles, beta-particles, and gamma-radiation are 95.3 %, 3.6 %, and 1.1 %, respectively.

(b) (4)

Figure 1: Radium-223 decay chain with physical half-lives and mode of decay

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Indication: 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.

Mechanism of action: The active moiety of Xofigo is the alpha particle-emitting isotope radium-223 (as radium Ra 223 dichloride), which mimics calcium and forms complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases. The alpha particle range from radium Ra 223 dichloride is less than 100 micrometers (less than 10 cell diameters) which limits damage to the surrounding normal tissue.

2.1.3 What are the proposed dosage and route of administration?

The proposed dose regimen of Xofigo is 50 kBq (1.35 µCi) per kg body weight, given at 4 week intervals for 6 intravenous injection (generally up to 1 minute). The dose of Xofigo in mass is 1.86 ng of radium-223 dichloride per a 70 kg male patients.

Xofigo is supplied in single use vials containing 6 mL of solution (1000 kBq/mL, 27 µCi/mL) at the reference date. The volume to be administered to a given patient should be calculated using the following procedure equation:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (50 kBq/kg body weight)}}{\text{DK factor} \times 1000\ \text{kBq/mL}}$$

where DK factor is the decay correction (DK) factor to correct for physical decay of radium-223. A table of DK factors is provided for each vial, based on the following formula for DK factor calculation:

$$DK = e^{\left(\frac{-\ln 2 \cdot d}{11.43}\right)}$$

where d is the number of days from reference date to the application date.

Xofigo should be received, used and administered only by authorized persons in designated clinical settings. Xofigo should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support the approval of Xofigo, the results of seven clinical trials including one randomized pivotal Phase 3 trial (BC1-06, ALSYMPCA), three randomized Phase 2 trials (BC1-02, BC1-03, BC1-04), and three Phase 1 trials (ATI-BC1, BC1-05, BC1-08) were submitted in this original NDA submission (Table 1).

The pivotal Phase 3 trial BC1-06 evaluated the proposed dosing regimen (50 kBq/kg body weight every four weeks for 6 injections) in CRPC patients with bone metastases. A total of 921 patients were randomized to receive either Xofigo (n=614) or Placebo (n=307). Both arm received best standard of care (BSoC) including local external beam radiotherapy, corticosteroids, anti-androgens, estrogens, estramustine and ketoconazole. Xofigo arm demonstrated a significantly improved OS (median:14.9 months) compared to the placebo arm (median:11.3 months), with a hazard ratio of 0.70 (95% CI: 0.58, 0.83). Most common adverse reactions (> 10%) in the Xofigo arm were diarrhea, nausea, vomiting, and thrombocytopenia.

Phase 1 trial ATI-BC1 evaluated the safety and tolerability of escalating doses of Xofigo in 31 patients with skeletal metastases from breast or prostate cancer. Single dose of Xofigo was tested in cohorts of 5 patients at dose levels of 46, 93, 163, 213 and 250 kBq/kg BW. Subsequently, multiple doses were tested at different schedule: 5 injections of 50 kBq/kg BW at 3-weeks intervals (n=3) or 2 injections of 125 kBq/kg BW at 6-weeks intervals (n=3). No dose

limiting toxicity (DLT) was observed up to 250 kBq/kg following single or divided doses. No maximum tolerated dose (MTD) was identified.

Randomized Phase 2 trial BC1-02 evaluated a dose of 50 kBq/kg BW every 4 weeks for 4 injections. This trial showed favorable reduction of bone alkaline phosphatase (ALP), skeletal-related events (SREs), and survival for patients treated with Xofigo compared to placebo.

Randomized Phase 2 trial BC1-04 evaluated the dose responses at dose levels of 25, 50 and 80 kBq/kg at 6-weeks intervals for three injections. Confirmed prostate specific antigen (PSA) response rates, the primary efficacy endpoint defined as a confirmed decrease of PSA from baseline of at least 50 %, were 0 %, 5.6 % and 12.8 % in 25, 50, and 80 kBq/kg dose groups, respectively. The median time to death was 548, 569 and 604 days, in the 25, 50, and 80 kBq/kg dose groups, respectively. Nonetheless, the dose of 50 kBq/kg instead of 80 kBq/kg was selected for further studies based on the similar improvement from baseline of biomarkers ALP and PSA (see Section 2.1.2).

Phase 2 trial BC1-03, evaluated the effect of a single dose of radium-223 dichloride at 5, 25, 50 and 100 kBq/kg body weight on pain relief. The best pain response was observed in the highest dose group (100 kBq/kg body weight) up to 8 weeks after an radium-223 dichloride injection.

Clinical pharmacology data were collected from three Phase 1 trials BC1-05, BC1-08, and ATI-BC1. Pharmacokinetics, biodistribution and dosimetry data were mainly obtained from 6 patients receiving two injections of 100 kBq/kg six weeks apart (Trial BC1-05) and in 10 patients receiving a single dose of 50, 100 or 200 kBq/kg (Trial BC1-8). The pharmacokinetic data from trial ATI-BC1 (N=24) was used for the dose proportionality evaluation only, as no standard sample with a National Institute of Standards and Technology (NIST) traceable radium-223 reference material was used to convert counts to radioactivity of radium-223. In trial BC1-05, the uptake of radioactivity in bone was obtained from planar whole body gamma camera scans at 4, 24, 48, 96, and 144 hours. However, uptake of radioactivity in bone was not available in trial BC1-08, as the single planar whole-body gamma camera scan at 24 hours post injection was insufficient to obtain valid data on the absorbed radiation dose in bone.

The effect on QT prolongation was evaluated in a sub-study of the Phase 3 trial BC1-06. A total of 29 patients participated in the sub study, 21 received radium-223 dichloride and 8 received placebo. The applicant concluded that there was no evidence that intravenous injection of radium-223 dichloride at a dose of 50 kBq/kg significantly prolongs the QTc interval.

Table 1. Clinical trials with Xofigo submitted in NDA 203971

Phase 1	Phase 2	Phase 3
ATI BC1 (n = 31) — *Safety and tolerability, preliminary efficacy and PK* — Prostate or breast cancer — Dose escalation — Single and multiple doses: 46 to 250 kBq/kg BW	**BC1-02** (n = 64) — *Efficacy and safety* — CRPC with painful skeletal metastases referred for palliative EBRT — Placebo-controlled, randomized, double blind — Multiple doses: 4 × 50 kBq/kg BW at 4-week intervals	**BC1-06** ALSYMPCA (n = 921) — *Efficacy and safety (pivotal study)* — CRPC with symptomatic skeletal metastases — Placebo-controlled, randomized, double blind — Multiple doses: 6 × 50 kBq/kg BW at 4-week intervals
BC1-05 (Europe) (n = 6) — *Biodistribution, PK, dosimetry* — Asymptomatic or symptomatic CRPC — Multiple doses: 2 × 100 kBq/kg BW at 6-week intervals	**BC1-04** (n = 122) — *Efficacy and safety* — Asymptomatic or symptomatic CRPC — Randomized, double blind — Multiple doses: 3 × 25, 50 or 80 kBq/kg BW at 6-week intervals	
BC1-08 (USA) (n = 10) — *Biodistribution, PK, dosimetry* — CRPC with skeletal metastases — Single doses: 50, 100, 200 kBq/kg BW	**BC1-03** (n = 100) — *Efficacy and safety* — CRPC with painful skeletal metastases — Randomized, double blind — Single doses: 5, 25, 50, 100 kBq/kg BW	

Source: Table 1-1 of NDA 203971 Submission Clinical Overview

2.2.2 What is the basis of the dose selection?

The proposed dosing regimen (i.e., intravenous injections of 50 kBq/kg BW each every 4 weeks for a total of 6 injections, was the same as tested in the pivotal Phase 3 trial. This dosing regimen was selected based on Phase 1 dose escalation trial ATI-BC1, Phase 2 trials BC1-02 and BC1-04.

In brief, Phase 1 trial ATI-BC1 established that the drug could be administered safely at a cumulative dose up to 250 kBq/kg body weight (as single dose, or as 5 doses of 50 kBq/Kg at 3-week intervals, or as 2 doses of 125 kBq/kg with a 6 week interval). No dose limiting toxicities (DLTs) were recorded. No MTD was determined. Based on the nadir count of neutropenia (15-20 days and recovery of 1 to 2 weeks) at the lowest dose of 50 kBq/kg, the schedule was extended to 4 weeks in subsequent studies.

A regimen of 50 kBq/kg was then tested at 4-week intervals for a total of 4 doses in Phase 2 trial BC1-02. Results showed that the regimen was efficacious, with improvement in bone-ALP, SREs, and overall survival.

Randomized Phase 2 trial BC1-04 evaluated the dose responses at dose levels of 25, 50 and 80 kBq/kg at 6-weeks intervals for three injections. The applicant concluded that 50 kBq/kg was an optimal dose for further evaluation, as PSA or bone-ALP improvement from baseline was similar between dose levels of 50 and 80 kBq/kg, and was better than dose level of 25 kBq/kg, as below:
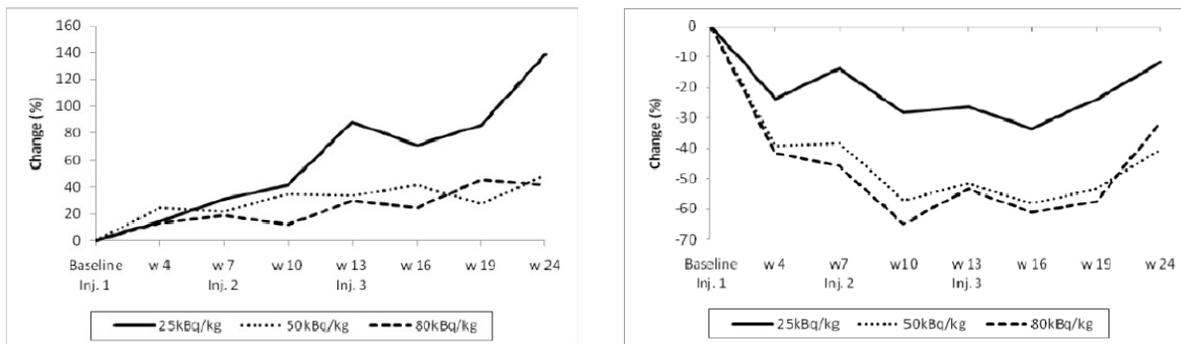
Figure 2: Median relative change from baseline in prostate-specific antigen (PSA) (left) and bone alkaline phosphatase (bone-ALP) (right) for dose groups of 25, 50, and 80 kBq/kg each every three weeks for a total of three injections

The proposed dosing regimen of 50 kBq/kg every 4 weeks for 6 injections may not be optimal, though it demonstrated favorable efficacy and safety profiles compared to the control arm in the pivotal trial BC1-06. Higher dose may further improve the OS benefit in the subpopualtion with low body weight or even in the overall patient population with acceptable safety profiles, based on the following findings:

- Exploratory analysis of pivotal trial BC1-06 indicated that the higher body weight (i.e., higher total dose) or higher IBW-normalized dose is related with better OS improvement but no changes in Grade 3 or worse adverse events (See Section 2.2.5). There was no evident relationship between body weight of patients and OS in the control arm.

- No dose-dependent adverse events were observed in Phase 1 and Phase 2 trials. Particularly, MTD was not determined at a cumulative dose up to 250 kBq/kg in Phase 1 trial ATI-BC1.

- The selection of a dose of 50 kBq/kg based on the changes from baseline of biomarkers (bone-ALP, PSA) shown in Figure 2 was questionable, as relationship between these tumor biomarkers and OS benefit is not known. In fact, dose level of 80 kBq/kg demonstrated best confirmed PSA response rate (the primary efficacy endpoint) and longer survival among the three dose groups: confirmed PSA response rates were 0 %, 5.6 % and 12.8 %, and the median time to death were 548, 569 and 604 days at dose levels of 25, 50 and 80 kBq/kg, respectively. Furthermore, Phase 2 trial BC1-03 demonstrated a dose-related effect on pain relief, with the best pain response observed in the highest dose group (100 kBq/kg body weight) up to 8 weeks after an radium-223 dichloride injection.

Therefore, a dose level higher than 50 kBq/kg is worth further evaluation. Based on the relationship between overall survival hazard ratio and IBW-normalized dose, 80 kBq/kg is an

appropriate dose to be further evaluated in a post-marketing trial (see Section 2.2.5).

The efficacy and safety of treatment with more than 6 injections have not been studied. Whether more than 6 injections of 50 kBq/kg every 4 weeks provides further improvement in overall survival is unknown.

2.2.3 What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of efficacy and safety?

The primary efficacy endpoint of the pivotal Phase 3 trial BC1-06 was overall survival (OS). As OS is an unambiguous endpoint, improvement in OS is generally considered as the gold standard for drug approval in oncology. OS was defined as the time interval from the date of randomization to the date of death due to any cause.

In the pivotal Phase 3 trial BC1-06, CRPC patients with bone metastases were randomized in a 2:1 ratio to receive either Xofigo (n=614) or placebo (n=307). The Xofigo arm demonstrated a significantly improved OS (median: 14.9 months) compared to the placebo arm (median:11.3 months), with a hazard ratio of 0.70 (95% CI: 0.58, 0.83). Most common adverse reactions (> 10%) in the Xofigo arm were diarrhea, nausea, vomiting, and thrombocytopenia.

2.2.4 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

As the antitumor effect of Xofigo resides in the radioactivity from the alpha particle emitting nuclide radium-223 and its daughters (Figure 1), rather than the mass of the radium-223 (1.86 ng for a 70 kg patient at a dose of 50 kBq/kg body weight), the measurement of total radioactivity in blood or plasma for pharmacokinetics is appropriate. However, it was noted that the radioactivity-time profiles in blood or plasma may be inadequate to evaluate the exposure-response relationship, as the radioactivity was cleared rapidly from the blood and distributed to bone, red marrow, and intestine (See Section 2.2.6). Therefore, the radioactivity in bone would be a more appropriate surrogate marker for exposure-response analysis. Unfortunately, such data were only available in six patients in Phase 2 BC1-05, which were too limited to draw any conclusion due to large variability.

See Section 2.6.

2.2.5 Exposure-response

As no pharmacokinetics or dosimetry data were collected from subjects in the pivotal Phase 3 trial, the efforts to establish traditional exposure-response relationships were precluded. However, the body weight based dosing regimen allows for an alternative approach to evaluate the relationship between dose and responses. Exploratory analyses were conducted to evaluate the impact of body weight and IBW-normalized dose on the efficacy and safety of Xofigo in the pivotal trial BC1-06.

2.2.5.1 Is there an evidence to indicate that higher body weight (i.e., higher total dose) related to better overall survival?

Yes. The separation of Kaplan-Meier curves of OS stratified by body weight quartiles (i.e., higher body weight is related with better overall survival) in the Xofigo arm (Figure 3 left) but not in the control arm (Figure 3, right) suggested that the effect of body weight on OS in the Xofigo arm is drug related. Furthermore, Figure 4 indicated that patients with lowest quartile of body weight (≤ 73 kg) did not have improved OS from the Xofigo treatment compared to the control arm.

Kaplan-Meier survival analyses for OS were performed using data of the pivotal Phase 3 trial BC1-06. A total of 921 patients (614 and 307 in Xofigo arm and Control arm, respectively) were grouped by quartiles of body weight (≤ 73, 73–82, 82–91 and > 91 kg). The Kaplan-Meier curves by body weight quartiles separated in Xofigo arm, with better OS for the higher body weight (Figure 3, left). The separation of Kaplan-Meier curves by body weight quartiles was not observed in the Control arm.
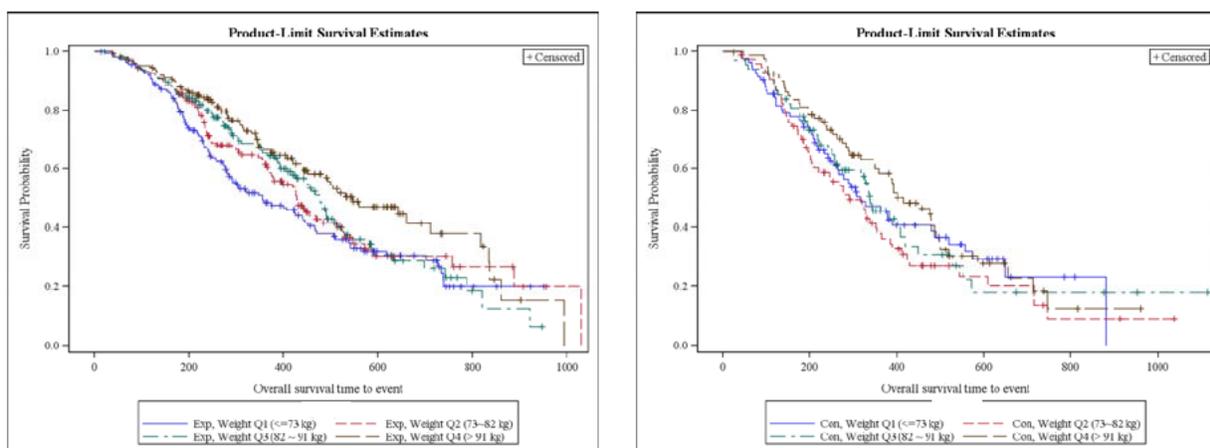
Figure 3: Kaplan-Meier curve of overall survival (OS) for the Xofigo arm (N=614) (left) and for the control arm (N=307) (right) by body weight quartiles ($\leq$73, 73–82, 82–91 and > 91 kg) of the randomized Phase 3 trial BC1-06.

Figure 4 showed the Kaplan-Meier curves of the Xofigo arm and the Control arm for each of the body weight quartiles. Hazard ratio (HR) compared to the control arm 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 total ALP $\geq$ 220 U/L), current use of bisphosphonates use (yes versus no), prior use of docetaxel (yes versus no), and baseline ECOG

≥ 2 (yes versus no).

Q1: HR = 0.94 (0.65, 1.34)   Q2: HR = 0.58 (0.40, 0.82)

Q3: HR = 0.70 (0.47, 1.04)   Q4: HR = 0.59 (0.40, 0.88)
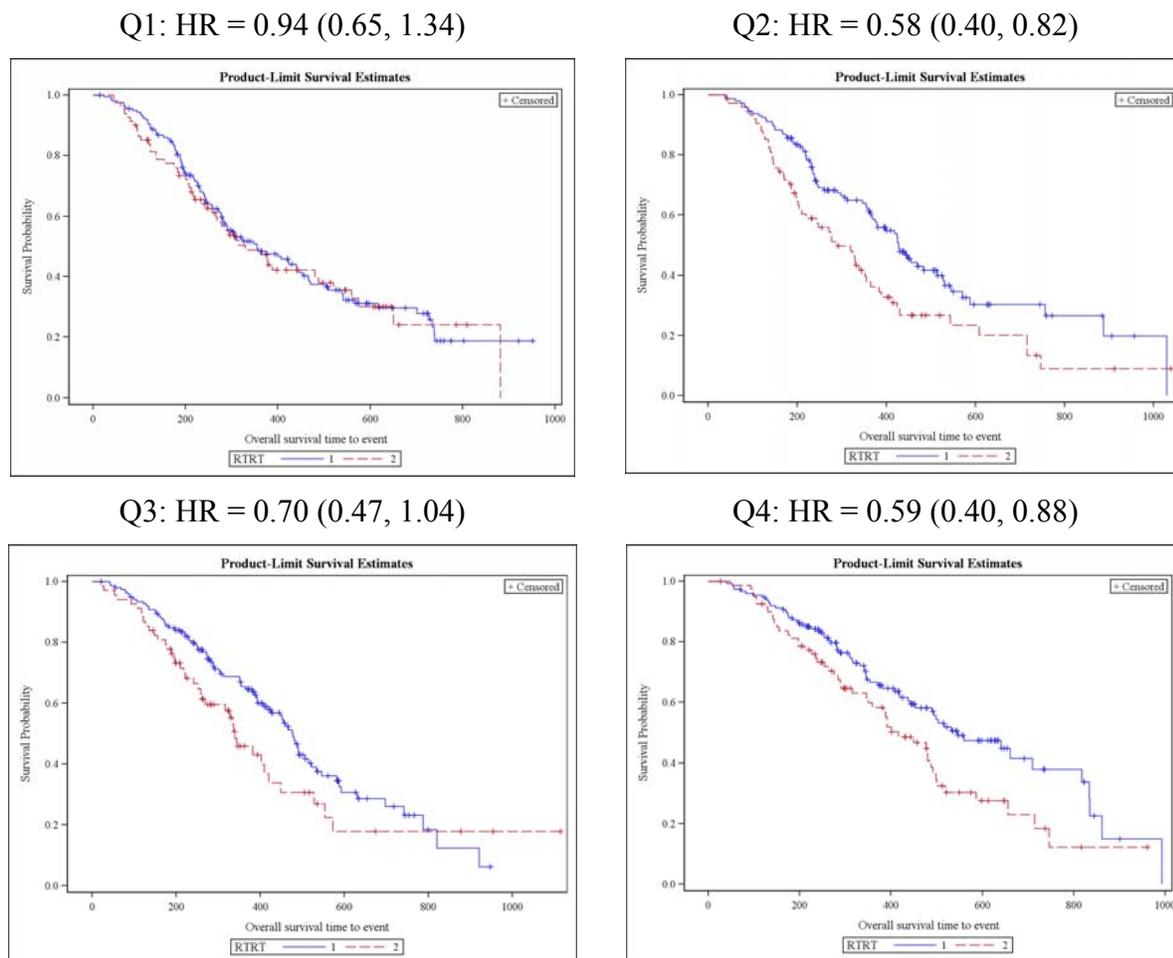
Figure 4: Kaplan-Meier curve of overall survival (OS) stratified by body weight quartiles: Q1 (≤ 73 kg) (top left), Q2 (73–82 kg) (top right), Q3 (82–91 kg) (bottom left), and Q4 (> 91 kg) (bottom right). The Kaplan-Meier curves for Xofigo and Control arms are represented in blue and red, respectively. Hazard ratio (HR) vs. the control arm 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 total ALP ≥ 220 U/L), current use of bisphosphonates use (yes versus no), prior use of docetaxel (yes versus no), and baseline ECOG ≥ 2 (yes versus no). Blue line represents the Xofigo arm, and red line represents the Control arm.

The baseline covariates of patients were summarized in Table 2. Among four quartiles of body weight, quartile 1 appeared to have lowest percentage of subjects received concurrent bisphosphonate, highest percentage patients with an ECOG >1, lowest percentage of Caucasians. Furthermore, the percentage of subjects with baseline total ALP < 220 U/L was lower in Xofigo treatment arm compared to Control arm (Table 2) in Quartile 1. The combination of the imbalance of these covariates may, along with low Xofigo dose, account for the lack of OS improvement in the first quartile of body weight.

Table 2. Summary of covariates per body weight quartiles in the pivotal trial BC1-06

Covariates	Overall Xofigo (N=614)	Overall Control (N=307)	BW Q1 (≤ 73 kg) Xofigo (N=160)	BW Q1 Control (N=81)	BW Q2 (>73 ≤ 82 kg) Xofigo (N=146)	BW Q2 Control (N=75)	BW Q3 (>82 ≤ 91 kg) Xofigo (N=154)	BW Q3 Control (N=68)	BW Q4 (> 91 kg) Xofigo (N=150)	BW Q4 Control (N=81)
Concurrent bisphosphonate use (%)	40.7	40.4	34.4	30 9	40.4	38.7	42.21	47.1	45.33	44.4
Total ALP < 220 U/L at screening (%)	56.7	55.1	46.9	56 8	58.2	52.0	60.4	55 9	62 0	54.3
Prior use of docetaxel (%)	57 3	56.7	53.1	48 2	52.7	52.7	62 3	62 3	60.7	60.7
Base line ECOG >1 (%)	12 5	13.4	16.9	18 5	13.7	13.3	5 84	10 3	13 3	9.88
Race (Caucasian %)	93.7	94 5	85.0	86.4	95.9	94.7	96 8	98 5	97 3	98.8
WHO Pain Score=3 (%)	31 6	29 3	31.9	30 9	29.5	26.7	33 8	32.4	31 3	28.4
External beam therapy within 12 weeks (%)	16.1	15 6	18.1	24.7	14.4	17.3	14 9	13 2	17 3	7.41
Age (year): [Mean (Range)]	70 (49, 90)	71 (44, 94)	72 (53, 87)	74 (57, 94)	72 (49, 90)	72 (52, 84)	69 (51, 88)	69 (55, 85)	67 (49, 83)	72 (53, 87)
Height (cm) [Mean (Range)]	174 (151, 195)	173 (124, 196)	170 (151, 189)	168 (149, 184)	173 (160, 190)	173 (157, 184)	175 (160, 193)	174 (124, 192)	178 (156, 195)	170 (151, 189)
Body Mass Index [Mean (Range)]	27.4 (16 6, 40 6)	27.6 (16.5, 59.1)	23 (16.6, 30.7)	23 (16 5, 30 6)	26.2 (21.6, 30.9)	26.3 (22.9, 32.5)	28 3 (23.1, 33.1)	28.7 (23 6, 59.1)	32 5 (24.7, 40 6)	32.2 (24.7, 40.4)
Ideal Body Weight [Mean (Range)]	69.4 (48.7, 88 6)	69.1 (24 3, 89.5)	65.6 (48.7, 83.1)	64 6 (46 9, 78 6)	68.7 (56.9, 84.0)	68.3 (54.2, 78.6)	70 9 (56 9, 86 8)	69 9 (24 2, 85 9)	72 9 (53 3, 88 6)	73.4 (56.0, 89.5)
Baseline hepatic function per NCI-ODWG criteria										
Normal function	78 0	74 9	71.9	79 0	77.4	70.7	81 8	69.1	82 0	79.0
Mild hepatic impairment	21 8	24.4	28.1	19 8	22.6	28.0	18 2	30 8	17 3	21.0
Moderate hepatic impairment	0.16	0.33	0	0	0	1.33	0	0	0 67	0
Baseline renal function										
Normal function (Clcr > 90 mL/min) (%)	61.7	57 0	43.1	35 8	51.4	50.7	72.1	66 2	82.7	77.8
Mild impairment (30 < Clcr ≤ 60 mL/min) (%)	26.4	28.7	35.0	30 9	34.9	34.7	20 8	30 9	15 3	19.8
Moderate impairment (60 < Clcr ≤ 90 mL/min) (%)	10 9	13.7	20.6	33 3	13.7	14.7	7.14	2 94	2 00	4.76
Severe impairment (Clcr ≤ 30 mL/min) (%)	0 33	0	1 25	0	0	0	0	0	0	0

2.2.5.2 Is higher body weight (i.e., higher total dose) related to worse safety profiles?

No, there is no evident relationship between body weight and safety. In the pivotal Phase 3 trial BC1-06, the incidence of Grade 3 or worse (Grade 3+) adverse events (AEs) in the Xofigo arm is similar across the body weight range, and slightly lower than that in the control arm (Figure 5). In addition, logistic regression analysis found that body weight has no significant impact on the incidence of thrombocytopenia.
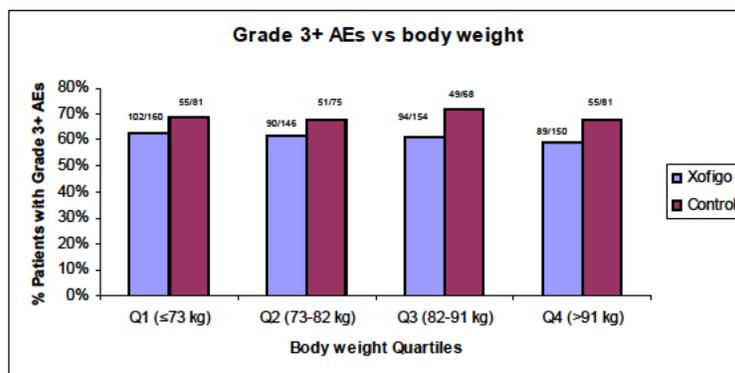
Figure 5: The effect of baseline body weight divided by quartiles (≤ 73, 73–82, 82–91 and > 91 kg) on the incidence of Grade 3 or worse (Grade 3+) adverse events (AEs) in the Xofigo and Control arms in the pivotal trial BC1-06. The numbers on the top of each bar represents the number of patients with Grade 3+ AE out of the total number patients in each quartile of body weight.
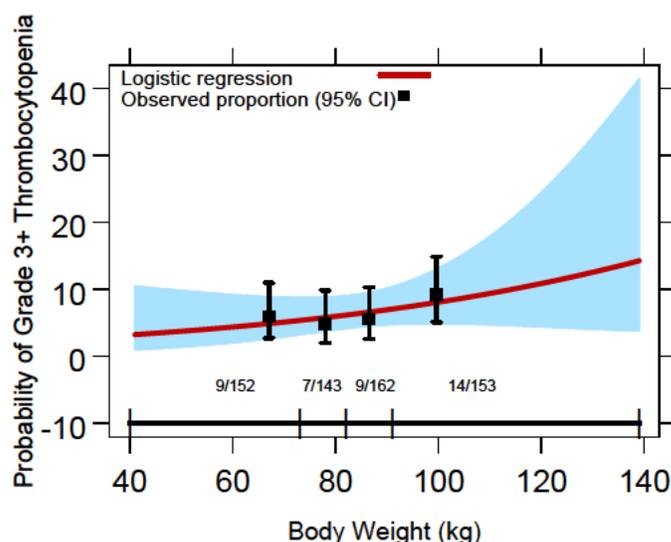
Figure 6: The relationship between body weight and the incidence of Grade 3+ thrombocytopenia using logistic regression model. Solid black symbols represent the observed proportion of patients experiencing Grade 3+ in each quartile of body weight ($\leq$ 73, 73–82, 82–91 and > 91 kg). The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represent the predicted mean and 95% confidence interval for the probability of Grade 3+ thrombocytopenia. The body weight range in each quartile is denoted by the horizontal black line along with the number of patients with Grade 3+ thrombocytopenia/total number of patients in each quartile.

2.2.5.3 Is higher ideal body weight (IBW) normalized dose related to better overall survival? Is the applicant's proposed dose of 80 kBq/kg total body weight acceptable for further evaluation in a post-marketing trial?

Yes. Exploratory analysis indicated that higher IBW-normalized dose is related with better overall survival. A dose of 80 kBq/kg body weight proposed by the applicant is acceptable for further evaluation in a post-marketing trial.

IBW-normalized dose vs. overall survival

As radium-223 does not have significant distribution into adipose tissue, patients with a larger TBW/IBW ratio (or larger relative weight difference defined as (TBW-IBW)/IBW*100%) may have a higher drug exposure in bone, and therefore a better efficacy response. Exploratory analyses were conducted to evaluate the relationship between relative weight difference and OS, or between IBW-normalized dose [using equation (TBW $\times$ 50 kBq/kg)/IBW] and overall survival (OS). Based on the findings, the potential effect of a dose of 80 kBq/kg per TBW on the overall survival was evaluated.

Methods:

Hazard ratio (HR) and 95% CI vs. the control arm for each of 10 quantiles of relative weight difference (or 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), prior use of docetaxel (yes versus no). The OS hazard ratio vs relative weight difference (or IBW-normalized dose) graph was plotted using smooth.spline function in R package based on the point estimate of HR (solid line) or 95% CIs (dashed lines) in order to see the overall trend. Three dotted vertical lines separate space for quartiles of relative weight difference (or IBW-normalized Xofigo dose). Each of the black tick above the x-axis represents a patient's relative weight difference or IBW-normalized Xofigo dose. Similar analysis was also conducted for the body weight (i.e., total dose of Xofigo) for comparison.

Results:

Figure 7 demonstrated the relationship between the relative weight difference (or IBW-normalized Xofigo dose) on the overall survival hazard ratio in the pivotal trial BC1-06. Compared to total body weight, a more clear trend was observed: the larger the relative weight difference (or higher IBW-normalized dose), the lower hazard ratio. There was no such clear trend observed for TBW, even though the plot of the OS hazard ratio for TBW is consistent with our previous analysis by dividing total body weight into quartiles in Section 2.2.5.1.
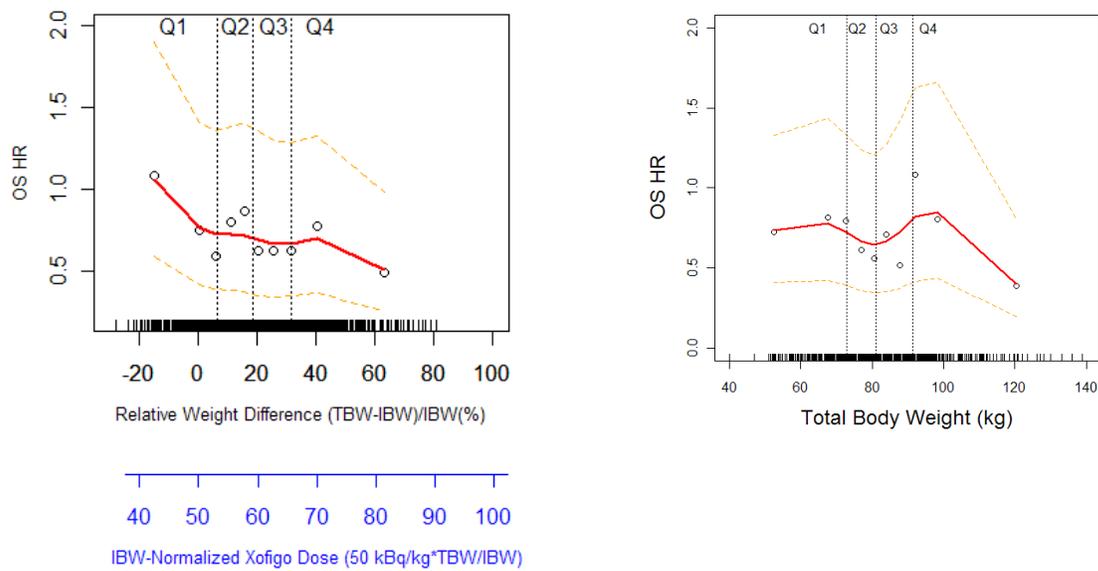
Figure 7: Left figure shows overall survival (OS) hazard ratios at different relative weight difference (%) (upper x-axis) or ideal body weight (IBW) normalized Xofigo dose (lower x-axis) in the pivotal trial BC1-06. Right figure shows OS hazard ratios at different total body weight (TBW). Relative weight difference was defined as [total body weight (TBW) – IBW]/IBW*100%. The IBW-normalized Xofigo dose was calculated for each patient using equation (TBW × 50 kBq/kg)/IBW. Hazard ratio (HR) vs. the control arm for each of 10 quantiles of relative weight difference (or 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). Scatter circles are the point estimates of hazard ratio for each of 10 quantiles. The solid red line was the smoothed trend line based on the point estimates (smooth factor=0.45) to illustrate the trend. Dashed orange lines was the smoothed 95% confidence interval trend line. Three dotted vertical lines separate space for quartiles of relative weight difference (or IBW-normalized Xofigo dose). Each of the black tick above the upper x-axis represents a patient's relative weight difference (or IBW-normalized Xofigo dose). Right figure for OS hazard ratio at different TBW used the same setting for hazard ratio estimation and graph plotting.

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

Per FDA's recommendation, the Applicant proposed a dose of 80 kBq/kg to be evaluated in a post-marketing trial in CRPC patients with bone metastases. The acceptability of this dose was evaluated using the relationship between IBW-normalized dose and overall survival hazard ratio in the pivotal trial.

Figure 8 demonstrated that the applicant's proposed dose of 80 kBq/kg TBW would 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.
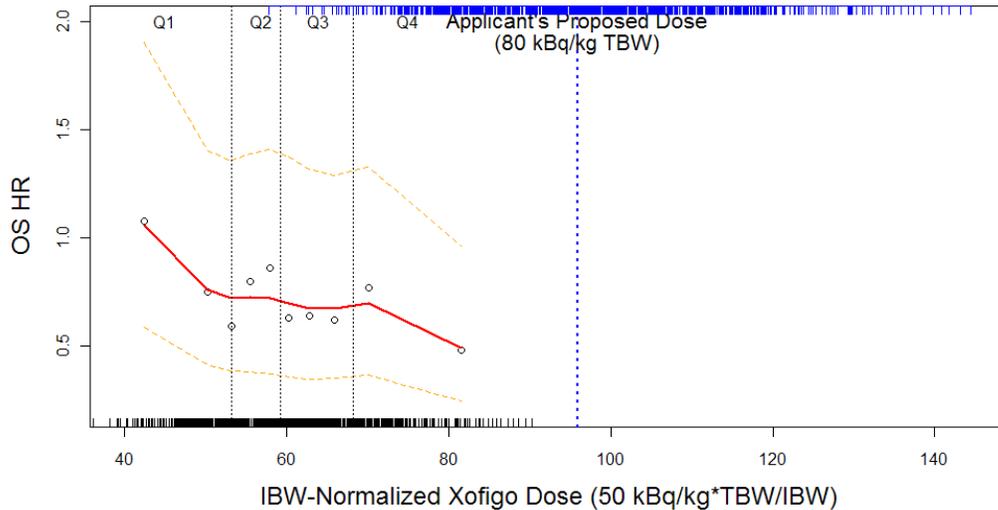
Figure 8: Overall survival (OS) hazard ratio at different ideal body weight (IBW) normalized Xofigo dose in the pivotal trial BC1-06. The IBW-normalized Xofigo dose was calculated for each patient using equation (TBW × 50 kBq/kg)/IBW. Hazard ratio (HR) vs. the control arm for each of 10 quantiles of IBW-normalized dose was estimated using a Cox proportional hazards model stratified by the following baseline covariates: total ALP (< 220 U/L versus total ALP ≥ 220 U/L), concurrent use of bisphosphonates use (yes versus no) and prior use of docetaxel (yes versus no). Scatter circles are the point estimate of hazard ratio for each of 10 quantiles. The solid red line was the smoothed line (smooth factor=0.45) based on the point estimate of hazard ratio to illustrate the trend. Dashed orange lines were the smoothed 95% confidence interval trend lines. Three dotted vertical lines separate space for 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 a ratio of 1.2 for TBW/IBW that was observed in the pivotal 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.

2.2.5.4 Does Xofigo prolong the QT or QTc interval?

The effect of Ra-223 on QTc interval was evaluated in a subgroup of 29 patients (21 received Xofigo and 8 received placebo) in the randomized clinical trial.

QT IRT review recommendations:

The QT Interdisciplinary Review Team (QT-IRT) concluded " ... the current QT study is inconclusive in its objective to adequately characterize the Xofigo's liability to prolong the QT interval. We note the following limitations in the trial design:

d. ECGs were only collected up to 4-6 hours post-dose. The sampling time points were inadequate to cover the potential delayed effect over the dosing interval (i.e., 24 hours)

e. No time-matched PK samples were obtained."

IRT-QTc team recommended the following that

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

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

Please see IRT-QTc review by Dr. Justin Earp (dated March 14, 2013 in DARRTs) for more information.

Clinical/Clinical Pharmacology Review Recommendations:

Clinical Pharmacology review team agrees that the trial design of the QT substudy has technical limitations. As a higher dose (i.e., 80 kBq/kg) will be requested to be evaluated in a post-marketing trial, QT IRT recommendations will be conveyed as comments to the applicant for QTc evaluation at 80 kBq/kg. At this time, however, the Clinical Pharmacology review team and the Clinical review team concluded that no further post-marketing QTc study is needed at a Xofigo dose of 50 kBq/kg, based on the following rationales:

1. As noted in the QT IRT review, "... there were no AEs of concern in the clinical program and we did not observe any large effects on the QTc interval in the current study.'

2. The fraction of radioactivity in blood or plasma after 4 hours post injection is low. After intravenous injection, radium-223 is rapidly cleared from blood and is distributed primarily into bone, or is excreted into intestine. Fifteen minutes post injection, about 20% of the injected radioactivity remained in blood. At 4 hours, about 4% of the injected radioactivity remained in blood, decreasing to less than 1% at 24 hours post injection.

3. Dosimetry data suggested low uptake in heart.

4. The dose of radium-223 in mass is low, which is 1.86 ng for a 70 kg patients with a single Xofigo dose of 50 kBq/kg.

The following labeling language is proposed and concurred by clinical team, clinical pharmacology team, and QT IRT:

"The effect of a single dose of 50 kBq/kg of Ra-223 on QTc interval was evaluated in a subgroup of 29 patients (21 received Xofigo and 8 received placebo) in the randomized clinical trial. No large changes in the mean QT interval (i.e., greater than 20 ms) were detected up to (b)(4) hours post dose. The potential for delayed effects on the QT interval after (b)(4) hours was not evaluated."

2.2.5.5 Is the proposed dosing regimen acceptable? Are there any unresolved dosing or administration issues?

The proposed dosing regimen (50 kBq/kg body weight, every 4 weeks for 6 injections) is acceptable from a clinical pharmacology perspective, as this dosing regimen has demonstrated favorable benefit in terms of OS with acceptable safety profile in the pivotal trial BC1-06. However, approximately 25% of patients population did not have OS benefit from the proposed dosing regimen of Xofigo compared to the control arm, possibly due to lower dose (i.e., lower body weight) and/or poorer prognostic factors. A higher dose (> 50 kBq/kg) may improve OS in this subpopulation or even in overall patient population.

Based on the relationship between overall hazard ratio and total dose or IBW-normalized dose in the pivotal trial, IBW appears a better body size descriptor for dosing than total body weight. However, a dose of 80 kBq/kg per total body weight (proposed by the applicant for further evaluation) still appears reasonable for further evaluation, as this dose based on total body weight will likely result in lower hazard ratio (higher OS benefit) for most patients. Therefore, a post-marketing clinical trial will be recommended to evaluate the efficacy and safety of a dose of 80 kBq/kg in CRPC patients with bone metastases. 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. We recommend that the applicant continues to conduct analyses to evaluate the impact of various body size descriptor (e.g., IBW, or TBW/IBW) on the efficacy and safety of future trials, especially in the post-marketing dose optimization trial(s).

Please also see Sections 2.2.2 and 2.2.5.

2.2.6 Pharmacokinetic characteristics of Xofigo in humans

The following is a summary for the pharmacokinetics of Xofigo in patients with advanced cancers with bone metastases:

- After intravenous injection, radium-223 is rapidly cleared from blood and is distributed primarily into bone, or is excreted into the intestine.

- Fifteen minutes post injection, about 20% of the injected radioactivity remained in blood. At 4 hours, about 4% of the injected radioactivity remained in blood, decreasing to less than 1% at 24 hours post injection.

- At 10 minutes post injection, radioactivity was observed in bone and intestine. The level of radioactivity in bone was in a range of 44% to 77% at 4 hours post injection. No significant uptake was seen in other organs.

- Radium-223 is an isotope which decays and is not metabolized.

- Fecal excretion is the major route of elimination from the body. At 48 hours after injection, cumulative fecal and urinary excretion was 13% (range: 0-34%) and 2% (range: 1-5%), respectively. There was no evidence of hepato-biliary excretion.

- The whole body measurements at 7 days after injection (after correcting for decay) indicates that approximately 63% of the injected radioactivity was excreted from the body.

2.2.6.1 What are the pharmacokinetic parameters of radium-223 in humans?

Pharmacokinetics:

After intravenous injection, radium-223 was rapidly cleared from blood. The percentage of the injected radioactivity remained in blood was $20 \pm 8\%$ (range: 9 -33%) at 15 minutes following injection. At 4 hours, only $4 \pm 1\%$ (range: 2-6%) of the radioactivity remained in the blood, which decreased to $0.4 \pm 0.2\%$ (range: 0.2-0.7%) at 72 hours. The radioactivity-time profile can be described by a four-exponential decay function in plasma and blood (Table 3).
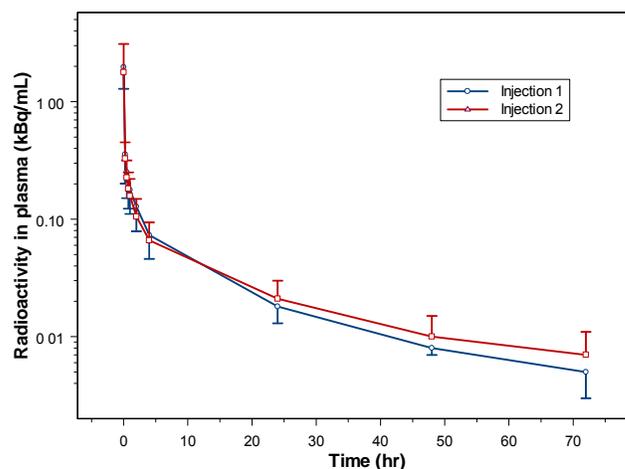
Figure 9: Plasma radioactivity-time profiles after the first and second injections of radium-223 dichloride at a 6-week interval in six subjects in Phase 1 trial BC1-05. The error bar represents standard deviation (SD).

Table 3. Pharmacokinetic parameters (mean ± SD) of radium-223 in blood and plasma of six patients in Phase 1 trial BC1-05

	Blood	Plasma
$AUC_{0-\infty}$ [kBq*h/mL]	1.51 ± 0.38	2.27 ± 0.66
CL [L/h]	6.1 ± 2.1	4.1 ± 1.5
V_c [L]	12.6 ± 8.2	8.1 ± 6.0
V_d [L]	273 ± 117	170 ± 69
$T_{1/2,1st}$ [h]*	ND	ND
$T_{1/2,2nd}$ [h]	0.16 ± 0.04	0.17 ± 0.01
$T_{1/2,3rd}$ [h]	2.0 ± 0.2	1.7 ± 0.1
$T_{1/2,4th}$ [h]	31.7 ± 7.7	28.9 ± 4.8

Source: Table 11-1 of the study report of BC1-05 submitted under NDA 203971

Note: Vc: central volume of distribution, Vd: apparent volume of distribution (calculated based on the 4th elimination phase); *$T_{1/2}$,1st is not determined (ND) due to limited number of sampling points within the initial distribution phase.

Radioactivity-time profiles in plasma and blood after multiple doses of Xofigo were only available in 6 male subjects following two injections of 100 kBq/kg at a 6-week interval in Phase 1 trial BC1-05. No apparent accumulation was observed, as the accumulation ratio of AUC between two injections was close to 1 (Table 4). Accumulation ratio for C_{max} was 1.5, possibly due to the high variability in the quick distribution of radium-223, difference in injection time (approximately 1 minute), or variability in times for sample collections.

Table 4. C_{max} and $AUC_{0-72hrs}$ in plasma measured by total radioactivity after the first and second injections of radium-223 dichloride in Phase 1 trial BC1-05

Subject	Cmax (kBq/mL)		$C_{max, \, Inj2/Inj1}$	AUC (kBq*hr/mL)		$AUC_{Inj2/Inj1}$
	Injection 1	Injection 2		Injection 1	Injection 2	
101	1.498	3.935	2.627	2.65	2.64	0.996
102	0.750	0.720	0.960	2.741	3.860	1.408
103	0.236	1.084	4.593	1.166	1.887	1.618
104	2.025	1.054	0.520	2.334	1.367	0.586
105	1.815	3.254	1.793	2.418	2.568	1.062
106	1.540	1.598	1.038	1.635	2.003	1.225
Geometric mean	1.070	1.601	1.496	2.068	2.266	1.096

Source: Modified from Table 3 of "Response to FDA Request for Information" submitted on February 01, 2013 under NDA 203971

Uptake and Excretion

After injection, the fraction of injected radioactivity remained in the body at 24 hours following injection was 99 ±7% (range: 84-100%). Radioactivity was rapidly distributed to bone. The radioactivity in bone at 4 hours was 61 ± 10% (range: 44-77%) of the injected radioactivity (Figure 10). The radioactivity passed to intestine was 49 ±16% (range: 19-69%) of the injected radioactivity at 4 hours post injection. Imaging data indicated that this fraction of radioactivity rapidly passes through small intestine wall and into the gut contents and then into the large intestine. In the majority of cases, the maximum radioactivity in the upper large intestine occurred at 24 hours and the maximum uptake in the lower large intestine occurs at 24–72 hours. No uptake of radioactivity was visible on scintillation camera images in normal organs such as the heart, liver, gallbladder, kidneys, urinary bladder, stomach and spleen.

Approximately 62.5 ± 27.2% of the injected radioactivity was excreted from the body within 7 days post injection, primarily via fecal excretion. Fecal excretion at 24 hours was 2 ± 5% (range: 0-13%) of the injected radioactivity. At 48 hours after injection, cumulative fecal excretion was 13 ± 12% (range: 0-34%). Two patients excreted no radioactivity in feces throughout the sampling period due to constipation. Urinary excretion at 24 hours was 2 ±1% (range: 1-4%) of the injected radioactivity. At 48 hours after injection, cumulative urine excretion was 2 ± 2% (range: 1-5%) of the injected radioactivity and the rate of excretion was decreasing.

Radioactivity in the hepato-biliary system was assessed by planar whole body gamma camera imaging. There was no evidence of hepato-biliary excretion demonstrated by no detection of radioactivity in the liver.
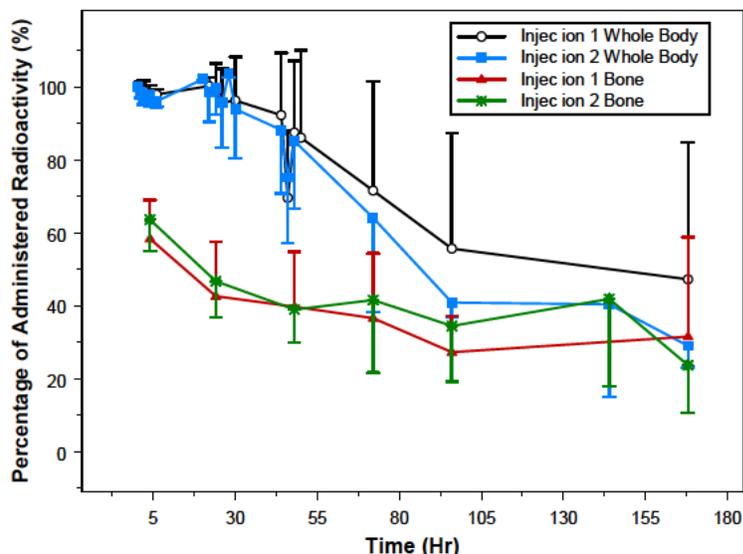
Figure 10: The percentage of total radioactivity retained in whole body and bone after the first and second injections of radium-223 dichloride at a 6-week interval in six subjects with advanced prostate cancer in Phase 1 trial BC1-05. The error bar represents standard deviation (SD).

Dosimetry:

The absorbed radiation dose calculation (including osteogenic cells) was performed in Phase 1 trial BC1-05 (Table 5) using program OLINDA/EXM (Organ Level INternal Dose Assessment/EXponential Modeling), a software based on the Medical Internal Radiation Dose algorithm, which is widely used for established beta and gamma emitting radionuclides. As radium-223 is primarily an alpha emitter, assumptions were made in the calculations for the intestine, red marrow and bone/osteogenic cells to provide the best possible absorbed radiation dose calculations for Xofigo, considering its observed biodistribution and specific characteristics.

Osteogenic cells, red marrow and lower large intestine wall received the highest absorbed radiation doses, corresponding to 1.15, 0.14 and 0.05 Gy/MBq, respectively. The calculated absorbed doses to all other organs including liver, kidney, heart were low (< 0.01 Gy/MBq, or 37 rad/mCi).

Table 5. Calculated absorbed radiation doses to different organs after intravenous injection of radium-223 dichloride at a dose of 50 kBq/kg body weight to a 73-kg adult

Target organ	Individual emission contributions (Gy/MBq)			Total	Total	SD	Organ Dose in a 73-kg Adult given 50 kBq/kg	
	Alpha	Beta	Photon	(Gy/MBq)	(rad/mCi)	(%)	Gy	rad
Adrenals	0.00E+00	2.35E-05	9.41E-05	0.00012	0.44	56	0.0004	0.04
Brain	0.00E+0	2.35E-05	7.52E-05	0.00010	0.37	80	0.0004	0.04
Breasts	0.00E+00	2.35E-05	2.53E-05	0.00005	0.18	120	0.0002	0.02
Gallbladder wall	0.00E+00	2.35E-05	2.05E-04	0.00023	0.85	14	0.0008	0.08
LLI Wall	0.00E+00	4.56E-02	8.49E-04	0.04645	171.88	83	0.1696	16.96
Small intestine wall	3.19E-03	3.60E-03	4.71E-04	0.00726	26.87	45	0.0265	2.65
Stomach wall	0.00E+00	2.35E-05	1.15E-04	0.00014	0.51	22	0.0005	0.05
ULI wall	0.00E+00	3.15E-02	8.24E-04	0.03232	119.58	50	0.1180	11.80
Heart wall	1.61E-03	7.07E-05	4.67E-05	0.00173	6.40	42	0.0063	0.63
Kidneys	2.99E-03	1.08E-04	1.06E-04	0.00320	11.86	36	0.0117	1.17
Liver	2.79E-03	1.02E-04	8.22E-05	0.00298	11.01	36	0.0109	1.09
Lungs	0.00E+00	2.35E-05	4.85E-05	0.00007	0.27	90	0.0003	0.03
Muscle	0.00E+00	2.35E-05	9.54E-05	0.00012	0.44	41	0.0004	0.04
Ovaries	0.00E+00	2.35E-05	4.62E-04	0.00049	1.80	40	0.0018	0.18
Pancreas	0.00E+00	2.35E-05	8.82E-05	0.00011	0.41	43	0.0004	0.04
Red marrow	1.32E-01	6.42E-03	2.02E-04	0.13879	513.51	41	0.5066	50.66
Osteogenic cells	1.14E+00	1.49E-02	2.98E-04	1.15206	4262.60	41	4.2050	420.50
Skin	0.00E+00	2.35E-05	4.86E-05	0.00007	0.27	79	0.0003	0.03
Spleen	0.00E+00	2.35E-05	6.65E-05	0.00009	0.33	54	0.0003	0.03
Testes	0.00E+00	2.35E-05	5.96E-05	0.00008	0.31	59	0.0003	0.03
Thymus	0.00E+00	2.35E-05	3.35E-05	0.00006	0.21	109	0.0002	0.02
Thyroid	0.00E+00	2.35E-05	4.80E-05	0.00007	0.26	96	0.0003	0.03
Urinary bladder wall	3.71E-03	1.61E-04	1.56E-04	0.00403	14.90	63	0.0147	1.47
Uterus	0.00E+00	2.35E-05	2.32E-04	0.00026	0.94	28	0.0009	0.09
Whole body	2.22E-02	8.08E-04	1.19E-04	0.02311	85.50	16	0.0843	8.43

LLI: lower large intestine; ULI: upper large intestine

Source: Table 2-3 in Section 2.7.2 Summary of Clinical Pharmacology under NDA 203971

2.2.6.2 How does the PK of the Xofigo in healthy subjects compare to that in patients?

It is unknown whether the PK of radium-223 in healthy subjects differs from that in patients, as Xofigo has only been studied in patients with advanced cancers.

2.2.6.3 Based on PK parameters, what is the degree of linearity or non-linearity based on the dose-concentration relationship?

Xofigo demonstrated linear pharmacokinetics at a dose range of 46 -250 kBq/kg in terms of dose proportionality, and time-independence after multiple doses.

Dose proportionality following single dose of Xofigo

In study ATI-BC1, the radioactivity-time profiles were available in 24 subjects after single injection of Xofigo at dose levels of 46, 93, 163, 213, 250 kBq/kg (Figure 11). Radioactivity

was measured as counts per minutes (cpm) per gram blood (cpm/g) instead of Curies or Becquerels, as a standard sample with a NIST traceable radium-223 reference material was not used.

Using $AUC_{0-168\ hrs}$ and C_{max} of radioactivity in blood after single injection of Xofigo in Phase 1 dose escalation trials ATI-BC1, a power model was applied to test the dose proportionality (Figure 12). The slope of the power model on logarithmic scale was 1.09 for C_{max} with a 90% confidence interval of (0.87, 1.32), and 1.02 for $AUC_{0-168\ hrs}$ with a 90% confidence interval of (0.86, 1.18). Therefore, the systemic exposure of radium-223 increases with dose in a proportional manner over a dose range from 46 kBq/kg to 250 kBq/kg.
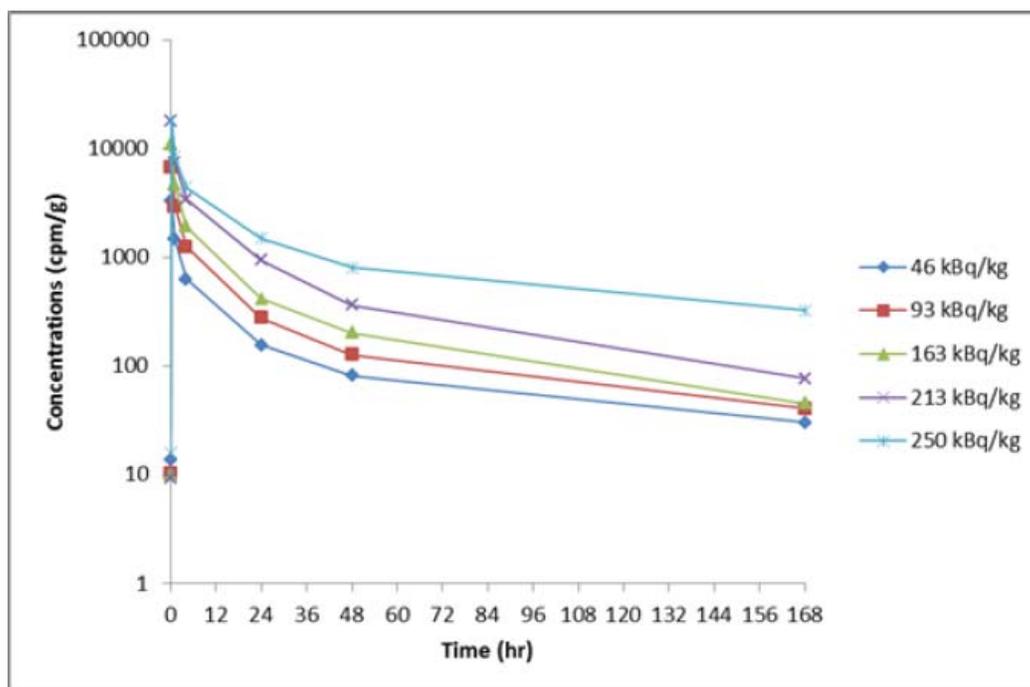
Figure 11: Mean radioactivity-time profiles in blood following a single intravenous injection of Xofigo at dose levels of 46, 93, 163, 213, and 250 kBq/kg body weight in Phase 1 trial ATI-BC1 trial. Radioactivity was measured as counts per minutes (cpm) per gram blood (cpm/g) instead of Curies or Becquerels, as a standard sample with a NIST traceable radium-223 reference material was not used.

Source: Table 2-1 in Section 2.7.2 Summary of Clinical Pharmacology under NDA 203971
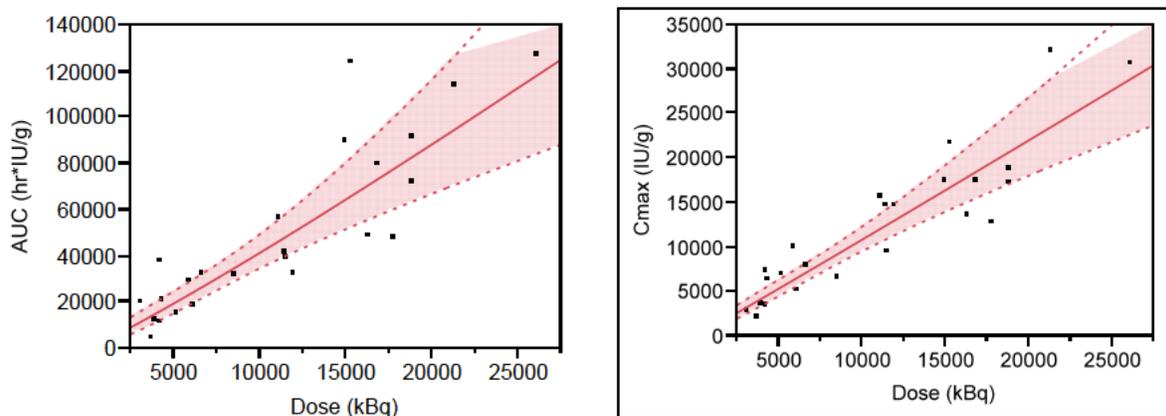
Figure 12: $AUC_{0-168hrs}$ (left) and C_{max} (right) of radioactivity in blood increased with doses, with a slope (90% confidence interval) of 1.09 (0.87, 1.32) for $AUC_{0-168hrs}$ and 1.02 (0.86, 1.18) for C_{max} after single intravenous injection of Xofigo dose ranging from 46 kBq/kg to 250 kBq/kg. The shaded area is the 90% confidence interval of the slope. The dots represents the observed C_{max} or $AUC_{0-168hrs}$ from 24 patients in Phase 1 dose escalation trials ATI-BC1.

Time independence

Xofigo demonstrated time independent pharmacokinetics, as evidenced by no noticeable changes in the radioactivity-time profiles in plasma (Figure 9), whole body, and bone (Figure 10) between two injections at dose level of 100 kBq/kg with an interval of 6 weeks.

2.3   INTRINSIC FACTORS

2.3.1   What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies or population PK analyses have been conducted to assess the effect of age, gender, race, body weight, height, body surface area (BSA), disease, genetic polymorphism, pregnancy, renal or hepatic dysfunction on Xofigo PK and/or responses. It is unknown whether intrinsic factors influence the uptake of radium-223 in bone due to limited data available.

No PK or dosimetry data were collected from subjects in the pivotal Phase 3 trial, therefore, the efforts to establish traditional exposure-response relationships were precluded. However, as Xofigo dose was administered per body weight, exploratory analyses were conducted to evaluate the impact of body weight and ideal body weight on the efficacy and safety. Results suggested that the higher total dose (i.e., body weight) or ideal body weight normalized dose is related with better OS improvement, but no changes in safety profiles across the body weight range.

See Sections 2.2.5.1 and 2.3.2.2.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy subjects vs. patients vs. specific populations, what dosing regimen adjustments, if any, are recommended for each of these groups? If dosing regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dose adjustments are recommended for specific patient populations.

2.3.2.1 Age

It is unclear whether age affect the PK in blood or dosimetry of radium-223 due to lack of data.

Safety and effectiveness of Xofigo have not been established in pediatric patients. Castration-resistant prostate cancer is rare in children.

Of the 600 patients treated with Xofigo in the pivotal trial BC1-06, 447 patients (74.5%) were 65 years of age and over, while 196 patients (32.7%) were 75 years of age and over. No overall differences in safety or effectiveness were observed between elderly and younger patients. No dosage adjustment is considered necessary in elderly patients.

2.3.2.2 Body size

The impact of body size on the PK is inconclusive due to limited data. The relationship between clearance and body weight based on data from Phase 1 trials BC1-05 (N=6) and BC1-08 (N=10) was shown in Figure 13. However, no conclusion can be drawn based on limited data with small sample size and inter-study variation.

Furthermore, as radium-223 is rapidly cleared from the blood and distributed to bone and intestine, the pharmacokinetics in blood may not be an appropriate indicator for exposure-response analyses. Though the calculated radiation doses of Xofigo in bone were available in six CRPC patients with bone metastases, the sample size is too small to conclude the relationship between total dose and calculated radiation doses.
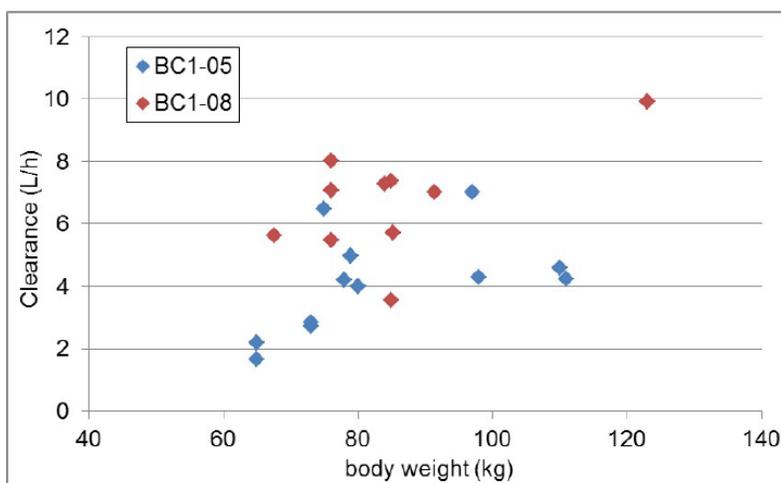
Figure 13: The impact of body weight on plasma clearance of radium-223 in Phase 1 trials BC1-05 (N=6) and BC1-08 (N=10)

Results of exploratory analyses evaluating the impact of total body weight or ideal body weight on the efficacy and safety suggested that the higher body weight (i.e., higher total dose) or higher IBW-normalized dose is related with better OS improvement, but no changes in safety profiles across the body weight range. See Section 2.2.5.

2.3.2.3 Sex

Sex is irrelevant in this NDA submission, as prostate cancer only occurs in males.

2.3.2.4 Hepatic impairment

No dedicated hepatic impairment trials or population PK analyses have been conducted. Hepatic impairment is unlikely to be a major factor to impact the PK of radium-223, since radium-223 is not metabolized by CYP enzymes and there was no evidence of hepato-biliary excretion from imaging data.

In the pivotal trial BC1-06, exploratory analyses were conducted to evaluate the impact of various degrees of hepatic impairment (per NCI organ dysfunction working group, NCI-ODWG) criteria on the safety (Grade 3+ AEs) and efficacy (OS) between Xofigo and Control arms. The analyses were conducted only for normal and mild hepatic impairment available, since patients with moderate or severe hepatic impairment were excluded from the pivotal trial.

The OS in patients with normal hepatic function was 16.1 months in patients treated with radium-223 dichloride compared to 12.4 months in the corresponding placebo group (Hazard ratio: 0.658). The OS in patients with mild hepatic impairment was 9.3 months in patients treated with radium-223 dichloride as compared to 7.9 months in patients treated with placebo (Hazard ratio: 0.869).

The incidence of Grade 3+ AEs was the slightly lower in the Xofigo arm than in the Control arm in both normal and mild hepatic impairment groups. As higher incidences of Grade 3+ AE were observed in patients with mild hepatic impairment in both the Xofigo and the Control arm, mild hepatic impairment at the baseline may be related with a more advanced stage of disease.

Based on subgroup analyses of the clinical data in the pivotal trial, no dose adjustment is needed for patients with mild hepatic impairment. However, no dose adjustments can be recommended for patients with moderate or severe hepatic impairment due to lack of data.
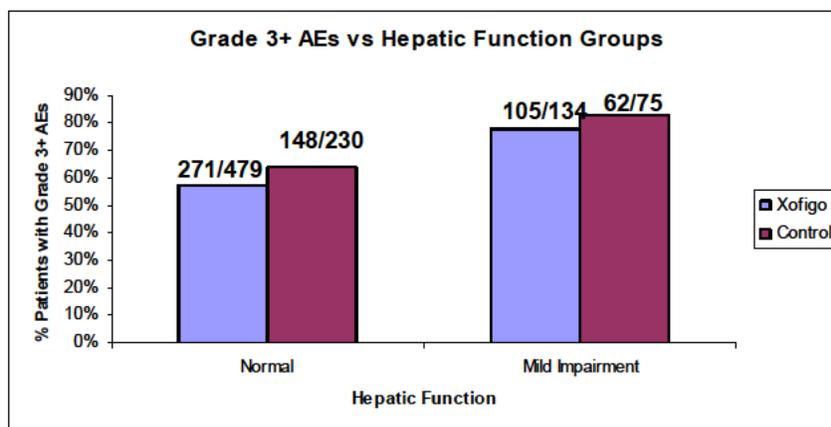
Figure 14: The effect of hepatic function on the incidence of Grade 3 or worse (Grade 3+) adverse events (AEs) in the Xofigo and Control arms in the pivotal trial BC1-06. Degrees of hepatic impairment were defined per NCI-ODWG (NCI organ dysfunction working group) criteria. The analyses were conducted only for normal and mild hepatic impairment, as patients with moderate or severe hepatic impairment were excluded from the pivotal trial. The numbers on the top of each bar represents the number of patients with Grade 3+ AE out of the total number patients according to the categories of hepatic functions in each arm.

2.3.2.5 Renal impairment

No formal renal impairment trials or population PK analyses have been conducted. Renal impairment is unlikely to be a major factor to impact the PK of radium-223, as only approximately 2% radioactivity recovered in urine within 48 hrs post-dose and low radioactivity uptake to kidney (Table 5).

Subgroup analyses were conducted for normal renal function (CLcr ≥ 90 mL/min), mild (60 mL/min ≤ CLcr < 90 mL/min), and moderate (30 mL/min ≤ CLcr < 60 mL/min) renal impairment groups available in the pivotal trial BC1-06. The incidence of Grade 3+ AEs was the slightly lower in Xofigo arm than in Control across normal, mild, and moderate renal impairment groups (Figure 15). Furthermore, there was no significant difference in the overall renal and urinary disorders. However, renal failure (including renal failure, renal failure acute, renal impairment, and renal tubular necrosis) appears slightly higher in the Xofigo arm than placebo across normal renal function, mild and moderate renal impairment groups (Table 6). Please refer to the clinical review for more information regarding the severity, etiology, and management of the renal failure in the pivotal trial.

Based on clinical data, no dose adjustment is needed for patients with mild and moderate renal impairment. However, no recommendations for dose adjustments can be made for patients with severe renal impairment (N = 2) due to inadequate clinical data.
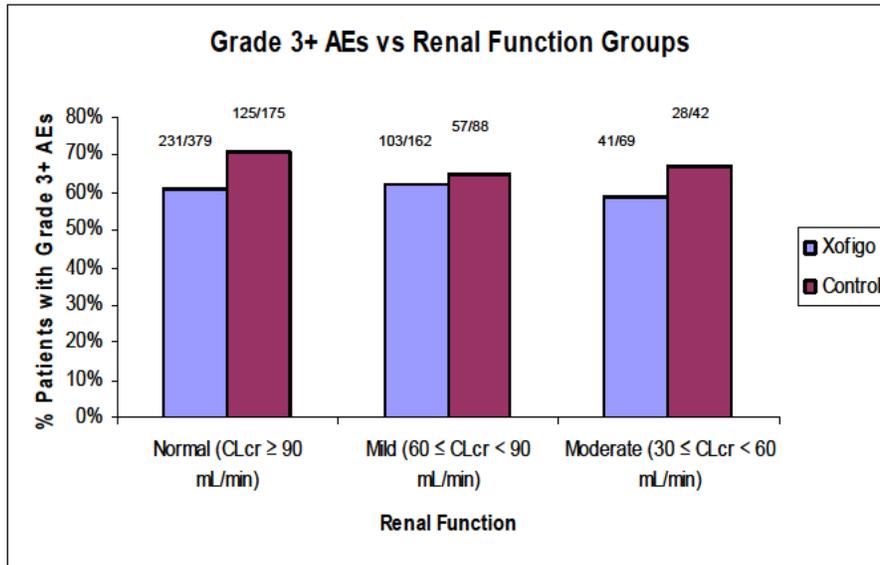
Figure 15: Bar graph for the effect of baseline renal function groups on the incidence of Grade 3 or worse (Grade 3+) adverse events (AEs) in the Xofigo and Control arms in the pivotal trial. Based on each patient's baseline creatinine clearance (CLcr), renal function groups were defined as normal renal function (CLcr ≥ 90 mL/min, N=379 for Xofigo and N=175 for Control), mild (60 mL/min ≤ CLcr < 90 mL/min, N=162 for Xofigo and N=88 for Control), moderate (30 mL/min ≤ CLcr < 60 mL/min, N=69 for Xofigo and N=42 for Control), and severe (CLcr < 30 mL/min, N=2 in Xofigo arm) renal impairment. The numbers on the top of each bar represents the number of patients with Grade 3+ AE out of the total number patients according to the categories of renal functions in each arm.

Table 6. Renal and urinary disorders by MedDRA system organ class and preferred term by normal, mild renal impairment and moderate renal impairment categories based on creatinine clearance in the safety population of the pivotal trial BC1-06

MedDRA Term	Normal CrCL > 90 mL/min		Mild CrCL > 60 – 90 mL/min		Moderate CrCL 30 – 60 mL/min		Severe CrCL < 30 mL/min	
	Xofigo (n=379) n (%)	Placebo (n=175) n (%)	Xofigo (n=162) n (%)	Placebo (n=88) n (%)	Xofigo (n=67) n (%)	Placebo (n=42) n (%)	Xofigo (n=2) n (%)	Placebo (n=0) n (%)
Renal and Urinary Disorders	69 (18.2)	34 (19.4)	33 (20.3)	19 (21.6)	9 (13.4)	14 (33.3)	0	0
Renal Failure	11 (2.90)	2 (1.14)	4 (2.47)	1 (1.14)	3 (4.48)	1 (2.38)	0	0
Renal failure	8 (2.11)	1 (0.57)	1 (0.62)	1 (1.14)	2 (2.99)	0	0	0
Renal failure acute	2 (0.53)	1 (0.57)	1 (0.62)	0	1 (1.49)	0	0	0
Renal impairment	1 (0.26)	0	1 (0.62)	0	0	1 (2.38)	0	0
Renal tubular necrosis	0	0	1 (0.62)	0	0	0	0	0

2.3.2.6 Race/Ethnicity

Radium-223 dichloride is an isotope and is not metabolized by enzymes known to show genetic polymorphisms. It is unlikely that the pharmacokinetics will be different based on race/ethnicity, though Xofigo has been studies mainly in Caucasians (93.9%, n=865), compared to Hispanics (0.2%, n=2), Blacks (1.4%, n=13), Asians (3.6%, n=33), and other races (0.9%, n=8) in the pivotal trial BC1-06.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No formal study have been conducted to evaluate the impact of extrinsic factors including drugs, herbal products, diet, smoking, and alcohol use on the exposure of radium-223 in humans.

As an isotope, radium-223 decays and is not metabolized. Therefore, the exposure of Xofigo in humans is unlikely to be affected by the cytochrome P450 (CYP450) enzymes based drug interactions.

Analysis using clinical efficacy and safety data in pivotal trial BC1-06 indicated that the co-administration of calcium channel blockers or bisphosphonates did not affect the OS and Grade 3+ AEs of Xofigo.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in-vivo* drug-drug interactions?

No, there is no *in vitro* basis to suspect *in vivo* drug-drug interactions. Being an isotope of element radium, radium-223 decays and is not metabolized. Therefore, the exposure of Xofigo in humans is unlikely to be affected by the cytochrome P450 (CYP450) enzymes based drug interactions.

2.4.2.2 Are there metabolic/transporter pathways that may be important?

Calcium channels blocker use

The mechanism for the transport of radium-223 in humans is unknown. It is hypothesized that radium-223, as a divalent cation the secretion/excretion of radium-223 from blood into the small intestine is through the transport mechanisms involved for other divalent cations (e.g. Ca, Mg, and Ba), such as calcium channels and/or divalent cation-selective TRP (transient receptor potential) channels. Therefore, we evaluated the impact of calcium channels blockers on the OS and safety of Xofigo. Subgroup analyses results suggested that the use of calcium channel blockers did not affect the OS and safety in pivotal trial BC1-06.

Safety analyses were conducted to evaluate the effect of use of calcium channels blockers on the incidences of Grade 3+ AEs in the pivotal trial BC1-06. For both Xofigo and Control arms, the incidences of Grade 3+ AEs are similar between patients who received calcium channel blockers and those patients who did not (Figure 16).
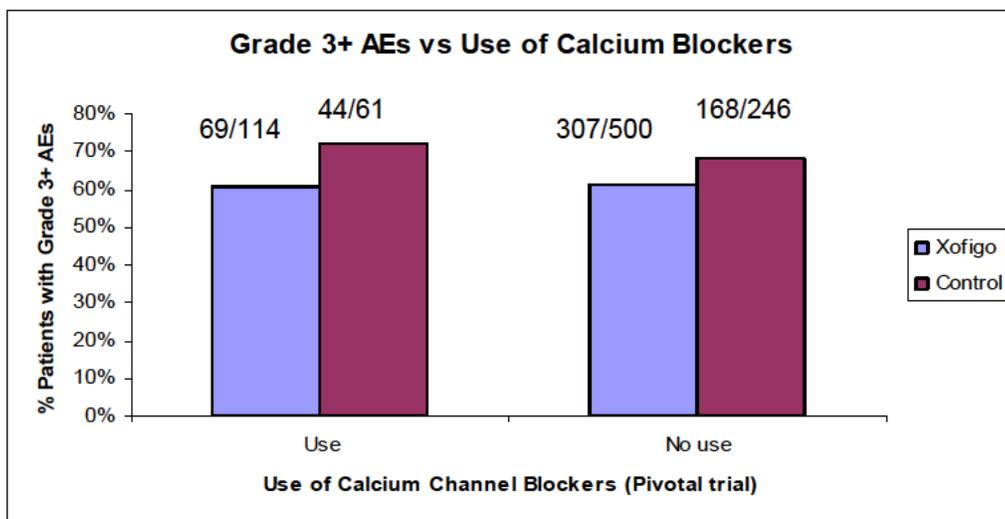
Figure 16: The effect of use of calcium channel blockers on the incidence of Grade 3 or worse (Grade 3+) adverse events (AEs) in the Xofigo and Control arms in the pivotal trial BC1-06. The numbers on the top of each bar represents the number of patients with Grade 3+ AE out of the total number patients according to the use of calcium channel blockers in each arm.

Analyses were also conducted to evaluate the effect of use of calcium channels blockers on the OS in the pivotal trial BC1-06. The hazard ratios were estimated between patients who received calcium channel blockers over those patients who did not in each arm using a Cox proportional hazards model adjusted by the following baseline covariates: total ALP (< 220 U/L versus total ALP ≥ 220 U/L), current use of bisphosphonates use (yes versus no), prior use of docetaxel (yes versus no). Hazard ratios (95% CI) were estimated as 0.99 (0.76, 1.29) and 1.03 (0.72, 1.48) in Xofigo arm and Control arm, respectively. Therefore, the use of calcium channel blockers did not affect the OS in the pivotal trial BC1-06.

Constipation status

We evaluated the effect of constipation on the safety of Xofigo in the pivotal trial BC1-06 (Figure 17), as constipation may lead to more AEs by retaining radium-223 in intestine for a long time. Compared to the incidences of Grade 3+ AEs observed in patients with and without constipation in the control arm (73.1% vs 67.8%), a higher difference in the incidences of Grade 3+ AEs was observed in patients with and without constipation in the Xofigo arm (75.4% vs 57.8%).
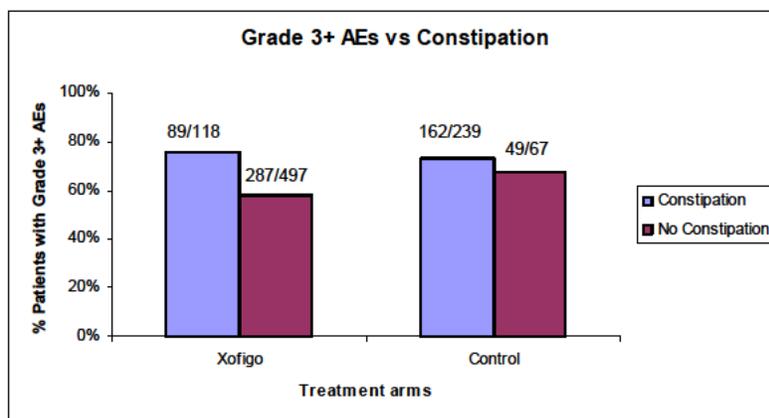
Figure 17: Bar graphs for the effect of constipation on the incidence of Grade 3 or worse (Grade 3+) adverse events (AEs) excluding constipation in the Xofigo and Control arms of the pivotal trial BC1-06. The numbers on the top of each bar represents the number of patients with Grade 3+ AE out of the total number patients according to constipation status in each arm.

Efficacy analyses were conducted to evaluate the effect of constipation status on the OS in the pivotal trial BC1-06. The hazard ratios were estimated between patients with constipation over patients without constipation in each arm using a Cox proportional hazards model adjusted by the following baseline covariates: total ALP (< 220 U/L versus total ALP ≥ 220 U/L), current use of bisphosphonates use (yes versus no), prior use of docetaxel (yes versus no). Hazard ratios (95% CI) were estimated as 0.97 (0.74, 1.26) (P = 0.88) and 1.21 (0.88, 1.66) (P = 0.25) in Xofigo arm and Control arm, respectively. Therefore, the status of constipation did not affect the OS in the pivotal trial BC1-06.

2.4.2.3 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

As one of the best standard of cares for CRPC patients with bone metastasis, bisphosphonates were received by 41% patients in the pivotal trial BC1-06. Exploratory analyses were performed to evaluate the impact of the current use of bisphosphonates on the safety (incidence of Grade 3+ AEs) and efficacy (OS) of the Xofigo treatment in the pivotal trial BC1-06.

Grade 3 or worse (Grade 3+) AEs

Similar incidences of Grade 3 + AEs were observed for patients who received bisphosphonates and those who did not in both Xofigo and control arms of the pivotal trial (Figure 18).
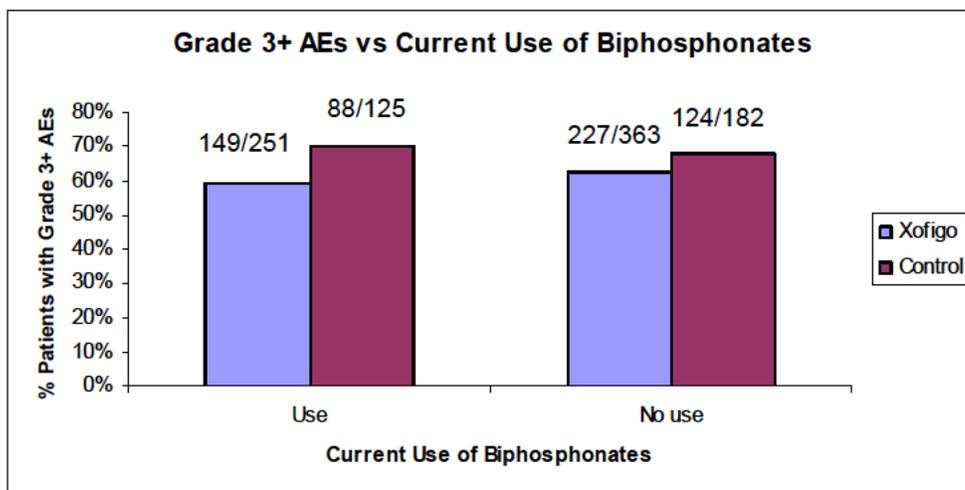
Figure 18: The effect of use of bisphosphonates on the incidence of Grade 3 or worse (Grade 3+) adverse events (AEs) in the Xofigo and Control arms in the pivotal trial BC1-06. The numbers on the top of each bar represents the number of patients with Grade 3+ AEs out of the total number patients (who received bisphosphonates or not) in each arm.

Efficacy analyses were conducted to evaluate the current use of bisphosphonates on the OS in the pivotal trial BC1-06. Hazard ratios (95% CI) were estimated as 0.70 (0.53, 0.93) and 0.74 (0.59, 0.92) in patients who received bisphosphonates and those who did not, respectively. Therefore, the concurrent use of bisphosphonates did not affect the OS in the pivotal trial BC1-06. Please refer to clinical and statistical reviews for more details.

2.4.2.4 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No.

2.5   GENERAL BIOPHARMACEUTICS

2.5.1   What is the composition of the to-be-marketed formulation?

The commercial formulation of Xofigo is supplied in single use vials containing 6 mL of solution (1000 kBq/mL, 27 µCi/mL at the reference date). The composition of the to-be-marketed Xofigo formulation is listed in Table 7.

Table 7. Composition of Xofigo drug product

Each 10 mL vial contains:

Composition	Reference to Standard	Function	Amount per vial	Amount per mL
Drug substance				
Radium-223 chloride	In-house	Drug substance	6000 kBq (3.2 ng) [a] at reference date	1000 kBq (0.53 ng) [a] at reference date
Excipients [b]				
Sodium chloride	Current Ph. Eur. / USP	Tonicity agent	37.8 mg	6.3 mg
Sodium citrate [c]	Current Ph. Eur. / USP	pH adjuster	43.2 mg	7.2 mg
Hydrochloric acid	Current Ph. Eur. / USP	pH adjuster	1.2 mg [d]	0.2 mg [d]
Water for injection	Current Ph. Eur. / USP			(b) (4)

a   Calculated as radium-223

b   (b) (4)

c

d

Source: NDA 203971 Section 3.2.P.1.02-02 drug product

2.6   ANALYTICAL SECTION

2.6.1   What bioanalytical methods are used to assess the pharmacokinetics of Xofigo?

Radium-223 decays in six steps via a chain of alpha and beta emissions into stable lead, Pb-207.

(b) (4)

The pharmacokinetics of Xofigo was measured using the total radioactivity detected by the gamma-ray emissions from radium-223 in the biological samples. Since the biological activity of Xofigo resides in the radioactivity rather than the mass of radium-223, the measurement of total radioactivity is acceptable. As there is no established method for measuring the radioactivity from the alpha particle emission, the radioactivity of the biological samples of Xofigo (the first alpha particle emitter radiopharmaceutical) was determined via counting the gamma-ray emissions from radium-223 in the biological samples.

The response of the measuring device to the gamma rays emitted from a sample (i.e. the detector efficiency) can be determined by use of the National Institute of Standards and Technology (NIST) traceable radium-223 reference material which contains a known radioactivity of radium-223. Thus, the counts (counts per minute (cpm) or counts per second

(cps)) recorded by the instrument can be converted to Curies or Becquerels of radium-223 using the known response of the instrument. NIST has performed radioactivity measurements in a variety of dose calibrators for radium-223 in various dose vials and syringes containing a range of volumes and activities. The dose calibrator measurement accuracies for radium-223 were shown to be within +/-5% for all geometries.

There are no metabolites identified and expected. Due to the physical properties of gamma rays, the biochemistry of the sample matrix has no effect on the measurement of the external emitted gamma emissions. The emission of gamma radiation is also independent of physical properties of the samples. Therefore, no specific storage conditions or sample processing is required prior to analysis.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. <u>Underlines</u> indicate the content that was added to the proposed label by the Agency and ~~strikethroughs~~ indicate content taken out from the proposed label by the Agency.

PROPOSED LABELING	AGENCY'S SUGGESTIONS

(b) (4)
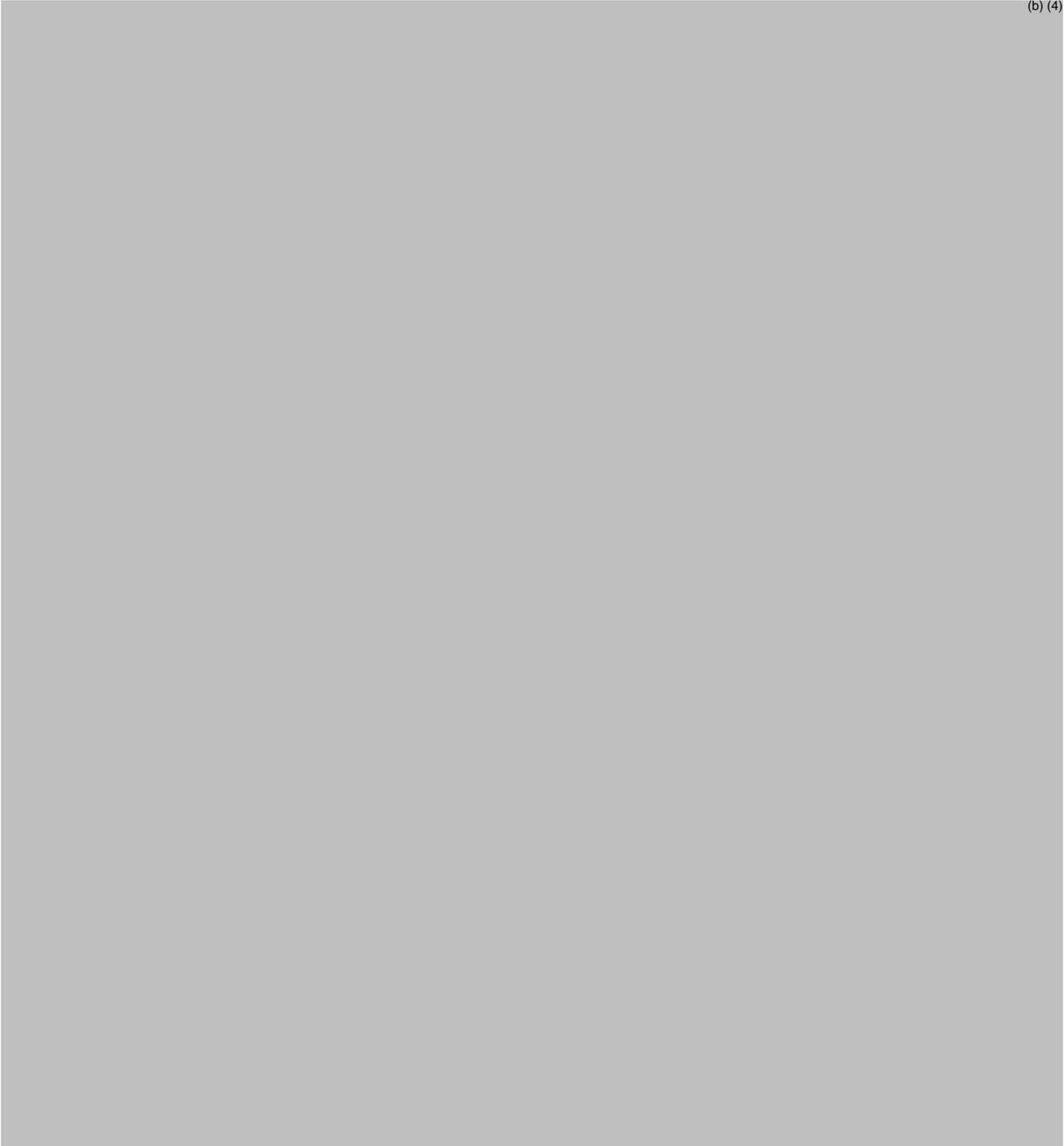
5 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 PHARMACOMETRIC REVIEW

The results of pharmacometric review has been incorporated into the QBR. This section only provide the Applicant's analysis, and the data source and methods for FDA reviewer's analysis.

4.1 APPLICANT'S ANALYSIS:

Body weight

The applicant conducted subgroup analysis to evaluate the effect of weight on the safety and efficacy of radium-223 dichloride in the pivotal Phase 3 Study. The data indicate that the median overall survival is higher in the radium-223 dichloride arm as compared to placebo for the three weight groups evaluated (< 80 kg, 80-100 kg and >100 kg). The improvement in survival is consistent with that observed for the whole ITT population. Data suggests that the incidence of TEAE in the sub-groups is similar to that seen for the overall population and comparable to the placebo arm for each sub-group. Based on the overall survival data (efficacy) and the TEAE (safety), body weight did not seem to have an effect on the safety and efficacy.

Table 3-8: Median overall survival in months for the ITT population for overall population and by weight categories (BC1-06)

	Radium-223 dichloride	Placebo	Hazard Ratio (95% CI)
Overall Population			
N	614	307	
Median (95% CI)	14.9 (13.9 – 16.1)	11.3 (10.4 – 12.8)	0.724 (0.607 – 0.865)
< 80 kg			
N	261	132	
Median (95% CI)	13.2 (11.4 – 14.6)	10.8 (8.8 – 12.4)	0.778 (0.592-1.024)
80 – 100 kg			
N	284	136	
Median (95% CI)	15.4 (14.0 – 16.9)	12.6 (10.7 – 15.7)	0.729 (0.553 – 0.960)
>100 kg			
N	65	37	
Median (95% CI)	21.7 (16.2 – NE)	11.8 (8.7 – 14.8)	0.344 (0.180 – 0.658)

NE = not estimable

Table 3-9: Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Overall Population and by Body Weight Categories - Safety Population (BC1-06)

MedDRA Term	Overall Population		Body Weight < 80 kg		Body Weight 80 kg - 100 kg		Body Weight > 100 kg	
	Radium-223	Placebo	Radium-223	Placebo	Radium-223	Placebo	Radium-223	Placebo
	(n=600)	(n=301)	(n=253)	(n=129)	(n=278)	(n=134)	(n=65)	(n=36)
	%	%	%	%	%	%	%	%
Patients with at Least One TEAE	93.0	96.3	93.7	96.1	93.5	96.3	87.7	97.2
Blood and Lymphatic System Disorders	38.7	35.2	44.3	38.8	36.7	32.1	26.2	33.3
Gastrointestinal Disorders	63.3	57.8	59.7	48.8	66.5	61.9	64.6	75.0
General Disorders and Administration Site Conditions	46.7	47.2	48.2	46.5	45.7	50.7	44.6	38.9
Infections and Infestations	30.5	32.6	29.2	33.3	32.7	35.8	27.7	16.7
Injury, Poisoning and Procedural Complications	11.3	6.3	9.9	6.2	11.9	6.7	15.4	5.6
Investigations	16.7	22.3	15.4	20.2	19.8	23.1	7.7	27.8
Metabolism and Nutrition Disorders	30.3	30.6	33.6	35.7	28.1	26.9	29.2	22.2
Musculoskeletal and Connective Tissue Disorders	58.2	69.4	57.3	67.4	59.7	67.9	56.9	83.3
Neoplasms Benign, Malignant and Unspecified Incl Cysts and Polyps	16.7	19.3	20.2	18.6	14.0	17.2	13.8	25.0
Nervous System Disorders	28.3	38.2	25.7	36.4	30.6	38.1	29.2	44.4
Psychiatric Disorders	14.5	18.3	14.6	17.8	14.7	18.7	13.8	19.4
Renal and Urinary Disorders	18.0	19.9	16.2	20.2	19.8	18.7	18.5	25.0
Respiratory, Thoracic and Mediastinal Disorders	19.7	19.3	20.2	20.9	19.8	20.1	18.5	11.1
Skin and Subcutaneous Tissue Disorders	11.7	11.3	13.8	14.7	9.7	7.5	12.3	13.9

Source: : Module 5.3.5.1, Report A58800, Table 23.3.1 (overall data), PH-36915, Section 13, P61.23.3.1-8.1, P61. 23.3.1-8.2, P61. 23.3.1-8.3 (weight categories)

Body Mass Index

The effect of body mass index on the safety and efficacy of radium-223 dichloride was evaluated using sub-group analysis from the pivotal Phase 3 Study. Table 3-10 shows the median overall survival for the overall population and by body mass index <30 kg/m^2 and > 30 kg/m^2 based on the intent to treat population. The data indicate that the median overall survival is higher in the radium-223 dichloride arm as compared to placebo for the two BMI groups evaluated. The improvement in survival is consistent with that observed for the whole ITT population. Table 3-11 shows the TEAE (treatment emergent adverse events) for the overall population and for body mass index sub-groups of <30 kg/m^2 and ≥30 kg/m^2 based on the safety population.

Data suggests that the incidence of TEAE in the sub-groups is similar to that seen for the overall population and comparable to the placebo arm for each sub-group. Based on the overall survival data (efficacy) and the TEAE (safety), BMI did not seem to have an effect on the safety and efficacy.

Table 3-10: Median overall survival in months for the ITT population for overall population and by body mass index categories (BC1-06)

	Radium-223 dichloride	Placebo	Hazard Ratio (95% CI)
Overall Population			
	614	268	
	14.9 (13.9 – 16.1)	11.3 (10.4 – 12.8)	0.724 (0.607 – 0.865)
<30 kg/m²			
	434	216	
	14.1 (12.8 – 15.5)	11.0 (9.1 – 12.8)	0.771 (0.624-0.953)
>=30 kg/m²			
	153	78	
	16.1 (14.5 – 18.4)	12.6 (10.4 – 15.7)	0.617 (0.431 – 0.883)

Source: : Module 5.3.5.1 Report PH-36915, Section 13, Table P61.9.1-1 (overall data), P61.9.1–15.1 – P61.9.1-15.2 (BMI categories)

Table 3-11: Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Overall Population and by Body Mass Index sub-groups - Safety Population (BC1-06)

MedDRA Term	Overall Population		BMI < 30kg/m²		BMI ≥ 30kg/m²	
	Radium-223	Placebo	Radium-223	Placebo	Radium-223	Placebo
	(n=600)	(n=301)	(n=423)	(n=212)	(n=152)	(n=77)
	%	%	%	%	%	%
Patients with at Least One TEAE	93.0	96.3	92.9	96.7	92.1	96.1
Blood and Lymphatic System Disorders	38.7	35.2	42.1	35.8	29.6	32.5
Gastrointestinal Disorders	63.3	57.8	62.6	55.7	63.8	63.6
General Disorders and Administration Site Conditions	46.7	47.2	47.5	48.1	44.1	48.1
Infections and Infestations	30.5	32.6	30.7	36.8	27.6	23.4
Injury, Poisoning and Procedural Complications	11.3	6.3	9.9	7.1	13.2	3.9
Investigations	16.7	22.3	17.5	22.6	13.2	23.4
Metabolism and Nutrition Disorders	30.3	30.6	30.3	31.1	27.6	27.3
Musculoskeletal and Connective Tissue Disorders	58.2	69.4	58.9	67.9	54.6	74.0
Neoplasms Benign, Malignant and Unspecified Incl Cysts and Polyps	16.7	19.3	18.4	19.3	11.8	18.2
Nervous System Disorders	28.3	38.2	26.7	35.4	30.9	42.9
Psychiatric Disorders	14.5	18.3	14.4	18.9	13.2	19.5
Renal and Urinary Disorders	18.0	19.9	16.3	20.3	21.7	20.8
Respiratory, Thoracic and Mediastinal Disorders	19.7	19.3	19.9	22.2	19.1	13.0
Skin and Subcutaneous Tissue Disorders	11.7	11.3	12.3	12.3	9.9	10.4

Source: Module 5.3.5.1, Report A58800, Section 14, Table 23.3.1 (overall data), Module 5.3.5.1, Report PH-36915, Section 13, Tables P61.23.3.1 – 14.1 and 14.2 (BMI categories).

Reviewer's comments: The review agrees to the applicant's analyses but disagrees to the

conclusion that body weight did not seem to have an effect on the efficacy. Higher body weight (particularly when body weight > 100 kg) is related with lower hazard ratio. Instead of arbitrary weight cutoff of <80, 80 to 100 and > 100 kg, the reviewer divided the data into quartiles of body weight to conduct the analysis. See results of the FDA reviewer's analysis discussed in relevant sections of the QBR.

4.2   FDA REVIEWER'S ANALYSIS

FDA reviewer conducted body weight-efficacy and body weight-safety relationship analyses using total body weight and ideal body weight. Since the dose is administered as per kg, higher body weight implies larger total dose.

4.2.1   Objectives

The objectives of the reviewer's analyses are:

- To explore the impact of total body weight or ideal body weight normalized dose on the overall survival in the pivotal trial

- To explore the impact of total body weight or and ideal body weight normalized dose on the incidence of Grade 3+ AEs in the pivotal trial

4.2.2   Methods

Kaplan Meier analysis was applied to establish a relationship between quartiles of total body weight and OS. Kaplan-Meier curve of overall survival (OS) stratified by body weight quartiles: Q1 ($\leq$ 73 kg), Q2 (73–82 kg), Q3 (82–91 kg), and Q4 (> 91 kg). Hazard ratio (HR) vs. the control arm for each quartile of total body weight was estimated using a Cox proportional hazards model adjusted by the following baseline covariates: total ALP (< 220 U/L versus total ALP $\geq$ 220 U/L), current use of bisphosphonates use (yes versus no), prior use of docetaxel (yes versus no), and baseline ECOG $\geq$ 2 (yes versus no).

Hazard ratio (HR) and 95% CI vs. the control arm for each of 10 quantiles of relative weight difference (or IBW-normalized dose) was estimated using a Cox proportional hazards model adjusted by the following baseline covariates: total ALP (< 220 U/L versus total ALP $\geq$ 220 U/L), concurrent use of bisphosphonates use (yes versus no), prior use of docetaxel (yes versus no). The OS hazard ratio vs relative weight difference graph was plotted in R package using smooth.spline function based on the point estimate (solid line) or 95% CI (dashed lines) in order to see the trend more clearly after smoothing out some noise.

Logistic regression method was applied to analyze the relationships between total body weight and thrombocytopenia. The incidence of Grade 3 or worse adverse events (Grade 3+ AEs) in patients was compared across quartiles of total body weight and ideal body weight normalized dose.

4.2.3   Datasets

Data sets used in the analysis are summarized in the table below:

Dataset description	Name	Link to EDR
Efficacy data for pivotal study BC1-06	surv.xpt	\\cdsesub1\EVSPROD\NDA203971\0000\m5\data sets\a58800\analysis\legacy\datasets
Safety data	ae.xpt	\\cdsesub1\EVSPROD\NDA203971\0000\m5\data sets\a58800\analysis\legacy\datasets
Drug administration data	disp.xpt	\\cdsesub1\EVSPROD\NDA203971\0000\m5\data sets\a58800\analysis\legacy\datasets
Demographic data	demog.xpt	\\cdsesub1\EVSPROD\NDA203971\0000\m5\data sets\a58800\analysis\legacy\datasets
Lab data	lab.xpt	\\cdsesub1\EVSPROD\NDA203971\0000\m5\data sets\a58800\analysis\legacy\datasets

4.2.4 Software

SAS 9.2, TIBCO Spotfire S-Plus 8.1, and R Package (Version 2.10.1) were used for the FDA reviewer's analyses.

4.2.5 Results

Please refer to Section 2.2.5 for the results.

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

/s/

PENGFEI SONG
04/09/2013

CHRISTY S JOHN
04/09/2013

NITIN MEHROTRA
04/09/2013

QI LIU
04/09/2013

NAM ATIQUR RAHMAN
04/10/2013

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	203971/000	Brand Name	Xofigo
Related IND	67521	Generic Name	Radium-223 Dichloride Injection
OCP Division	V	Drug Class	Therapeutic alpha particle-emitting pharmaceutical
Medical Division	DOP1	Applicant	Bayer
OCP Reviewer	Pengfei Song	Indication(s)	Castration-resistant prostate cancer with bone metastases
OCP Team Leader	Qi Liu	Dosage Form	Single-use vial containing 6000 kBq/6 mL (0.162 mCi/6 mL)
Pharmacometrics Reviewer	Pengfei Song	Dosing Regimen	50 kBq (0.00135 mCi) per kg body weight, given at 4 week intervals for 6 injections
Pharmacometrics Team Leader	Nitin Mehrotra	Route of Administration	IV Injection
Priority Classification	Priority	OND Action Date	5/17/2013
Date of Submission	12/14/2012	PDUFA V Due Date	8/14/2013

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods				**Not provided. The applicant provided written response to FDA request why it is not provided.**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	x	3		• **Study ATI BC1: Dose escalation (46 to 250 kBq/kg BW) study in 31 patients (Safety, PK)** • **Study BC1-05 (Europe) in 6 patients (2x100 kBq/kg BW) (biodistribution, PK, dosimetry)** • **Study BC1-08 (USA) in 10 patients (50, 100, 200 kBq/kg single dose) (biodistribution, PK, dosimetry)**
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				

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single dose:		3		• **Phase 1 Trial ATI BC1** • **Phase 1 Trial BC1-08** • **Phase 2 Trial BC1-03**
multiple dose:	x	5		• **Phase 1 Trial ATI BC1** • **Phase 1 Trial BC1-05** • **Phase 2 Trial BC1-02** • **Phase 2 Trial BC1-04** • **Phase 3 Trial BC1-06**
Dose proportionality -	x	1		• **Phase 1 Study ATI BC1**
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	X	1		**Phase 2 Study BC1-04: Dose-response relationship used for dose selection (3X25, 50, 80 kBq/kg BW at 6 week intervals)**
Phase 3:				
QT evaluation	X	1		**Substudy of Pivotal trial in 29 patients (21 receiving Xofigo and eight receiving placebo).**
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		7		

Clinical Pharmacology Filing Form/Checklist for NDA 203971

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On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	

Clinical Pharmacology Filing Form/Checklist for NDA 203971

CLINICAL PHARMACOLOGY
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17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Pengfei Song   01/10/2013
Reviewing Clinical Pharmacologist   Date

Qi Liu   01/10/2013
Team Leader/Supervisor   Date

Clinical Pharmacology Filing Form/Checklist for NDA 203971

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

/s/

PENGFEI SONG
02/12/2013

QI LIU
02/15/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	203-971
Submission Date	12/14/12
Product name, generic name of the active	Xofigo® Injection (radium Ra 223 dichloride)
Dosage form and strength	Injectable Solution
Route of Administration	Intravenous
Indication	Treatment of castration-resistant prostate cancer patients with bone metastases.
Applicant	Bayer HealthCare Pharmaceuticals Inc.
Clinical Division	DOP1
Type of Submission	505(b)(1)
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Supervisor	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the dissolution test part of the DP specifications?		x	Not Applicable.
2.	Does the application contain the dissolution method development report?		x	Not Applicable.
3.	Is there a validation package for the analytical method and dissolution methodology?		x	Not Applicable.
4.	Does the application include a biowaiver request?		x	Not Applicable.
5.	Is there information provided to support the biowaiver request?		x	Not Applicable.
6.	Does the application include an IVIVC model?		x	Not Applicable.
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	Not Applicable.
8.	Is information on mixing the product with foods or liquids included?		x	Not Applicable.
9.	Is there any in *vivo* BA or BE information in the submission?		x	There is PK and biodistribution data on the proposed commercial formulation. This information will be reviewed by the Office of Clinical Pharmacology.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

<table>
<tr><td colspan="5" align="center">B. FILING CONCLUSION</td></tr>
<tr><td></td><td align="center">Parameter</td><td>Yes</td><td>No</td><td>Comment</td></tr>
<tr><td>10.</td><td>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</td><td>x</td><td></td><td></td></tr>
<tr><td>11.</td><td>If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.</td><td>-</td><td>-</td><td></td></tr>
<tr><td>12.</td><td>Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?</td><td></td><td>x</td><td></td></tr>
</table>

{See appended electronic signature page}

Kareen Riviere, Ph.D.   1/8/13
Biopharmaceutics Reviewer   Date
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D.   1/8/13
Biopharmaceutics Team Leader   Date
Office of New Drug Quality Assessment

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

INITIAL BIOPHARMACEUTICS ASSESSMENT

The drug product is supplied as a ready-to-use sterile solution for injection in 10 mL glass vials with a fill volume of 6 mL. The declared radioactivity concentration is 1000 kBq/mL (0.0270 mCi/mL) at the reference date.

The formulations used throughout clinical development were based on the same qualitative composition with some differences in excipient concentrations. The Applicant denoted manufacturing process modifications developed and implemented during the supply for nonclinical and clinical studies as processes I, II, and III. The composition of the formulations are provided in Table 1.

Table 1. Comparative Composition of Radium 223 Dichloride Formulations from Different Manufacturing Processes

Component	Function	Process I	Process II	Process III (b) (4)
Radium-223 Chloride	active pharmaceutical ingredient			
Drug Substance Vehicle				
Sodium chloride	tonicity Agent			
Sodium citrate	Ph adjuster			
Hydrochloric acid	Ph adjuster			
(b) (4)	(b) (4)			
Water for injection				(b) (4)

Source: Module 2.3.S, Section 2.6, Table 2-7

An overview on the formulations used during the clinical development of radium- 223 dichloride is provided is in Table 2.

Table 2. Formulations used During the Clinical Development of Radium- 223 Dichloride

Study Phase	Study no. Algeta / Bayer	Report No.	Type of Study / Short Title	Manufacturing Process
1	ATI-BC1 / 15522	A58312	Safety and tolerability, pharmacokinetics	I
	BC1-05 / 15302	A58309	Biodistribution, pharmacokinetics and dosimetry	I
	BC1-08 / 15303	A58798	Biodistribution, pharmacokinetics and dosimetry	II
2	BC1-02 / 15280	A58302	Efficacy and safety, double blind, placebo-controlled	I
	BC1-03 / 15305	A58307	Efficacy and safety, double blind, dose ranging	I
	BC1-04 / 15304	A58308	Efficacy and safety, double blind, placebo-controlled	I
3	BC1-06 / 15245	A58800	Pivotal study on efficacy and safety, double blind, placebo-controlled	II, III[1]

[1.] In the reported study part, drug substance solution based on process II was used. In subjects who switched from placebo to active treatment after unblinding of this study, drug substance solutions based on process II and III were used.

Source Module 3.2S Section 2.6, Table 1

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

The proposed commercial product has the same composition as the clinical formulation containing drug substance obtained from process II/ III. Therefore, according to Table 2 above, there is PK and biodistribution data on the proposed to be marketed formulation and the proposed to be marketed formulation was tested in pivotal Phase 3 efficacy and safety study. Thus, no further Biopharmaceutics review is needed for this NDA.

RECOMMENDATION:

The ONDQA Biopharmaceutics team has reviewed NDA 203971 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

Comment to the Clinical Division
Since there is available pharmacokinetic, safety, and efficacy information for the proposed to be marketed formulation, a biowaiver is not needed for this product. Therefore, no further Biopharmaceutics review is needed for this NDA.