EU RISK MANAGEMENT PLAN (RMP)

XOFIGO®

BAY 88-8223
(Radium-223 Dichloride)

No. 7.1

Date of Report:
18 JUN 2025

[redacted]

XOFIGO®
(Radium-223 Dichloride)
EU Risk Management Plan

EU Risk Management Plan for Xofigo® (Radium-223 dichloride)

RMP version to be assessed as part of this application:

RMP Version number: 7.1

Data lock point for this RMP: 30 MAY 2025

Date of final sign-off: 18 JUN 2025

Rationale for submitting an updated RMP:

Category 1 study 20510 (RADIANT), a phase IV randomised open-label multicentre study conducted according to an agreed protocol in order to further characterise the efficacy and safety with Radium-223 dichloride in the authorised indication, is ongoing. The occurrence of the required 508 death events for the analysis of the primary endpoint overall survival are currently projected to occur in Q4 of 2025. Consequently, the final clinical study report (CSR) submission will move out, from the prior planned timepoint in Q4 2025 into Q2 of 2026.

Category 3 study 17739 (PEACE-III) is a Phase III study sponsored by the academic consortium European Organisation for Research and Treatment of Cancer (EORTC) met the timepoint of primary completion in FEB 2024 and topline results from the data analysis by EORTC were presented in SEP 2024 at the European Society for Medical Oncology (ESMO) 2024 Congress. Data from the trial demonstrated that Xofigo® (radium-223 dichloride) in combination with enzalutamide as first-line therapy for patients with metastatic castration resistant prostate cancer (mCRPC) and bone metastases significantly improves radiographic progression-free survival (rPFS), with favourable overall survival at interim analysis and favourable safety results. The study is ongoing.

As this study was not originally designed for regulatory submission purposes, the original informed consent did not include regulatory submission as a permissible use of participant data. Accordingly, an additional informed consent (reconsent) was required. As a result of preliminary discussions with the German health authority BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) and US Food and Drug Administration (FDA) it was decided to postpone the subsequent submission until final overall survival (OS) results are available. This will lead to a delay in the submission of the Bayer clinical study report (CSR) to Q4 2025.

Summary of significant changes in this RMP from Version 6.1 to 7.1:

Part II: Module SVII – Important potential risk “Secondary malignancies” was renamed to “Second primary malignancies” to reflect correct terminology for risk assessment (change was performed throughout the RMP). The risk characterisation was not changed.

Conclusion on completed Study 16913 (REASSURE) was added.

Part II: Module SV – Estimated post-authorisation exposure was updated.

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Part III.2 – Additional pharmacovigilance activities and Part III.3 – Summary table of additional pharmacovigilance activities – Milestones for the following studies were updated:

Milestones updated for Category 1 – 20510 – RADIANT.

Milestones updated for Category 3 – 17739 – PEACE-3.

Category 3 Studies 20702 and 16913 (REASSURE) were removed due to completion.

Part IV.2 – List of the Planned and Ongoing Imposed Post-authorisation Efficacy Studies – Milestones for Category 1 – 20510 – RADIANT Study were updated.

Part V.2 – Additional risk minimisation measures – Removal of Dear Healthcare Professional Communication (DHPC) letter due to completion.

Part V.3 –Summary of risk minimisation measures – Removal of Category 3 Studies 20702 and 16913 (REASSURE), and DHPC letter due to completion.

Part VI.II.B – Summary of Important Risks – Removal of Category 3 Studies 20702 and 16913 (REASSURE), and DHPC letter due to completion.

Part VI.II.C.1 – Studies which are conditions of the marketing authorisation – Update of milestones for Study 20510 (RADIANT)

Part VI.II.C.2 – Other studies in post-authorisation development plan – Removal of Studies 20702 and 16913 (REASSURE) due to completion and update of milestones for Study 17739 (PEACE-3).

Part VII Annex 2 – Status for Studies 20702 and 16913 (REASSURE) was changed to completed. Update of milestones for Studies 20519 (RADIANT) and 17739 (PEACE-3).

Part VII Annex 8 – Updated to reflect the significant changes to the RMP over time.

Other RMP versions under evaluation: Not applicable.

Details of the currently approved RMP:

Version number: 6.1

Approved with procedure: EMEA/H/C/002653/R/0049

Date of approval (opinion date): 26 NOV 2024

QPPV signature:

EU QPPV name Dr. Jutta Pospisil

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List of abbreviations

AA	Abiraterone Acetate
ADR	Adverse Drug Reaction
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AML	Acute Myeloid Leukaemia
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
ATC	The Anatomical Therapeutic Chemical (Atc) Classification System
b. w.	Body Weight
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BFI	Brief Fatigue Inventory
BHA	Bone Health Agent
BMQ	Bayer Meddra Query
BPI	Brief Pain Inventory
Bq	Becquerel
BRCA	Breast Cancer Gene
CHMP	The Committee for Medicinal Products For Human Use
CI	Confidence Interval
CLCR	Creatinine Clearance
CRPC	Castration-Resistant Prostate Cancer

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CSR	Clinical Study Report
CTC(AE)	Common Terminology Criteria for Adverse Events
DDR	DNA Damage Response
DHPC	Dear Healthcare Professional Communication
DLP	Data Lock Point
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECOG	Eastern Cooperative Oncology Group
EAIR	Exposure-Adjusted Incidence Rate
EAP	Early Access Program
EBRT	External Beam Radiation Therapy
EC	European Commission
EEA	European Economic Area
ESMO	European Society for Medical Oncology
eGFR	Estimated Glomerular Filtration Rate
HER	Electronic Health Record
EMA	European Medicines Agency
EOD4	Extent of Disease 4
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EU	European Union
FACT-P	The Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration

FPFV	First Patient First Visit
GLOBOCAN	Global Burden of Cancer Study
Gy	Gray
Hb	Haemoglobin
HDI	Human Development Index
HLGT	High-Level Group Term
HR	Hazard Ratio
HRPC	Hormone Refractory Prostate Cancer
ICSR	Individual Case Safety Report
IDMC	Independent Data Monitoring Committee
IRD	Incidence Rate Difference
IRR	Incidence Rate Ratio
KBq	Kilobecquerel
LHRH	Luteinising hormone-releasing hormone
LLT	Lowest Level Term
LPLV	Last Patient Last Visit
MAH	Marketing-Authorisation Holder
MBq	Megabecquerel
mCi	Millicurie
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activites
MLG	MedDRA Labelling Group

MTG	MedDRA Term Group
n/N	Number
NCA	National Competent Authority
NCI	National Cancer Institute
NIST	National Institute of Standards and Technology
NOS	Not Otherwise Specified
NPCR	National Program of Cancer Registries
ONJ	Osteonecrosis of the jaw
OR	Odds Ratio
OS	Overall Survival
P	Prednisone
PAES	Post-Authorisation Efficacy Study
PARP	Poly (ADP-Ribose) Polymerase
PASS	Post-Authorisation Safety Study
PBMQ	Product-SPECIFIC BAYER MEDDRA QUERY
PBRER	Periodic Benefit-Risk Evaluation Report
PCBaSe	Prostate Cancer data Base Sweden
PCCTC	Prostate Cancer Clinical Trials Consortium
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PRECISE	Treatment Patterns and rates of bone fractures in mCRPC PatiEnts treated with Radium-223 in Routine Clinical PractIce in SwedEn
PSMA	Prostate-Specific Membrane Antigen

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PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QoL	Quality Of Life
QPPV	Qualified Person for Pharmacovigilance
Ra-223	Radium-223 Dichloride
REASSURE	Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
RMP	Risk Management Plan
rPFS1	Radiological Progression-Free Survival
SAE	Serious Adverse Event
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SMR	Standardised Morbidity Ratio
SRE	Skeletal-Related Event
SSE	Symptomatic Skeletal Event
TBC	To Be Confirmed
TEAE	Treatment Emergent Adverse Event
UK	United Kingdom
ULN	Upper Limit Of Normal
US	United States
WHO	World Health Organisation

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Part I: Product(s) Overview

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Table Part I.1 – Product(s) overview

Active substance(s) (INN or common name)	Radium-223 dichloride
Pharmacotherapeutic group(s) (ATC Code)	V10XX03
Marketing Authorisation Holder	Bayer AG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Xofigo®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Xofigo® is a therapeutic alpha particle-emitting pharmaceutical with targeted anti-tumour effect on bone metastases. The active moiety of Xofigo® is the isotope Radium-223 (as Radium-223 dichloride). Radium-223 is an alpha particle-emitter with a half-life of 11.4 days. The specific activity of Radium-223 is 1.9 MBq/ng.
	Summary of mode of action: The active moiety of Xofigo® mimics calcium and selectively targets bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 keV/micrometre) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in a potent and localised anti-tumour effect. The alpha particle range from Radium-223 is less than 100 micrometres (less than 10 cell diameters) which minimises damage to the surrounding normal tissue.
	Important information about its composition: Each ml of solution contains 1,100 kBq (1,000 kBq prior

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Table Part I.1 – Product(s) overview

	implementation of National Institute of Standards and Technology [NIST] update)[1] Radium-223 dichloride, corresponding to 0.58 ng (0.53 ng prior implementation of NIST update)[1] Radium-223 dichloride at reference date. Radium-223 is present in the solution as a free ion.
Hyperlink to the Product Information	**Module 1.3.1**
Indication(s) in the EEA	Current: Xofigo® monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases, and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current: The dose regimen of Xofigo® is an activity of 55 kBq per kg body weight, given at 4-week intervals for 6 injections. No dose adjustments are to be considered in elderly patients, and in patients with hepatic or renal impairment.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): Clear, colourless and sterile isotonic solution for injection, with pH between 6.0 and 8.0. Each vial contains 6 ml of solution (6.0 MBq [6.6 MBq after implementation of NIST update][1], 0.162 mCi [0.178 mCi after implementation of NIST update][1]) Radium-223 dichloride at the reference date).
	Proposed (if applicable): Not applicable.

[1] Updated dose per revised NIST standardisation. The amount of radioactivity in the administered dose is unchanged; only the numerical value of the dose changed due to the revised standard.

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Table Part I.1 – Product(s) overview

Is/will the product be subject to additional monitoring in the EU?	Yes.

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Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Indication: CRPC with bone metastases

Xofigo® monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other LHRH analogues), or ineligible for any available systemic mCRPC treatment.

SI.1.1 Incidence and Prevalence

Globally, prostate cancer is the second most common cancer in men. According to the most recent World Health Organisation Global Burden of Cancer Study (GLOBOCAN) data (1, 2), an estimated 1.4 million men worldwide were newly diagnosed with prostate cancer in 2020, accounting for 14.6% of the cancers diagnosed in men. Incidence rates vary dramatically from 6.3 (South Central Asia) to 83.4 (Northern Europe) per 100,000 men across regions.
The incidence rate of prostate cancer is three-fold higher in countries with a high/very high development index (37.5 per 100,000) than in those with a low/medium human development index (HDI) (11.3 per 100,000). The 2020 incidence rate of prostate cancer was 63.4 per 100,000 men in Europe, with a 5-year prevalence estimate of 518.11 per 100,000 men.

For Germany, the Robert Koch Institute 2017 cancer report stated that the age standardised prostate cancer incidence rate in 2014 was 94.3 per 100,000 men (3). They estimated that this rate will be the same in 2018, with 57,370 new prostate cancer cases in 2014 and 60,700 new cases in 2018, respectively. The 5- and 10-year prevalence was estimated at 271,800 and 494,800 cases, respectively.

The 2018 analysis of the United States (US) National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program estimated that the age-adjusted incidence rate for prostate cancer was 111.3 per 100,000 men per year for the period of 2014-2018 (4). Of the newly diagnosed prostate cancer cases, 74% were diagnosed at the local stage, 13% at the regional stage, 7% at metastatic stage, and 6% were unstaged. A total of 248,530 incident cases were estimated for 2021, accounting for 13.1% of all new cancer cases. It was estimated that 3,245,430 men were living with prostate cancer in the US in 2018, and of these an estimated 227,180 are metastatic at initial diagnosis in addition to those who may progress after the initial diagnosis of localized disease.

Bone metastases in prostate cancer

Bone is the most common site for metastases in patients with prostate cancer. In a retrospective cohort study, Gandaglia *et al*. (5) identified patients aged ≥65 years in the SEER Medicare insurance program-linked database presenting with metastatic prostate cancer between 1991 and 2009. Of the 3,857 identified patients, 80.2% (n=3,093) had bone

metastases, 10.9% (n=422) had both, bone and visceral metastases, 6.1% (n=234) had visceral metastases, and 2.8% (n=108) had lymph node metastases. Roghmann *et al*. conducted a retrospective analysis of the US Nationwide Inpatient Sample database for the period of 1998–2010 (6). A weighted estimate of 443,929 patients with prostate cancer and bone metastases was recorded in US hospitals, which represents an overall national incidence of 23.74 per 100,000 men per year.

Although only a minority of men with newly diagnosed prostate cancer manifests bone metastases, a significant proportion will develop bone metastases over the course of the disease. In a population-based cohort study from Denmark, 23,087 incident cases of prostate cancer were identified in the time period 1999 to 2007 through the Danish National Patient Registry (7). At diagnosis, 3% of the patients had bone metastases recorded, the cumulative incidence increased to 7.7 % after one year and 16.6 % after five years of prostate cancer diagnosis. A validation study in the same database suggests that the true incidence of bone metastases is even higher (8). Approximately half of the patients in whom bone metastases developed also had a skeletal related event (SRE), defined as radiation to the bone, fracture or surgery to the bone. Diagnosis of bone metastases implicated a poor survival prognosis. One-year survival in this cohort was 87% (95% CI: 86.5-87.4) in men without bone metastases, 47.4 % (95% CI: 44.1-50.6) in those with bone metastases but no SRE and 39.9% (95% CI: 35.6-44.2) in men with bone metastases and SRE. Corresponding 5-year- survival was 55.8 % (95% CI: 54.9-56.7), 2.7% (95% CI: 2.2-3.4) and 0.7 % (95% CI: 0.6-1.0), respectively.

Among a cohort of 3,297 men with prostate cancer metastatic to bone identified in the SEER-Medicare database by McDougall *et al*. (9), 40% experienced ≥1 SRE (median follow-up, 19 months). Compared with men who remained SRE-free, men with ≥1 SRE had a twofold higher risk for death (hazard ratio [HR] = 2.29, 95% CI: 2.09-2.51). Pathological fracture was associated with the highest risk for death (HR = 2.77, 95% CI: 2.38-3.23). Among men with ≥1 SRE, emergency department visits were twice as frequent (incidence rate ratio = 2.0, 95% CI: 1.77-2.28) and hospitalizations were nearly 4 times as frequent (incidence rate ratio = 3.75, 95% CI: 3.20-4.40).

Castration resistance

Prostate cancer progression depends on androgen receptor signalling. CRPC is an advanced form of prostate cancer characterised by disease progression following surgical castration or pharmaceutical castration by androgen deprivation therapy (ADT) (10). Epidemiological data on CRPC incidence is scarce. In a systematic literature review, Kirby *et al*. (10) identified 5 studies reporting CRPC prevalence data. The data indicated that 10-20% of prostate cancer patients develop CRPC within approximately 5 years of follow-up. Two studies reported the prevalence of bone metastases present at diagnosis of CRPC. Together, ≥84% of the patients were shown to have metastases at diagnosis. Of those patients with no metastases present at diagnosis of CRPC, 33% could expect to develop them within 2 years. Most deaths are associated with development of mCRPC (11).

SI.1.2 Demographics of the Population in the Authorised Indication and Risk Factors

The risk of prostate cancer increases with age. According to the most recent NCI SEER cancer statistics review (12), prostate cancer is most frequently diagnosed among men aged 55 to 74 years (see Table SI.1), with a median age at diagnosis of 66 years.

Table SI.1: Percent of New Prostate Cancer Cases by Age Group in the US (12) from 2014-2018

Age (years)	Proportion (%)
<45	0.3
45-54	7.7
55-64	32.0
65-74	40.5
75-84	15.5
≥85	4.0

SEER Cancer Statistics Review 2014-2018

Prostate cancer risk is positively associated with a family history of prostate cancer. In a prospective cohort study from the United Kingdom (UK) by Perez-Cornago *et al*. (13) with 219,335 men, a family history of prostate cancer was associated with a hazard ratio (HR) of 1.94, (95% CI: 1.77-2.13). Randazzo *et al*. (14) analysed prostate cancer incidence in 4,932 Swiss men undergoing testing every 4 years, where 334 of those men had a positive prostate cancer family history. During a median follow-up duration of 11.6 years (interquartile range 10.3-13.3 years), the cumulative prostate cancer incidence was 18% in the subjects with a positive family history and 12% in those without family history, corresponding to an odds ratio (OR) of 1.6 (95% CI: 1.2-2.2; p=0.001).

In the prospective cohort study conducted by Perez-Cornago *et al*. (13) in the UK with 205,839 White, 1,077 mixed, 5,765 Asian, 3,279 Black, and 1,926 men of other ethnicity, the HR for Black vs White ethnicity was 2.61 (95% CI: 2.10–3.24), with no other ethnic group having an increased risk, as compared to Whites. Table SI.2 presents the age-adjusted incidence rates of prostate cancer by race in the US as reported by the NCI in 2018 (12).

Table SI.2: Prostate Cancer Incidence by Race/Ethnicity (12)

Race/ethnicity	Incidence per 100,000
All Races	111.3
White	104.1
White Hispanic	90.9
White Non-Hispanic	114.5
Black	175.8
Asian/Pacific Islander	57.7
American Indian/Alaska Native	53.1
Hispanic	90.9

SEER Cancer Statistics Review 2014-2018, Age-adjusted

Akinyemiju *et al*. (15) analysed SEER 2010-2013 data of 189,195 prostate cancer patients, (16.34% non-Hispanic Blacks, 73.88% non-Hispanic Whites, and 9.78% Hispanics). Non-Hispanic Blacks (OR=1.39, 95% CI: 1.31-1.48) and Hispanics (OR=1.39, 95% CI: 1.29-1.49) were more likely to have metastasis to the bone.

Saltus *et al*. conducted a retrospective cohort study of the US men aged ≥65 years with CRPC using the SEER-Medicare database during 2000-2011 and reported all patients were 65 years and older and the mean age at cohort entry was 76.6 years (65-100). The majority of patients was White (83.65), followed by Blacks (9.8%), Asian (2.1%), Hispanic (2.1%) (16).

No lifestyle factors associated with an increased prostate cancer risk were identified in the Perez-Cornago *et al*. study (13) and in a prospective cohort study with 75,216 men in the US (17).

SI.1.3 The Main Existing Treatment Options

Over the last two decades, the approval of life-prolonging therapies in mCRPC has substantially improved outcomes in men with mCRPC. These therapies include the use of cytotoxic chemotherapy with docetaxel and, cabazitaxel in post-docetaxel patients; novel anti-androgen receptor pathway-targeted agents, including abiraterone and enzalutamide; immunotherapy, such as sipuleucel-T (during initial therapy for asymptomatic or minimally symptomatic patients with mCRPC (18)); and the targeted alpha therapy Radium 223 dichloride.

Several well-known guidelines (18-21) recommend NAH drugs or docetaxel in addition to traditional ADT as the first-line treatment. Recent data show that patients are regularly treated systemically beyond the second-line treatment. All systemic therapy options (abiraterone acetate, cabazitaxel, docetaxel, enzalutamide, pembrolizumab, Radium-223-dichloride, PARP inhibitors [olaparib and rucaparib], as monotherapy or in combination with abiraterone) are also used in the third and later therapy lines. Lu-177-PSMA-617 was recently approved (based on positive results in the recently completed Phase III VISION trial (22)) for third line treatment. New treatment options in clinical development include AKT inhibitors and further

PSMA targeted drugs like Th-227-PSMA and as well as several other PARP inhibitors (e.g., talazoparib and niraparib).

In patients with painful bone metastases, external beam radiotherapy although effective, remains a palliative intervention even when given as a single fraction. Approval has been granted in many countries, including the US and EU, for bisphosphonate zoledronic acid and denosumab, both of which delay the onset of SREs in CRPC patients with bone metastases. Apart from Radium-223 dichloride, however, no bone-targeted drug has been associated with improved survival (20).

The implementation of the existing treatment guidelines for the use of therapeutic options in the treatment of mCRPC differs between geographic regions. Various databases and registers provide information on the therapies used in different treatment lines. While docetaxel is approved for first-line treatment of mCRPC, more recently, NAH added to backbone ADT has replaced docetaxel as the first-line treatment of choice in this condition (20, 21). Recent data show that patients are regularly treated systemically beyond the second-line. All systemic therapy options (abiraterone acetate, cabazitaxel, docetaxel, enzalutamide, PARP inhibitors, Lu-177-PSMA-617 and Radium-223-dichloride) are also used in the third and later therapy lines.

An analysis of mCRPC patients in the Flatiron Health database, which contains real-world EHR data from more than 2 million patients with cancer, in the period from JAN 2013 to JUN 2017 showed that among 2,559 mCRPC patients, the androgen receptor targeted therapies abiraterone and enzalutamide were the most common first- and second-line treatments in mCRPC patients (65.35% of first-line and 53.56% of second-line therapies), and they were frequently used back-to-back. The most common third-line therapies were docetaxel (24.40%), enzalutamide (16.43%) and abiraterone (14.25%), while the most common fourth-line therapies were docetaxel (25.26%), cabazitaxel (22.63%), and enzalutamide (8.95%). The percentage of patients treated with Radium-223 monotherapy use increased over subsequent lines of therapy, at 2.37% in the first-line setting, 3.30% in the second-line setting, 7.97% in the third-line setting, and 8.42% in the fourth-line setting (23, 24).

SI.1.4 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Prostate cancer deaths are typically the result of mCRPC, and historically the median survival for men with mCRPC has been less than 2 years (25). As outlined in section SI.1.1, the most common site of metastases is the skeletal system.

The Eurostat 2020 report (26) states that 65,216 men died from prostate cancer in the EU-27 in 2017, equivalent to 5.7% of all deaths from cancer and 2.9% of the total number of deaths from any cause among both genders. The share of male deaths attributed to prostate cancer was 2.9%, double the share for the whole population.

A diagnosis of prostate cancer that is localised or regional carries a lower risk of mortality from the disease compared to cancer metastasized to distant sites. In the US, the (2014-2018) 5-year survival rate was 100.0% for localised and regional prostate cancer, respectively, but

30.6% for metastatic prostate cancer (12). Among the above-mentioned 3,093 men with bone metastases identified in the SEER-Medicare-linked database in the retrospective cohort study by Gandaglia *et al*. (5), median overall survival and cancer-specific survival were 24 months (95% CI: 22.9-25.1) and 32 months (95% CI: 29.9-34.0), respectively. In a recent Danish population-based cohort study assessing survival after diagnosis of bone metastasis by primary cancer type, 1-year, 3-year and 5-year survival estimates were 35% (95% CI: 34-37), 12% (95% CI: 11-13), and 6% (95% CI: 5-7), respectively, among the 5,941 included prostate cancer patients with bone metastasis (27).

The development of bone metastases is not only a serious threat to the patients' survival, but also to the quality of life (QoL). Both survival and QoL are impacted by the extent of metastases (28). Skeletal related events (SREs) involving bone metastasis typically consist of high-morbidity clinical episodes, including pathological fractures, spinal cord compression, bone metastasis that requires surgical stabilisation, or radiotherapy for pain relief or prevention of fractures (9).

The Japanese Foundation for Promotion of Cancer Research estimated that 12,200 deaths due to prostate cancer occurred in 2017, accounting for 5% of all cancer deaths in men (29). For Korea, the National Cancer Center reports that 3.5% of all 47,079 cancer deaths in men, occurred due to prostate cancer (30). In China, the estimated number of deaths due to prostate cancer in 2015 was 26,600 (31).

In the study cohort of patients identified in SEER-Medicare data, the average time from initial diagnosis of prostate cancer to development of CRPC was 42 months. The majority (62%) had an interval of more than 2 years from initial prostate cancer to development of CRPC and only 15% of the cohort developing within 1 year of the initial diagnosis (Saltus 2019). Among the CPRC patients (n = 2,234), 75% (n = 1,689) died during the follow-up. The median survival time after cohort entry was 1.2 years (95%CI: 1.1-1.3), and the survival probabilities at 1,3,5 years were 56% (95%CI: 54-58), 17% (95%CI: 15-18), and 9% (95%CI: 7-11), respectively (16).

In the population-based cohort study from Denmark described in Section SI.1.1 (7), the 1- and 5-year cumulative incidence of SREs in patients with bone metastasis was 46.1% (95% CI: 44.4-47.8) and 53.8% (95% CI: 52.0-55.5), respectively. Of the 1,691 men with at least 1 SRE after bone metastasis diagnosis, the most frequently recorded SREs were radiation to bone in 60.1%, followed by spinal cord compression in 26.4%, pathological or osteoporotic fracture in 10.0% and surgery to bone in 3.5%. Diagnosis of bone metastases implicated a poor survival prognosis. One-year survival was 87.0% (95% CI: 86.5-87.4) in patients without bone metastases, 47.4% (95% CI: 44.1-50.6) in those with bone metastases but no SRE, and 39.9% (95% CI: 35.6-44.2) in men with bone metastases and SRE. Corresponding 5-year survival was 55.8 % (95% CI: 54.9-56.7), 2.7% (95% CI: 2.2-3.4), and 0.7 % (95% CI: 0.6-1.0), respectively.

Among a cohort of 3,297 men with prostate cancer metastatic to bone identified in the SEER-Medicare database by McDougall *et al*. (9), 40% experienced ≥1 SRE (median follow-up, 19 months). Compared with men who remained SRE-free, men with ≥1 SRE had a twofold higher risk for death (HR=2.29, 95% CI: 2.09-2.51). Pathological fracture was

associated with the highest risk for death (HR=2.77, 95% CI: 2.38-3.23). Among men with ≥1 SRE, emergency department visits were twice as frequent (incidence rate ratio [IRR] = 2.0, 95% CI: 1.77-2.28) and hospitalisations were nearly 4 times as frequent (IRR=3.75, 95% CI: 3.20-4.40).

SI.1.5 Concomitant medication(s) in the target population

CRPC patients usually receive anti-hormone treatment such as human luteinizing hormone-releasing hormone agonists/ antagonists or antiandrogens, glucocorticoids, oestrogen, pain medication (opioids and non-opioids) and external beam radiation therapy (EBRT). Xofigo® is contraindicated in combination with abiraterone acetate and prednisone/prednisolone due to safety issues of fracture. In addition, as preventive measures for osteoporosis or fractures many patients receive bisphosphonates (etidronic acid, clodronic acid, pamidronic acid, alendronic acid, tiludronic acid, ibandronic acid, risedronic acid, and zoledronic acid) and denosumab.

SI.1.6 Important Comorbidities

Important comorbidities in the target population comprise typical and frequent conditions related to the age, or genetic predisposition such as Breast Cancer Gene (BRCA) or DNA damage response (DDR) genes or treatments received for the underlying cancer (32). There is also evidence of an increased risk of thromboembolic events from underlying malignancy. However, there are also other increased risks such as cardiovascular disease, diabetes mellitus, and metabolic syndrome and increased risk of bone loss and fractures in patients receiving ADT for prostate cancer (33-38).Pre-existing chronic conditions associated with the secondary osteoporosis and additional risk factors of osteopenia and osteoporosis (such as advanced age, low bone mineral density, low body weight, family history of osteoporosis, cigarette smoking, excessive alcohol consumption) might also significantly contribute to the development of bone tissue loss and bone fractures in prostate cancer patients. Osteoporosis can be a silent disease because it can weaken bones over the years without causing symptoms. Some medications widely used for prostate cancer treatment are also associated with the high risk of developing osteoporosis and osteoporosis-related fractures which include chemotherapy, corticosteroids, ADTs, anti-androgens, and gonadotropin-releasing hormone agonists. Multifactorial etiology of the bone fractures in prostate cancer patients includes disease-associated risk (including bone metastases), medications-associated risk and pre-existing risk which makes the clear differentiation of the main cause of bone fractures challenging.

In a retrospective analysis of a cohort of 3,106 patients who died of prostate cancer between JAN 2001 and DEC 2013, selected from Quebec public health care insurance databases (mean age at death 77.8 years, 95% CI: 77.5-78.0), the following comorbidities were present (39): diabetes in 592 patients (19.1%), dyslipidaemia in 1,195 (38.5%), hypertension in 2,040 (65.7%), coronary artery disease in 830 (26.7%), chronic heart failure in 335 (10.8%), arrhythmia in 499 (16.1%), and cerebrovascular disease in 140 (4.5%).

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Key safety findings from non-clinical studies and relevance to human usage:

Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single- and repeat-dose toxicity	
• In rats, the main findings were reduced body weight gain, haematological changes, reduced serum alkaline phosphatase and microscopic findings in the bone marrow (depletion of haematopoietic cells, fibrosis), spleen (secondary extra-medullary haematopoiesis) and bone (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/disorganisation of the physis/growth line). These findings were related to radiation-induced impairment of haematopoiesis and a reduction of osteogenesis and started at the lowest activity of 22 kilobecquerel (kBq) per kg body weight (0.4 times the clinically recommended dose). • In dogs, haematological changes were observed starting at the lowest activity of 55 kBq/kg, the clinically recommended dose. Dose-limiting myelotoxicity was seen in dogs after single administration of 497 kBq Radium-223 dichloride per kg body weight (9 times the clinically recommended activity).	• Overall systemic toxicity effects are consistent with mode of action of Radium-223 dichloride to target new bone formation, e.g., bone metastases. Radiation-induced impairment of haematopoiesis and inhibition of osteogenesis have potential relevance in patients with advanced cancer. Specific non-clinical findings most relevant to human usage are described in greater detail below.
<u>Late bone marrow effects:</u> • In rats given a single injection of 0, 1,027, 2,054 or 3,081 kBq/kg (0, 1,135, 2,270 or 3,404 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update)[2] of Radium-223 dichloride, followed by a 29 day observation period, a slight to moderate proliferative fibro-osseous lesion in the femur was seen in all treated groups and minimal to slight fibrosis of the sternum was seen in males given 2,054 KBq/kg (2,270 kBq/kg after implementation of NIST update)[2] and in both sexes given 3,081 kBq/kg (3,404 kBq/kg after implementation of NIST update)[2]. In single and repeated-dose (every 4-weeks x 4) rat toxicity study with an extended observation period of 12 months after the last dose, minimal to slight fibro-osseous lesion in the sternum was seen in males	• The late bone marrow effects of fibrosis seen histopathologically in Radium-223 dichloride non-clinical toxicity studies have potential relevance for the patient population of cancer patients with advanced cancer.

[2] Updated dose per revised NIST standardisation. The amount of radioactivity in the administered dose is unchanged; only the numerical value of the dose changed due to the revised standard.

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
given the single high dose of 1,300 kBq/kg (1,436 kBq/kg after implementation of NIST update)[2] and the repeated mid dose of 325 kBq/kg x 4 (359 kBq/kg x 4 after implementation of NIST update)[2], and in both sexes given the repeated high dose of 650 kBq/kg x4 (718 kBq/kg x 4 after implementation of NIST update)[2]. In a 12-month repeated-dose rat study (once per month x12 followed by a 4-week observation period) fibrosis associated with decreased cellularity of the bone marrow was seen in the marrow cavity of the sternum in male and female rats given 100 kBq/kg (110 kBq/kg after implementation of NIST update)[2] Radium-223 dichloride. • In dogs given a total of 6 injections of the human therapeutic dose of 50 kBq/kg (55 kBq/kg after implementation of NIST update)[2] Radium-223 dichloride (once every 4 weeks, followed by a 4 week observation period) the bone marrow of the proximal femur was more gelatinous than in controls and there was a general decline in the sternal and vertebral bone marrow haematopoietic cellularity. The marrow hypocellularity was largely caused by minimal to marked myelofibrosis (the replacement of haematopoietic cells in the marrow cavity by fibrous tissue) and minimal to slight marrow infiltration of vacuolated/granulated histocytes. <u>Bone effects in rodents:</u> • Depletion of osteoblasts and osteocytes was seen in mice and rats given single doses and in rats given repeated doses of Radium-223 dichloride. Associated effects seen after an extended period after single administration or with repeated administration include abnormal/disorganised growth plate, hyperostosis, decreased bone mass, fibro-osseous lesion in the bone socket of teeth, loss of teeth, and abnormal tooth growth/morphology. • Refer to subsection “bone fractures” in the “safety pharmacology” section below for additional information on the currently ongoing studies assessing the possible role of Radium-223 dichloride in bone fractures.	• Effects are consistent with mode of action of Radium-223 dichloride to target new bone formation, e.g., bone metastases. The adverse bone effects in rats may not be that relevant for the adult human patient population since, unlike adult humans, rodents have continuously growing bone, including growth plates and teeth. These adverse effects, however, could be relevant if off-label use in children occurs.
Reproductive and developmental toxicity • Specific reproductive and developmental toxicity studies have not been conducted. Histopathological	• A radiation dosimetry study of Radium-223 dichloride in patients

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
evaluations of reproductive tissues from systemic toxicity studies revealed an effect on the testis (minimal numbers of abnormal spermatocytes [giant cells] in some tubules) in males given a single dose of 2,054 or 3,081 kBq/kg (2,270 or 3,404 kBq/kg after implementation of NIST update)[3] Radium-223 dichloride and an effect on the uterus (endometrial stromal polyps) seen after an extended period in female rats given a single dose of 325 or 1,300 kBq/kg (359 or 1,436 kBq/kg after implementation of NIST update)[3], or given repeated doses of 325 kBq/kg x4 or 650 kBq/kg x 4 (359 kBq/kg x4 or 718 kBq/kg x 4 after implementation of NIST update)[3] Radium-223 dichloride.	with CRPC and bone metastases showed no specific uptake of Radium-223 dichloride in the testes, with a very low calculated total absorbed dose (0.00008 Gy/MBq). • The potential for Radium-223 dichloride to cause toxic effects in the male gonads in cancer patients with CRPC is therefore very low but cannot be excluded. • There is potential for adverse reproductive or developmental effects of Radium-223 dichloride in women of child-bearing age or in children. • Due to the known effects of radiation, there is potential for adverse effects on male and female reproduction, including fertility, and on the developing foetus, including teratogenicity.
Genotoxicity • Studies on the mutagenic potential of Radium-223 dichloride have not been performed. Alpha particles emitted by radionuclides, irrespective of their source, cause chromosomal aberrations in circulating lymphocytes and gene mutations in humans *in vivo*.	• There is potential that second primary malignancies could develop in patients treated with Radium-223 dichloride, however the risk may be low as median life expectancy of the target population is much shorter than the latency period of radiation-induced second primary malignancies.
Carcinogenicity • Studies on the carcinogenic potential of Radium-223 dichloride have not been performed. Alpha particles emitted by radionuclides, irrespective of their source, are carcinogenic in humans. • The presence of neoplastic changes, other than	• There is potential that second primary malignancies could develop in patients treated with Radium-223 dichloride, however the risk may be low as median life expectancy of the target

[3] Updated dose per revised NIST standardisation. The amount of radioactivity in the administered dose is unchanged; only the numerical value of the dose changed due to the revised standard.

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
osteosarcomas, was reported in the longer term (12 to 15 month) rat intravenous toxicity studies conducted with Radium-223 dichloride. Large experimental animal studies with parenterally administered Radium, primarily using dogs, but some using rats and mice, have demonstrated that Radium-224, Radium-226, and Radium-228 can induce bone cancers and leukaemias in these species. • The most unexpected finding was the induction of intraocular melanomas in beagle dogs by Radium-226. These tumours have not been seen in any of the human studies.	population is much shorter than the latency period of radiation-induced second primary malignancies.
Safety pharmacology • No significant effects were seen on vital organ systems, i.e., cardiovascular (dog), respiratory or central nervous systems (rat), after single dose administration of activities from 497 to 1,100 kBq per kg body weight (9 [dog] to 20 [rat] times the clinically recommended activity).	
<u>Bone fractures:</u> • Studies in the murine model of intratibial prostate cancer cell growth comparing effects in tumour-bearing bone versus contralateral non-tumour bearing bone were conducted. The aim of the non-clinical studies was to determine the individual effects of abiraterone acetate (AA) versus prednisone (P) versus AA & P combination therapy versus Radium-223 dichloride (Ra-223) and potential synergistic effects of combination therapy. Regarding efficacy, PSA levels were similarly reduced at sacrifice upon Ra-223, AA, AA/P, and Ra-223/AA/P treatment indicating the absence of triple combination-specific additive anti-tumor effects. An AA/P treatment-induced reduction of Ra-223 incorporation may mediate the lack of additive anti-tumor effects in the Ra-223/AA/P group. Regarding bone health, Ra-223/AA/P specifically induced a transient increase in bone resorption and inhibited both periosteal and trabecular new bone formation but did not lead to structural or biomechanical bone changes. This preclinical mechanism may nevertheless contribute to the increased fragility observed in the clinics and may explain the beneficial clinical effects of bone	• An increased risk of bone fractures was observed in the Ra-223/AA/P arm of the 15396/ ERA-223 study. No clear pattern of fractures leading to the imbalance between the treatment arms has been identified. Preclinical mechanisms may nevertheless contribute to the increased fragility observed in the clinics and may explain the beneficial clinical effects of bone resorption-inhibiting bisphosphonates and denosumab. However, several species- and model-related factors may limit the translational relevance of these findings. • Xofigo® is contraindicated in combination with abiraterone acetate and prednisone/prednisolone (see SmPC Section 4.4).

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
resorption-inhibiting bisphosphonates and denosumab. However, several species- and model-related factors may limit the translational relevance of these findings.	
Ocular toxicity: • Intravenous injected Radium-22 in dogs was deposited in the melanin granules of pigmented cells and rod like organelles of the tapetum lucidum in the eye. • Retinal detachment was seen in dogs after a single injection of Radium-223 dichloride at dose levels 150 kBq/kg and 450 kBq/kg (166 kBq/kg and 497 kBq/kg respectively after implementation of NIST update)[4].	• Since humans do not have a tapetum lucidum, the clinical relevance of these findings for humans is uncertain. No case of retinal detachment has been reported in clinical trials.
Other toxicity-related information or data Osteosarcoma in rats: • Osteosarcomas, a known effect of bone-seeking radionuclides particularly in skeletally immature and growing animals, were observed after an extended period of greater than 6 months in rats given a single injection or 4 monthly injections of 325 kBq/kg (359 kBq/kg after implementation of NIST update)[3] each followed by a 12-month observation period, and in rats given 12 monthly injections of 25 to 100 kBq (28 to 110 kBq after implementation of NIST update)[3] each followed by a 4-week observation period. In the 12-month study, after more than 6 months of treatment, the osteosarcomas were principally seen in bone and skeletal muscle, but metastases were also observed in the lung and (in 1 rat) the adrenal gland. • In these long-term rat studies, animals were found dead or were sacrificed for humane reasons mainly due to osteosarcomas.	• No case of osteosarcoma has been reported in clinical studies with Radium-223 dichloride. The risk for patients to develop osteosarcomas is unknown at present.

CRPC: Castration-resistant prostate cancer, Gy: Gray, kBq: Kilobecquerel, MBq: Megabecquerel, NIST: National Institute of Standards and Technology.

[4] Updated dose per revised NIST standardisation. The amount of radioactivity in the administered dose is unchanged; only the numerical value of the dose changed due to the revised standard.

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There is no need for additional non-clinical data if the product is to be used in special populations.

Conclusions on Non-Clinical Data

The following list of safety concerns have been identified from non-clinical data and will be included as important identified/potential risk or missing information in Part II: Module SVII:

Table SII.2: List of safety concerns identified from non-clinical data

Safety concerns
Important identified risks (confirmed by clinical data) • Bone fractures*
Important potential risks (not refuted by clinical data or which are of unknown significance): • Late bone marrow toxicity • Myelodysplastic syndrome/ Acute myeloid leukaemia • Bone sarcoma • Second primary malignancies (other than myelo-dysplastic syndrome/acute myeloid leukaemia and bone sarcoma)
Missing information • None

* The increased risk of bone fractures was first identified in clinical studies. Non-clinical studies to further characterise the risk are currently ongoing.

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Exposure data was pooled for integrated analysis and includes datasets from 12 clinical studies described in Table SIII.1. In addition, safety data from the recently completed re-treatment safety study 16506 recruiting 44 subjects with castration-resistant prostate cancer with bone metastases, and the data from the post-authorisation safety study (PASS) 17399 are presented in Part II: Module SVII. PASS 17399 was a single-arm descriptive observational drug utilisation study based on secondary data collection of 310 patients treated with Xofigo® in Sweden.

Study 15396 (ERA 223), a phase III randomised, double-blind, placebo-controlled trial of Radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant mCRPC (ERA 223) is not included in the pooled data as all patients received combination treatment with abiraterone and prednisone. A total of 806 patients were included in 15396.

Table SIII.1: Clinical studies for integrated analysis of safety

Study #	Description
ATI-BC-1; 15522	A phase I open-label, multicentre, dose-escalating study of Radium-223 dichloride in advanced prostate or breast cancer patients with skeletal metastases.
BC1-02; 15280	A phase II randomised, placebo-controlled, multicentre study in prostate cancer patients with painful bone metastases to evaluate the efficacy of repeated Radium-223 dichloride injections.
BC1-03; 15305	A phase II double-blind, dose-response, multicentre study of Radium-223 dichloride for the palliation of painful bone metastases in hormone refractory prostate cancer.
BC1-04; 15304	A phase II double blind, randomised, dose finding, repeat dose, multicentre study of Radium-223 dichloride for the treatment of patients with hormone refractory prostate cancer and skeletal metastases.
BC1-05; 15302	A phase I open-label, dosimetry, biodistribution and pharmacokinetic study of Radium-223 dichloride in patients with hormone refractory prostate cancer and skeletal metastases.
BC1-06; ALSYMPCA; 15245	A phase III double-blind, randomised, multiple dose multicentre study of Radium-223 dichloride in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases.
BC1-08; 15303	A phase I, open-label, single ascending-dose study to assess safety, pharmacokinetics, biodistribution and radiation dosimetry of intravenous doses of Radium-223 dichloride injection in patients with hormone refractory prostate cancer and skeletal metastases.
15354	Uncontrolled, open-label, non-randomised phase I study to investigate safety, biodistribution, radiation dosimetry and pharmacokinetics of a single dose of Radium-223 dichloride in Japanese patients with castration-resistant prostate cancer and bone metastases.
15397	A phase III, single-arm, international, prospective, interventional, open-label, multicentre study of Radium-223 dichloride in the treatment of patients with

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Table SIII.1: Clinical studies for integrated analysis of safety

Study #	Description
	castration-resistant prostate cancer with bone metastases.
16430	A single-arm, open-label, multicentre, phase II study of Radium-223 dichloride in the treatment of Japanese patients with symptomatic castration-resistant prostate cancer with bone metastases.
16507	A three arm randomised, open-label phase II study of standard dose versus high dose and versus extended standard dose Radium-223 dichloride in castration-resistant prostate cancer metastatic to the bone.
16544	A randomised open-label phase IIa study evaluating quantified bone scan response following treatment with Radium-223 dichloride alone or in combination with abiraterone acetate or enzalutamide in subjects with castration-resistant prostate cancer who have bone metastases.

For the purpose of exposure and event rate analyses, these twelve studies are further subdivided in 3 data pools.

- **Pool 1**: Safety data from the randomised, double-blind, placebo-controlled studies BC1-02 (Phase II) and BC1-06 (Phase III).
  Rationale: Trials in this pool, with a DLP of 15 JUL 2011, though using different length of treatment, i.e., 4 treatments in BC1-02 versus 6 treatments in BC1-06, used a randomised controlled design, allowing, taking time into consideration, direct analytical comparisons between the Xofigo® and placebo arm. They also both used a dose of 50 kBq/kg (55 kBq/kg after implementation of the NIST update)[5] given at 4 week intervals.
- **Pool 2**: Safety data from single and multiple dose uncontrolled phase I and phase II studies, i.e., from studies ATI-BC-1, BC1-03, BC1-04, BC1-05 and BC1-08 and randomised, double-blind, placebo-controlled studies BC1-02 and BC1-06 were pooled for an integrated analysis.
  Rationale: Safety data from all clinical studies with Xofigo® with a DLP of 15 JUL 2011. These included randomised, double-blind, placebo-controlled studies BC1-02 and BC1-06 and other studies i.e., ATI-BC-1, BC1-03, BC1-04, BC1-05 and BC1-08. Dose of Xofigo® ranged from 5 kBq/kg (6 kBq/kg after implementation of the NIST update)6 body weight (b.w.) to 250 kBq/kg (276 kBq/kg after implementation of the NIST update)6 b.w. in these studies. Subject populations were comparable, in that they all had prostate cancer with bone metastases and there were 10 patients with breast cancer and with bone metastases in ATI-BC-1, which were included in the analysis.

[5] Updated dose per revised NIST standardisation. The amount of radioactivity in the administered dose is unchanged; only the numerical value of the dose changed due to the revised standard.

- **Pool 3**: Xofigo® monotherapy pool including safety data from single dose uncontrolled phase I study 15354, single arm open label phase II 16430 and phase III 15397 studies, randomised open label phase II studies 16507 and 16544, and the randomised, double-blind, placebo-controlled phase III study BC1-06.
  Rationale: Trials in this monotherapy pool, with a DLP of 01 JUN 2018, were selected as they offer safety information with Xofigo® treatment only in a relatively large number of patients (1,028). Pooled safety data includes the entire safety population in trials 15354, 15397 and 16430, Xofigo® arm in trial BC1-06 (main study period), Xofigo® monotherapy arm in study 16544, and the standard Xofigo® dose arm in study 16507. All patients in the pool 3 were male.

Detailed data on demographics and exposure to Radium-223 dichloride are available for 633 patients in pool 1, for 904 patients in pool 2, and for 1,028 patients in pool 3.

In pool 2, there are 2 subjects who were treated twice during the study ATI-BC-1.
As 9 months had elapsed between the two treatment periods in both cases, data from both the original injection and the re-injection are summarised separately, thereby counting these subjects twice each.

Detailed exposure data analysis is presented in Table SIII.2 through Table SIII.19:

Table SIII.2: Duration of exposure (safety analysis set) – pool 1

Indication: CRPC with bone metastases

	Xofigo®		Placebo	
Duration of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
≤ 4 weeks	24	5.23	32	7.30
> 4 weeks - 8 weeks	36	38.47	41	47.30
> 8 weeks - 12 weeks	51	105.23	37	79.17
> 12 weeks – 16 weeks	82	241.23	50	148.80
> 16 weeks - 20 weeks	70	289.47	36	150.00
> 20 weeks - 24 weeks	349	1,696.90	132	640.70
> 24 weeks	21	122.43	4	23.43
Total	**633**	**2,498.97**	**332**	**1,096.70**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp3.sas 22OCT12 14:29
Source: Integrated Analysis of Safety for Alpharadin – Table 1.1.3/1 - Data on file

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Table SIII.3: Duration of exposure (safety analysis set) – pool 2

Indication: CRPC/breast cancer with bone metastases		
Duration of exposure	**Persons**	**Person time[a]**
≤ 6 weeks	191	42.63
6 > - ≤12 weeks	91	183.13
12 > - ≤ 24 weeks	601	2,521.57
> 24 weeks	21	122.43
Total	**904**	**2,869.77**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp.sas 22OCT12 14:28
Source: Integrated Analysis of Safety for Alpharadin – Table 4.1.3/1.1 - Data on file

Table SIII.4: Duration of exposure (safety analysis set) – pool 3

Indication: CRPC with bone metastases		
Duration of exposure	**Persons**	**Person time[a]**
≤ 6 weeks	135	87.0
6 > - ≤12 weeks	95	193.3
12 > - ≤ 24 weeks	739	3,302.8
> 24 weeks	59	351.9
Total	**1,028**	**3,935.0**

[a] in months (for calculation, a month equals 30 days)
Note: exposure is derived as (Day of last dose minus day of first dose) + 1
Global Integrated Analysis: /by sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
Source: 20180612_bay888223_rmp_update - Data on file

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Table SIII.5: Duration of exposure by number of injections (safety analysis set) – pool 1

Indication: CRPC with bone metastases				
	Xofigo®		**Placebo**	
Number of injections	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
1 injection	19	0.63	25	0.83
2 injections	39	39.33	41	41.00
3 injections	50	100.67	38	75.43
4 injections	88	261.40	55	161.63
5 injections	49	195.40	29	117.90
6 injections	388	1,901.53	144	699.90
> 6 injections	0	0	0	0
Total	**633**	**2,498.97**	**332**	**1,096.70**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp3.sas 22OCT12 14:29
Source: Integrated Analysis of Safety for Alpharadin – Table 1.1.3/2 - Data on file

Table SIII.6: Duration of exposure by number of injections (safety analysis set) – pool 2

Indication: CRPC/breast cancer with bone metastases		
Number of injections	**Persons**	**Person time[a]**
1 injection	153	5.10
2 injections	68	97.60
3 injections	155	400.93
4 injections	89	263.53
5 injections	51	201.07
6 injections	388	1,901.53
> 6 injections	0	0
Total	**904**	**2,869.77**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp.sas 22OCT12 14:28
Source: Integrated Analysis of Safety for Alpharadin - Table 4.1.3/2.1 - Data on file

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Table SIII.7: Duration of exposure by number of injections (safety analysis set) – pool 3

Indication: CRPC with bone metastases		
Number of injections	**Persons**	**Person time[a]**
1 injection	48	1.6
2 injections	94	97.4
3 injections	85	174.0
4 injections	111	336.6
5 injections	84	337.6
6 injections	606	2,987.8
Total	**1,028**	**3,935.0**

[a] in months (for calculation, a month equals 30 days)
Note: exposure is derived as (Day of last dose minus day of first dose)+1
Global Integrated Analysis: /by-sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
Source: 20180612_bay888223_rmp_update - Data on file

Table SIII.8: Duration of exposure by age group (safety analysis set) – pool 1

Indication: CRPC with bone metastases				
	Xofigo®		**Placebo**	
Age group	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
< 65 years	157	626.70	76	246.07
65-74 years	266	1,063.80	148	501.83
75-84 years	200	781.83	101	334.23
85+ years	10	26.63	7	14.57
Total	**633**	**2,498.97**	**332**	**1,096.70**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp5.sas 22OCT12 14:29
Source: Integrated Analysis of Safety for Alpharadin – Table 1.1.3/5 - Data on file

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Table SIII.9: Duration of exposure by age group (safety analysis set) – pool 2

Indication: CRPC/breast cancer with bone metastases

Age group	Persons	Person time[a]
< 65 years	234	718.67
65-74 years	384	1,232.80
75-84 years	273	883.20
85+ years	13	35.10
Total	**904**	**2,869.77**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp5.sas 22OCT12 14:29
Source: Integrated Analysis of Safety for Alpharadin – Table 4.1.3/5 - Data on file

Table SIII.10: Duration of exposure by age group (safety analysis set) – pool 3

Indication: CRPC with bone metastases

Age group	Persons	Person time[a]
< 65 years	251	940.7
65-74 years	440	1,705.7
75-84 years	319	1,235.8
85+ years	18	52.7
Total	**1,028**	**3,935.0**

[a] in months (for calculation, a month equals 30 days)
Note: exposure is derived as (Day of last dose minus day of first dose)+1
Global Integrated Analysis: /by-sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
Source: 20180612_bay888223_rmp_update - Data on file

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Table SIII.11: Duration of exposure by gender (safety analysis set) – pool 1

Indication: CRPC with bone metastases

	Xofigo®		Placebo	
Gender	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Male	633	24,98.97	332	1,096.70
Female	0	0	0	0
Total	**633**	**2,498.97**	**332**	**1,096.70**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp3.sas 22OCT12 14:29
Source: Integrated Analysis of Safety for Alpharadin – Table 1.1.3/4.6 - Data on file

Table SIII.12: Duration of exposure by gender (safety analysis set) – pool 2

Indication: CRPC/breast cancer with bone metastases

Gender	**Persons**	**Person time[a]**
Male	894	2,869.43
Female	10	0.33
Total	**904**	**2,869.77**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp.sas 22OCT12 14:28
Source: Integrated Analysis of Safety for Alpharadin – Table 4.1.3/4.6.1 - Data on file

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Table SIII.13: Duration of exposure by ethnic or racial origin (safety analysis set) – pool 1

Indication: CRPC with bone metastases

	Xofigo®		Placebo	
Race	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
White	595	2,346.33	315	1,032.90
Black or African American	10	37.13	3	9.63
Asian	21	92.60	12	49.37
Other	7	22.90	2	4.80
Total	**633**	**2,498.97**	**332**	**1,096.70**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp3.sas 22OCT12 14:29
Source: Integrated Analysis of Safety for Alpharadin – Table 1.1.3/4.2 - Data on file

Table SIII.14: Duration of exposure by ethnic or racial origin (safety analysis set) – pool 2

Indication: CRPC/breast cancer with bone metastases

Race	**Persons**	**Person time[a]**
White	862	2,709.93
Black or African American	10	37.13
Asian	23	96.93
Other	9	25.77
Total	**904**	**2,869.77**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp.sas 22OCT12 14:28
Source: Integrated Analysis of Safety for Alpharadin – Table 4.1.3/4.2.1 - Data on file

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Table SIII.15: Duration of exposure by ethnic or racial origin (safety analysis set) – pool 3

Indication: CRPC with bone metastases

Race	Persons	Person time[a]
White	675	2,659.9
Black or African American	14	46.9
Asian	325	1,182.7
Other	7	22.9
Not reported	7	22.5
Total	**1,028**	**3,935.0**

[a] in months (for calculation, a month equals 30 days)
Note: exposure is derived as (Day of last dose minus day of first dose) + 1
Global Integrated Analysis: /by-sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
Source: 20180612_bay888223_rmp_update - Data on file

Table SIII.16: Duration of exposure by kidney function at baseline (safety analysis set) – pool 1

Indication: CRPC with bone metastases

	Xofigo®		Placebo	
Kidney function at baseline	Persons	Person time[a]	Persons	Person time[a]
eGFR ≥60 mL/min/1.73m²	567	2,253.50	285	940.83
eGFR <60 mL/min/1.73m²	66	245.47	46	153.00
Missing	0	0	1	2.87
Total	**633**	**2,498.97**	**332**	**1,096.70**

[a] in months
eGFR = estimated glomerular filtration time
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp3.sas 22OCT12 14:29
Source: Integrated Analysis of Safety for Alpharadin – Table 1.1.3/4.3 - Data on file

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Table SIII.17: Duration of exposure by kidney function at baseline (safety analysis set) – pool 2

Indication: CRPC/breast cancer with bone metastases		
Kidney function at baseline	**Persons**	**Person time[a]**
eGFR ≥60 mL/min/1.73m²	802	2,573.90
eGFR <60 mL/min/1.73m²	92	272.87
Missing	10	23.00
Total	**904**	**2,869.77**

[a] in months
eGFR = estimated glomerular filtration time
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp.sas 22OCT12 14:28
Source: Integrated Analysis of Safety for Alpharadin – Table 4.1.3/4.3.1 - Data on file

Table SIII.18: Duration of exposure by hepatic function at baseline (safety analysis set) – pool 1

Indication: CRPC with bone metastases				
	Xofigo®		**Placebo**	
Hepatic function at baseline	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Normal (0)	480	1,969.10	241	853.03
Impaired (1,2,3)	149	513.47	89	236.10
Missing	4	16.40	2	7.57
Total	**633**	**2,498.97**	**332**	**1,096.70**

[a] in months
ALT = Alanine transaminase, AST = Aspartate transaminase, ULN = Upper limit of normal
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Hepatic Function at Baseline:
[0 = max(baseline AST/ULN, baseline ALT/ULN)<=1, 1 = 1 < max(baseline AST/ULN, baseline ALT/ULN)<=3
2 = 3 < max(baseline AST/ULN, baseline ALT/ULN)<=5, 3 = 5 < max(baseline AST/ULN, baseline ALT/ULN)
0 = (bilirubin/ULN) <= 1, 1 = 1< baseline bilirubin/ULN <= 1.5, 2 = (1.5< baseline bilirubin/ULN<=3)
3 = (3 < baseline bilirubin/ULN), classified as the max of AST/ALT and bilirubin scores]
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp3.sas 22OCT12 14:29
Source: Integrated Analysis of Safety for Alpharadin – Table 1.1.3/4.4 - Data on file

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Table SIII.19: Duration of exposure by hepatic function at baseline (safety analysis set) – pool 2

Indication: CRPC/breast cancer with bone metastases		
Hepatic function at baseline	**Persons**	**Person time[a]**
Normal (0)	674	2,262.20
Impaired (1,2,3)	218	578.27
Missing	12	29.30
Total	**904**	**2,869.77**

[a] in months
No subjects were missing
Person Time for each subject is calculated as the date of the last injection of study treatment - date of the injection + 1.
Total is the sum of person-time in months
Hepatic Function at Baseline:
[0 = max(baseline AST/ULN, baseline ALT/ULN)<=1, 1 = 1 < max(baseline AST/ULN, baseline ALT/ULN)<=3
2 = 3 < max(baseline AST/ULN, baseline ALT/ULN)<=5, 3 = 5 < max(baseline AST/ULN, baseline ALT/ULN)
0 = (bilirubin/ULN) <= 1, 1 = 1< baseline bilirubin/ULN <= 1.5, 2 = (1.5< baseline bilirubin/ULN<=3)
3 = (3 < baseline bilirubin/ULN), classified as the max of AST/ALT and bilirubin scores]
Global Biostatistics: Program: /proj/004/b3375/prod/programs/texp.sas 22OCT12 14:28
Source: Integrated Analysis of Safety for Alpharadin – Table 4.1.3/4.4.1 - Data on file

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Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria for the pivotal study BC1-06 are presented below:

Table SIV.1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Prior hemibody external radiotherapy. Systemic radiotherapy with strontium-89, samarium-153, rhenium-186 or rhenium-188 for the treatment of bone metastases within previous 24 weeks	To reduce the risk of cumulative radiation effects on the bone marrow	No	Addressed in the Summary of Product Characteristics (SmPC); (Section 4.4 Special warnings and precautions for use).
Treatment with cytotoxic chemotherapy within previous 4 weeks, or failure to recover from adverse events due to cytotoxic chemotherapy administered more than 4 weeks ago (however ongoing neuropathy is permitted)	To reduce the potential risk of additive effects on the bone marrow.	No	Addressed in the SmPC (Section 4.4 Special warnings and precautions for use).
a) Baseline haematological laboratory values prior to first injection: Absolute neutrophil count (ANC) < 1.5 x 10^9/L Platelet count <100 x10^9/L Haemoglobin (Hb) < 10.0 g/dL (100 g/L; 6.2 mmol/L) b) Haematology before further injections: Should be at least Common Toxicity Criteria grade 2 prior to next injection	To reduce the risk of high grade bone marrow suppression	No	Addressed in the SmPC (Section 4.4 Special warnings and precautions for use).

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Table SIV.1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Imminent or established spinal cord compression	In case of imminent or established spinal cord compression, the standard treatment (external beam radiation therapy or surgical intervention, e.g., laminectomy, along with usage of dexamethasone) is initiated without any delay. Xofigo® cannot replace standard of care for spinal cord compression	No	Addressed in the SmPC (Section 4.4 Special warnings and precautions for use).
Patients with Crohn's disease or Ulcerative colitis	To reduce the risk of radiation contamination and any potential complications in the bowel as Xofigo® is excreted via gastrointestinal tract in the faeces	Yes	Addressed in the SmPC (Section 4.4 Special warnings and precautions for use).
Blood transfusion or erythropoietin stimulating agents within previous 4 weeks	To reduce the risk of radiation-induced bone marrow suppression in bone marrow compromised patients. Hb values at baseline should reflect the real bone marrow capacity and should not be confounded by blood transfusions of erythropoietin	No	In study BC1-06 there was no increased incidence of anaemia in the Xofigo® arm compared to placebo. Hence it is concluded that there is no or only a limited effect on the red cell line. Addressed in the SmPC (Section 4.4 Special warnings and precautions for use).

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Table SIV.1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
	stimulating agents		
Bone marrow dysplasia	To reduce the risk of additive effects on the bone marrow	Yes	Addressed in the SmPC (Section 4.4 Special warnings and precautions for use).
Creatinine > 1.5 upper limit of normal (ULN)	Standard exclusion criterion in oncology studies to reduce the impact of comorbidities on the efficacy measurement. No safety concern with respect to kidney function was anticipated	No	Since excretion in urine is minimal and the major route of elimination is via the faeces, renal impairment is not expected to affect the pharmacokinetics of Xofigo®.
Aspartate transaminase and alanine transaminase > 2.5 ULN	Standard exclusion criterion in oncology studies to reduce the impact of comorbidities on the efficacy measurement. No safety concern with respect to hepatic function was anticipated.	No	Since Xofigo® is neither metabolised by the liver nor eliminated via the bile, hepatic impairment is not expected to affect the pharmacokinetics of Xofigo®.
Any uncontrolled infection	Standard exclusion criterion in oncology studies to reduce the impact of comorbidities on the efficacy measurement. In addition, to reduce the risk of worsening of the infection in case of radiation-induced neutropenia	No	The benefit-risk should be evaluated on individual patient basis. In study BC1-06, the overall subject incidence of infection in the treatment arm was not higher compared to placebo arm.

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Table SIV.1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Cardiac failure New York Heart Association III or IV	Standard exclusion criterion in oncology studies to reduce the impact of comorbidities on the efficacy measurement	No	No significant cardiovascular effects were observed in pre-clinical studies in vivo, including after a single-dose administration in dogs of doses equivalent of up to 9 times the clinically recommended activity in humans. In study BC1-06 there was no higher rate of cardiac failure in the treatment arm compared to placebo arm.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. The level of detection for the clinical trial programme with Xofigo® is presented below:

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Table SIV.2: Limitations to detect adverse reactions in clinical trial development programmes

Ability to detect adverse reaction	Limitation of trial program	Discussion of implications for target population
Which are rare	904 patients were treated with Xofigo® in the development program. Hence, the upper limit of the 95% confidence interval of an undetected adverse reaction is not higher than 3/904 (0.3%).	It is unlikely that a rare adverse reaction will impact the benefit/risk balance of Xofigo® in a target population with a life-threatening disease.
Due to prolonged exposure Due to cumulative effects	Xofigo® was evaluated in up to 6 injections and in a single dose of up to 250 kBq per kg (276 kBq per kg after implementation of National Institute of Standards and Technology [NIST] update)[6].	Prolonged and high cumulative exposure may result in increased bone marrow toxicity and increase the risk for late bone marrow toxicity and second primary malignancies including bone sarcoma and myelodysplastic syndrome/ acute myeloid leukaemia.
Which have a long latency	Long-term follow-up for adverse events such as bone fractures, late bone marrow toxicity, second primary malignancies including bone sarcoma and myelodysplastic syndrome/acute myeloid leukaemia are ongoing.	Considering the reduced life-expectancy of the target population the implications are limited.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3: Exposure of special populations typically under-represented in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. Xofigo® is not to be used in women who are or may be pregnant.
Breastfeeding women	Not included in the clinical development program. Xofigo® is not to be used in women who are or may be breast-feeding.
Paediatric patients	The safety and efficacy of Xofigo® in children and adolescents below 18 years of age have not been studied. The European

[6] Updated dose per revised NIST standardisation. The amount of radioactivity in the administered dose is unchanged; only the numerical value of the dose changed due to the revised standard.

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Table SIV.3: Exposure of special populations typically under-represented in clinical trial development programmes

Type of special population	Exposure
	Medicines Agency (EMA) has issued a class waiver for the treatment of prostate carcinoma: (EMA/820860/2010 – EMA decision P/345/2010 of 20 DEC 2010 on a class waiver on condition(s) in accordance with Regulation of the European Commission (EC) No 1901/2006 of the European Parliament and of the Council). As this tumour only rarely occurs in children, it is considered not feasible to do a trial with Radium-223 dichloride in paediatric populations with prostate carcinoma. Based on the above considerations Bayer has obtained EMA confirmation that the scope of the EMA decision on the class waiver for prostate carcinoma as of 03 DEC 2007 is applicable to Xofigo® for the treatment of castration-resistant prostate cancer with bone metastases**.**
Elderly	Of the 633 patients treated with Xofigo® in pool 1, 157 were <65 years, 266 were 65-74 years, 200 were 75-84 years and 10 were >85 years of age. In pool 3, 251 of 1,028 patients were <65 years, 440 were 65-74 years, 319 were 75-84 years and 18 were >85 years of age (see Part II: Module SIII, Table SIII.8; Table SIII.9; Table SIII.10). No overall differences in safety or effectiveness were observed between elderly (aged ≥ 65 years) and younger patients (aged < 65 years). No dose adjustment is considered necessary in elderly patients.
Patients with relevant comorbidities: Patients with hepatic impairment	Safety and efficacy of Xofigo® have not been studied in patients with hepatic impairment. Since Radium-223 dichloride is neither metabolised by the liver nor eliminated via the bile, hepatic impairment is not expected to affect the pharmacokinetics of Xofigo®. No dose adjustment is considered necessary in patients with hepatic impairment.
Patients with relevant comorbidities: Patients with renal impairment	In the phase III clinical study no relevant differences in safety or efficacy were observed between patients with mild renal impairment (creatinine clearance [CLCR]: 50 to 80 ml/min) and normal renal function. Limited data are available on patients with moderate (CLCR: 30 to 50 ml/min) renal impairment. No data are available on patients with severe (CLCR <30 ml/min) renal impairment or end-stage renal disease. However, since excretion in urine is minimal and the major route of elimination is via the faeces, renal impairment is not expected to affect the pharmacokinetics of Radium-223 dichloride. No dose adjustment is considered necessary in patients with renal impairment.
Patients with a disease severity different from inclusion criteria in clinical trials	The study population in the BC1-06 clinical trial included patients with multiple skeletal metastases (≥ 2 hot spots) on bone scintigraphy within the previous 12 weeks. Patients with a history of visceral metastasis, or visceral metastasis as

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Table SIV.3: Exposure of special populations typically under-represented in clinical trial development programmes

Type of special population	Exposure
	assessed by abdominal/pelvic computed tomography or X-ray within the previous 8 weeks, were excluded.
Population with relevant different ethnic origin	In clinical studies included in pool 1, 595 of 633 of patients treated with Radium-223 dichloride were Caucasians, 21 Asians, and 10 Black or African-American. In pool 2, 862 patients of 904 patients were Caucasian, 23 were Asian, and 9 were “Other”. In pool 3, 675 of 1,028 patients were Caucasian, 325 were Asian, 14 Black or African American, 7 were “Other”, and the ethnic origin was not reported in 7 patients (see Part II: Module SIII, Table SIII.14, Table SIII.15, and Table SIII.16).
Subpopulations carrying relevant genetic polymorphisms	There is no sub-population known carrying any relevant genetic polymorphism.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The patient exposure to the marketed product Xofigo® was calculated using the number of sold vials divided by the mean number of injections (n=5.1) as established in the BC1-06 (ALSYMPCA) pivotal Phase III study.

Patients exposed to the marketed product = Number of vials sold/ mean number of injections (n=5.1).

SV.1.2 Exposure

It is estimated that approximately 108,578 patients were cumulatively exposed to the marketed product worldwide since market approval in the United States (15 MAY 2013) until 30 APR 2025.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Xofigo® (an alpha particle-emitting pharmaceutical) should be received, used and administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings. The receipt, storage, use, transfer and disposal of Xofigo® are subject to the regulations and/or appropriate licences of the competent official organisation. A controlled distribution will limit any potential risk of misuse for illegal purposes. At present no potential for misuse or illegal use has been identified.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable. According to the EMA's guidance on the format of the RMP in the EU GVP Module V, Revision 2, effective since 31 MAR 2017, Section 1 of Module SVII is expected to be submitted only for initial marketing authorisation applications.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

As communicated in the PBRER/PSUR No. 12 (15 MAY 2020 – 14 MAY 2021), the MAH found no evidence suggestive of a potential risk for 'Increased formation of visceral and nodal metastases' in the labelled indication. The comprehensive review of information received from the safety database, clinical trials, literature and epidemiology reveals no findings of significance that affect the benefit risk profile of Xofigo®. The MAH assessment was endorsed by PRAC in the final PSUR assessment report (Procedure No.: EMEA/H/C/PSUSA/00010132/202105) and the MAH has thus removed the important potential risk 'Increased formation of visceral and nodal metastases' from the list of safety concerns.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

General information

In the EU RMP version 4.1 (versus version 3.1) data from the completed Category 1 study PRECISE (20437) have been added below and to Section SVII.3.1.1.

In the EU RMP version 2.4 (versus version 2.0) data from three studies have been added (studies 15396, 16506, and 17399). Data for the studies 16506 and 17399 was also previously presented in the EU RMP version 2.1.

In addition, the results of pooled analyses of monotherapy populations from six Xofigo® studies are presented as pool 3.

Study 20437 (PRECISE):

This study was an observational comparative cohort study. The primary objective in this study was to estimate the effect of Radium-223 on the incidence of bone fractures compared with other standard treatments for mCRPC. The secondary objectives were to estimate the effect of Radium-223 on OS and prostate cancer–specific survival compared with other standard treatments for mCRPC and to estimate heterogeneity of the estimates by line of treatment (first, second, and subsequent). The study addressed the important identified risk of bone fractures. A brief summary of the study results is provided in Section SVII.3.1.1.

Study 16506:

A re-treatment safety study of Radium-223 dichloride in subjects with CRPC with bone metastases who received an initial course of six doses of Radium-223 dichloride 50 kBq/kg every four weeks.

Overall, 44 subjects had received at least 1 dose of study treatment and were included in the safety analysis set. The mean (standard deviation [SD]) overall time under treatment was 132.7 days (54.14). Potential for cumulative toxicity on the haematopoietic system was a particular focus of this study at the time the protocol was written.

Study 17399 (PASS):

A Drug Utilisation Study of Xofigo® Use in Sweden.

This was a single-arm descriptive observational drug utilisation study based on secondary data collection of patients treated with Xofigo® in Sweden. Patients receiving Xofigo® with data recorded at nuclear medicine centres in Sweden between 01 JUL 2014 and 30 JUN 2016 were included in the study. Patients participating in clinical trials were excluded. Data from 12 out of 17 centres treating patients in Sweden during the time period was obtained. A total of 310 patients were included in the study. This PASS was conducted to evaluate the important potential risks for off-label use of Xofigo®.

Study 15396/ ERA-223:

Radium-223 dichloride and abiraterone acetate compared to placebo and abiraterone acetate for men with cancer of the prostate when medical or surgical castration does not work and when the cancer has spread to the bone, has not been treated with chemotherapy and is causing no or only mild symptoms.

This study was a phase III multinational, multicentre, randomised, double blind, placebo controlled, study with a randomisation allocation ratio of 1:1 (Radium-223 dichloride plus abiraterone acetate plus prednisone/prednisolone: placebo plus abiraterone acetate plus prednisone/prednisolone). In this study, 806 subjects were randomised to receive study treatment (Radium-223 dichloride or placebo in addition to abiraterone acetate plus prednisone/ prednisolone for the first 6 cycles followed by abiraterone acetate plus prednisone/prednisolone thereafter) until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria are met). The study was unblinded on 16 NOV 2017 based on the IDMC recommendation.

Unless stated otherwise, AE frequencies from clinical trials are based on clinical data from Phase I-III clinical studies detailed below.

Results are displayed for patients valid for safety (Pool 1: Xofigo® N=633, placebo N = 332; Pool 2: Xofigo® N=904, placebo: N=0; Pool 3: Xofigo® N=1,028, placebo: N = 0).

The clinical studies included for integrated analysis of safety are shown in Table SVII.1.

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Table SVII.1: Clinical studies for integrated analysis of safety

Study #	Description
ATI-BC-1; 15522	A phase I open-label, multicentre, dose-escalating study of Radium-223 dichloride in advanced prostate or breast cancer patients with skeletal metastases.
BC1-02; 15280	A phase II randomised, placebo-controlled, multicentre study in prostate cancer patients with painful bone metastases to evaluate the efficacy of repeated Radium-223 dichloride injections.
BC1-03; 15305	A phase II double-blind, dose-response, multicentre study of Radium-223 dichloride for the palliation of painful bone metastases in hormone refractory prostate cancer.
BC1-04; 15304	A phase II double blind, randomised, dose finding, repeat dose, multicentre study of Radium-223 dichloride for the treatment of patients with hormone refractory prostate cancer and skeletal metastases.
BC1-05; 15302	A phase I open-label, dosimetry, biodistribution and pharmacokinetic study of Radium-223 dichloride in patients with hormone refractory prostate cancer and skeletal metastases.
BC1-06; ALSYMPCA; 15245	A phase III double-blind, randomised, multiple dose multicentre study of Radium-223 dichloride in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases.
BC1-08; 15303	A phase I, open-label, single ascending-dose study to assess safety, pharmacokinetics, biodistribution and radiation dosimetry of intravenous doses of Radium-223 dichloride injection in patients with hormone refractory prostate cancer and skeletal metastases.
15354	Uncontrolled, open-label, non-randomised phase I study to investigate safety, biodistribution, radiation dosimetry and pharmacokinetics of a single dose of Radium-223 dichloride in Japanese patients with castration-resistant prostate cancer and bone metastases.
15397	A phase III, single-arm, international, prospective, interventional, open-label, multicentre study of Radium-223 dichloride in the treatment of patients CRPC with bone metastases.
16430	A single-arm, open-label, multicentre, phase II study of Radium-223 dichloride in the treatment of Japanese patients with symptomatic CRPC with bone metastases.
16507	A three arm randomised, open-label phase II study of standard dose versus high dose and versus extended standard dose Radium-223 dichloride in castration-resistant prostate cancer metastatic to the bone.
16544	A randomised open-label phase IIa study evaluating quantified bone scan response following treatment with Radium-223 dichloride alone or in combination with abiraterone acetate or enzalutamide in subjects with castration-resistant prostate cancer who have bone metastases.

For the purpose of exposure and event rate analyses, these twelve studies are further subdivided in 3 data pools.

- **Pool 1**: Safety data from the randomised, double-blind, placebo-controlled studies BC1-02 (Phase II) and BC1-06 (Phase III).

Rationale: Trials in this pool, with a DLP of 15 JUL 2011, though using different length of treatment, i.e. 4 treatments in BC1-02 versus 6 treatments in BC1-06, used a randomised controlled design, allowing, taking time into consideration, direct analytical comparisons between the Xofigo® and placebo arm. They also both used a dose of 50 kBq/kg (55 kBq/kg after implementation of the National Institute of Standards and Technology [NIST] update)[7] given at 4-week intervals. The duration of reporting period for AEs in this pool was set as a time at risk of minimum of (84 days, days of death relative to last treatment) corresponding to a window of 12 weeks after last study drug administration.

- **Pool 2**: Safety data from single and multiple dose uncontrolled phase I and phase II studies, i.e., from studies ATI-BC-1, BC1-03, BC1-04, BC1-05 and BC1-08 and randomised, double-blind, placebo-controlled studies BC1-02 and BC1-06 were pooled for an integrated analysis.
  Rationale: Safety data from all clinical studies with Xofigo® with a DLP of 15 JUL 2011. These included randomised, double-blind, placebo-controlled studies BC1-02 and BC1-06 and other studies i.e., ATI-BC-1, BC1-03, BC1-04, BC1-05 and BC1-08. Dose of Xofigo® ranged from 5 kBq/kg (6 kBq/kg after implementation of the NIST update) body weight (b.w.) to 250 kBq/kg (276 kBq/kg after implementation of the NIST update) b.w. in these studies. Subject populations were comparable, in that they all had prostate cancer with bone metastases and there were 10 patients with breast cancer and with bone metastases in ATI-BC-1, which were included in the analysis. The duration of reporting period for AEs in this pool was set as a time at risk of minimum of (84 days, days of death relative to last treatment) corresponding to a window of 12 weeks after last study drug administration.
- **Pool 3**: Xofigo® monotherapy pool including safety data from single dose uncontrolled phase I study 15354, single arm open label phase II (16430) and phase III (15397) studies, randomised open label phase II studies 16507 and 16544, and randomised, double-blind, placebo-controlled phase III study BC1-06.
  Rationale: Trials in this monotherapy pool, with a DLP of 01 JUN 2018, were selected as they offer safety information with Xofigo® treatment only in a relatively large number of patients (1,028). Pooled safety data includes the entire safety population in trials 15354, 15397 and 16430, Xofigo® arm in trial BC1-06 (main study period), Xofigo® monotherapy arm in study 16544, and the standard Xofigo® dose arm in study 16507. All patients in the pool 3 were male. The duration of reporting period for AEs in this pool was set as a time at risk of minimum of (30 days, days of death relative to last treatment).

Detailed data on demographics and exposure to Radium-223 dichloride are available for 633 patients in pool 1, for 904 patients in pool 2, and for 1,028 patients in pool 3.

[7] Updated dose per revised NIST standardisation. The amount of radioactivity in the administered dose is unchanged; only the numerical value of the dose changed due to the revised standard.

In pool 2, there are 2 subjects who were treated twice during the study ATI-BC-1. As 9 months had elapsed between the two treatment periods in both cases, data from both the original injection and the re-injection are summarised separately, thereby counting these subjects twice each.

It is estimated that approximately 46,679 patients were cumulatively exposed to the marketed product worldwide since market approval in the United States (15 MAY 2013) until 30 APR 2018. No new safety concerns have been identified from the post marketing safety data.

In the following, the important identified risks are defined as the most important identified AEs/ADRs that are serious or frequent and that might have an impact on the balance of benefits and risks of Xofigo®, and for which there is a high level of evidence for a causal association to Xofigo®. Important potential risks are defined as those important AEs/ADRs that are serious or frequent and that also might have an impact on the balance of benefits and risks of Xofigo®, and for which a causal association cannot be excluded, although an integrated view of the available data does not strongly suggest causation.

SVII.3.1.1. Important Identified Risk: Bone Fractures

MedDRA High-Level Group Term (HLGT): Fractures. Refer to **Annex 7.1** for List of PTs included.

MedDRA Version 14.1 was used for coding of pools 1 and 2, MedDRA version 21.0 for pool 3. MedDRA Version 20.1 for ERA-223 Study.

Potential mechanisms:

Root cause analysis on the new signal of increased risk of bone fractures with the combination of Radium-223 dichloride with abiraterone/ prednisone is currently ongoing. The current mode of action hypothesis is that fractures are promoted by triplet specific synergistic pro-osteoclastic and anti-osteoblastic effects. Preclinical experiments to characterise the individual effects of the three drugs and, more importantly, potential synergistic effects in combination in osteoblastic prostate cancer bone lesions and non-tumour bearing bone have been finalised and are summarised in Part II: Module SII, Table SII.1.

Evidence source(s) and strength of evidence:

Data from Bayer Global Pharmacovigilance database and clinical studies with Xofigo®.

Characterisation of the risk:

On a cumulative basis and from all sources, there are 373 case reports of bone fractures in Xofigo®-treated patients in the Bayer Global Pharmacovigilance database (DLP 01 JUN 2018). 136 (36.5%) of these reports originated in the United States, 39 (10.5%) in Japan, 35 (9.4%) in Great Britain, 23 (6.2%) in Sweden, 18 (4.8%) in Germany, 16 (4.3% each) in Norway and Spain, with the rest of the 90 (24.1%) reports originating in other countries. A total of 126 (33.8%) of cases originated in the EU-28 countries. 355 (95.2%) of all cases were serious, and 358 (96.0%) were medically confirmed. The majority of the cases (295 [79.1%]) were reported in clinical trials, further 75 (20.1%)

spontaneous reports, 2 (0.5%) cases were identified from the literature, with an additional one case being a published report from a study. The majority of the cases (272 [72.9%]) were judged as not related to study drug (related: 101 [27.1%]). Cumulatively across all 373 cases, a total of 428 fractures were recorded, with some patients presenting with multiple fracture PT events.

Frequency with 95% confidence interval (CI):

Clinical trials

In the randomised, blinded trial population (pool 1), the HLGT Fractures yielded 35 cases (5.5%) in the patient arms treated with Xofigo®, compared to 19 cases (5.7%) in the placebo treatment arms. In all clinical trial populations treated with Xofigo® (pool 2), a total of 41 cases were reported, corresponding to an incidence of 4.5%. In the Xofigo® monotherapy studies (pool 3), a total of 45 cases were reported (4.4%) (see Table SVII.2).

Other clinical trial data

ERA-223:

In ERA-223 the number of patients with at least one fracture was higher in the Radium-223 dichloride plus abiraterone/prednisone treatment arm (108 patients [27.6%]) than in the placebo plus abiraterone/prednisone treatment arm (37 patients (9.4%]) (see Table SVII.4).

All fractures include SSE fractures (symptomatic pathological fractures), treatment emergent fractures, and all drug related fractures reported during the follow-up period.

Overall, no clear pattern of fractures has been identified that led to the imbalance between the treatment arms. At baseline, there was no skeletal survey or bone mineral density test conducted. Most fractures occurred within the first year in both treatment groups.

PRECISE (20437):

This study was an observational comparative cohort study which assessed patients receiving treatment for mCRPC recorded in the Prostate Cancer data Base Sweden (PCBaSe) during the study period (NOV 2013 – DEC 2018), without evidence of having received Radium-223 before the study period.

The effect of Radium-223 was assessed in different lines of treatment for mCRPC (first, second, third/fourth). Cohorts were supposed to be analysed together when there was no evidence of effect heterogeneity. The comparator group comprised patients receiving standard of care. Patients could contribute as individuals to multiple line of treatment-specific cohorts, if eligible, and to both arms in different cohorts.

The size of the complete-case population was 1,434 individuals: 681 in the Radium-223 group (76.4% of the eligible population) and 753 in the comparator group (76.9% of the eligible population).

The results from this real-world study have shown, that the risk of fractures in patients receiving Radium-223 as monotherapy was similar to the risk observed in other observational studies and clinical trials.

The effect estimates for the cumulative incidence of bone fractures did not point to a large difference and were compatible with a small, if any, increase in the risk associated with Radium-223 use versus a comparator in the first and second lines of treatment. The 95% CI around the effect estimates were consistent with no difference, and with both a small increase and a small decrease in the 36-month fracture incidence difference.

A decreased risk of mortality associated with Radium-223 use was observed in the second and third/fourth-line cohorts, where Radium-223 is predominantly used in clinical practice.
A moderately increased risk of all-cause and prostate cancer–specific mortality was observed with Radium-223 use in the first-line cohort. The observed associations in survival need to be interpreted with caution because of the likelihood of unmeasured confounding.

The results of this study did not change the benefit-risk assessment of Radium-223.

Seriousness/outcomes:

Clinical trials

In general, the crude incidence rates and the outcomes of HLGT Fractures were comparable across pools 1 and 2 and were similar to placebo arms (Table SVII.3). In the Xofigo®-treated populations the total number of serious bone fractures cases was 19 (3.0%) in pool 1, 22 (2.4%) in pool 2, 18 (1.8%) in pool 3, and 12 (3.6%) in the placebo arms. Approximately equal number of all fracture cases were recovered/ resolved when compared with cases which did not resolve or recover. Thus, in the Xofigo® population in pool 1, 15 (2.4%) of cases recovered versus 15 (2.4%) cases which did not resolve (9 [2.7%] *vs*. 7 [2.1%] in the placebo arms). Likewise, in pool 2, 17 (1.9%) of all cases recovered *vs*. 18 (2.0%) of all cases which did not recover. In pool 3, 17 (1.7%) of all cases recovered *vs*. 23 (2.4%) which did not recover. Of the cases which resolved with sequelae in the Xofigo®-treated populations, 5 (0.8%) were reported in pool 1, 5 (0.6%) in pool 2, 5 (0.5%) in pool 3; whereas 2 (0.6%) cases were reported in the placebo arms of pool 1. The outcome was reported as missing or unknown in one case each in the placebo populations in pool 1 and in Xofigo® arms in pool 2.

Hospitalisation was required or prolonged in 18 (2.8%) cases in Xofigo®-treated patients in pool 1, 21 (2.3%) in pool 2, 17 (1.7%) in pool 3, versus 12 (3.6%) cases in the placebo arms of pool 1. Permanent treatment discontinuation was required in 3 cases each in the Xofigo® populations of pools 1 and 2, and in 2 cases each in pool 3 and in the placebo arms of the pool 1.

In summary, no pattern suggestive of an imbalance between Xofigo® and placebo-treated patients was observed in fracture rates, seriousness or outcomes across any of the pools.

Other clinical trial data

In ERA-223 the majority of fractures in the active treatment arm were CTCAE grade 1 and 2 in 68 subjects out of 108 (62.9%). Asymptomatic fractures (CTCAE Grade 1) were observed in 22 subjects out of 108 (20.4%). Fractures with a CTCAE grade 2 which are symptomatic but only immobilisation is required have been observed in 46 subjects out of 108 (42.6%). Fractures for which operative intervention was indicated (CTCAE grade 3) were observed in 39 subjects out of 108 (36.1%). Only one subject presented with a fracture which required

urgent surgical intervention (CTCAE grade 4). A list of all fractures in ERA-223 by treatment arm after or on the first study medication date by MedDRA preferred term and worst CTCAE grade is presented in Table SVII.4.

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Table SVII.2: Incidence rates of TEAE "bone fractures"* by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: HLGT Fractures

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)
Worst CTCAE Grade	Crude Incidence Rate	Crude Incidence Rate	Crude Incidence Rate	Crude Incidence Rate
Grade 1	2 (0.32)	2 (0.60)	2 (0.22)	5 (0.49)
Grade 2	17 (2.69)	6 (1.81)	19 (2.10)	25 (2.43)
Grade 3	16 (2.53)	10 (3.01)	20 (2.21)	15 (1.46)
Grade 4	0 (0.0)	1 (0.30)	0 (0.0)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All [95% CI for rate (%)]	35 (5.53) [3.88; 7.61]	19 (5.72) [3.48; 8.79]	41 (4.54) [3.27; 6.10]	45 (4.38) [3.21; 5.81]
Risk difference (in %) [95% CI]		-0.44 [-3.52; 2.64]		
EAIR [95% CI]	35 (0.106) [0.074; 0.148]	19 (0.124) [0.075; 0.194]	41 (0.098) [0.070; 0.133]	45 (0.113) [0.083, 0.152]
IRD for EAIR [95% CI]		-0.022 [-0.089; 0.044]		

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.

CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, EAIR = Exposure-adjusted incidence rate, HLGT = High-Level Group Term, IRD = Incidence rate difference, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = Treatment emergent adverse event

*This table lists all fractures which were reported as an adverse event.

[a]MedDRA version 14.1. CTCAE Version 3

[b]MedDRA version 21.0. CTCAE Version 4.03

Sources:

Global Integrated Analysis: /by-sasp/patdb/ia/888223/stat/2018/prod_0615_rmp_saf/pgms/t_eoi_rmp.sas enaja 25JUN2018 18:26

Global Integrated Analysis: sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08

20180612_bay888223_rmp_update - Data on file

20180625_bay888223_rmp2_update – Data on file

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Table SVII.3: Incidence rates of serious TEAE "bone fractures"* and outcomes of all TEAEs by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: HLGT Fractures

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)
Serious adverse event	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**
All (serious)	19 (3.00)	12 (3.61)	22 (2.43)	18 (1.75)
[95% CI for rate (%)]	[1.82; 4.65]	[1.88; 6.23]	[1.53; 3.66]	[1.04, 2.75]
Worst outcome				
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not recovered/ resolved	15 (2.37)	7 (2.11)	18 (1.99)	23 (2.24)
Recovering/resolving	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Recovered/resolved with sequelae	5 (0.79)	2 (0.60)	5 (0.55)	5 (0.49)
Recovered/resolved	15 (2.37)	9 (2.71)	17 (1.88)	17 (1.65)
Missing/Unknown	0 (0.0)	1 (0.30)	1 (0.11)	0 (0.0)
Hospitalisation[d]	18 (2.84)	12 (3.61)	21 (2.32)	17 (1.65)
[95% CI for rate (%)]	[1.69; 4.46]	[1.88; 6.23]	[1.44; 3.53]	[0.97, 2.63]
Discontinuation[e]	3 (0.47)	2 (0.60)	3 (0.33)	2 (0.19)
[95% CI for rate (%)]				

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.
CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, HLGT = High-Level Group Term, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = Treatment emergent adverse event
*This table lists all fractures which were reported as an adverse event.
[a]MedDRA version 14.1. CTCAE Version 3
[b]MedDRA version 21.0. CTCAE Version 4.03
[d]Required or prolonged
[e]Adverse events leading to permanent study drug discontinuation
Sources:
Global Integrated Analysis:
/by-sasp/patdb/ia/888223/stat/2018/prod_0615_rmp_saf/pgms/t_eoi_rmp.sas enaja 25JUN2018 18:26
Global Integrated Analysis:
sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
20180612_bay888223_rmp_update - Data on file
20180625_bay888223_rmp2_update – Data on file

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Table SVII.4: All fractures after or on the first study medication date by MedDRA and Worst CTCAE grade (Safety Analysis Set)

System organ class Preferred term	Worst CTCAE grade	Radium-223 + Abi/Pred N=392 (100%)	Placebo + Abi/ Pred N=394 (100%)	Total N=786 (100%)
Number (%) of subjects	Total	108 (27.6%)	37 (9.4%)	145 (18.4%)
	Grade 1	22 (5.6%)	12 (3.0%)	34 (4.3%)
	Grade 2	46 (11.7%)	12 (3.0%)	58 (7.4%)
	Grade 3	39 (9.9%)	13 (3.3%)	52 (6.6%)
	Grade 4	1 (0.3%)	0	1 (0.1%)
Injury, poisoning and procedural complications	Total	58 (14.8%)	16 (4.1%)	74 (9.4%)
	Grade 1	19 (4.8%)	8 (2.0%)	27 (3.4%)
	Grade 2	23 (5.9%)	5 (1.3%)	28 (3.6%)
	Grade 3	16 (4.1%)	3 (0.8%)	19 (2.4%)
Clavicle fracture	Total	2 (0.5%)	0	2 (0.3%)
	Grade 2	1 (0.3%)	0	1 (0.1%)
	Grade 3	1 (0.3%)	0	1 (0.1%)
Femoral neck fracture	Total	1 (0.3%)	0	1 (0.1%)
	Grade 3	1 (0.3%)	0	1 (0.1%)
Femur fracture	Total	1 (0.3%)	1 (0.3%)	2 (0.3%)
	Grade 3	1 (0.3%)	1 (0.3%)	2 (0.3%)
Hand fracture	Total	0	1 (0.3%)	1 (0.1%)
	Grade 2	0	1 (0.3%)	1 (0.1%)
Humerus fracture	Total	2 (0.5%)	0	2 (0.3%)
	Grade 2	2 (0.5%)	0	2 (0.3%)
Ilium fracture	Total	1 (0.3%)	0	1 (0.1%)
	Grade 1	1 (0.3%)	0	1 (0.1%)
Lower limb fracture	Total	1 (0.3%)	0	1 (0.1%)
	Grade 3	1 (0.3%)	0	1 (0.1%)
Lumbar vertebral fracture	Total	3 (0.8%)	0	3 (0.4%)
	Grade 2	2 (0.5%)	0	2 (0.3%)
	Grade 3	1 (0.3%)	0	1 (0.1%)

Table SVII.4: All fractures after or on the first study medication date by MedDRA and Worst CTCAE grade (Safety Analysis Set)

System organ class Preferred term	Worst CTCAE grade	Radium-223 + Abi/Pred N=392 (100%)	Placebo + Abi/ Pred N=394 (100%)	Total N=786 (100%)
Pubis fracture	Total	1 (0.3%)	0	1 (0.1%)
	Grade 1	1 (0.3%)	0	1 (0.1%)
Radius fracture	Total	0	1 (0.3%)	1 (0.1%)
	Grade 3	0	1 (0.3%)	1 (0.1%)
Rib fracture	Total	2 (0.5%)	0	2 (0.3%)
	Grade 1	2 (0.5%)	0	2 (0.3%)
Scapula fracture	Total	1 (0.3%)	0	1 (0.1%)
	Grade 2	1 (0.3%)	0	1 (0.1%)
Spinal compression fracture	Total	5 (1.3%)	1 (0.3%)	6 (0.8%)
	Grade 2	4 (1.0%)	1 (0.3%)	5 (0.6%)
	Grade 3	1 (0.3%)	0	1 (0.1%)
Stress fracture	Total	1 (0.3%)	0	1 (0.1%)
	Grade 2	1 (0.3%)	0	1 (0.1%)
Thoracic vertebral fracture	Total	3 (0.8%)	0	3 (0.4%)
	Grade 1	1 (0.3%)	0	1 (0.1%)
	Grade 2	2 (0.5%)	0	2 (0.3%)
Tooth fracture	Total	1 (0.3%)	1 (0.3%)	2 (0.3%)
	Grade 1	0	1 (0.3%)	1 (0.1%)
	Grade 3	1 (0.3%)	0	1 (0.1%)
Traumatic fracture	Total	39 (9.9%)	12 (3.0%)	51 (6.5%)
	Grade 1	17 (4.3%)	7 (1.8%)	24 (3.1%)
	Grade 2	13 (3.3%)	4 (1.0%)	17 (2.2%)
	Grade 3	9 (2.3%)	1 (0.3%)	10 (1.3%)
Ulna fracture	Total	0	1 (0.3%)	1 (0.1%)
	Grade 3	0	1 (0.3%)	1 (0.1%)

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Table SVII.4: All fractures after or on the first study medication date by MedDRA and Worst CTCAE grade (Safety Analysis Set)

System organ class Preferred term	Worst CTCAE grade	Radium-223 + Abi/Pred N=392 (100%)	Placebo + Abi/ Pred N=394 (100%)	Total N=786 (100%)
Musculoskeletal and connective tissue disorders	Total	61 (15.6%)	22 (5.6%)	83 (10.6%)
	Grade 1	8 (2.0%)	4 (.0%)	12 (1.5%)
	Grade 2	28 (7.1%)	7 (1.8%)	35 (4.5%)
	Grade 3	24 (6.1%)	10 (2.5%)	34 (4.3%)
	Grade 4	1 (0.3%)	0	1 (0.1%)
	Missing		1 (0.3%)	1 (0.1%)
Osteoporotic fracture	Total	23 (5.9%)	1 (0.3%)	24 (3.1%)
	Grade 1	5 (1.3%)	0	5 (0.6%)
	Grade 2	13 (3.3%)	0	13 (1.7%)
	Grade 3	4 (1.0%)	1 (0.3%)	5 (0.6%)
	Grade 4	1 (0.3%)	0	1 (0.1%)
Pathological fracture	Total	39 (9.9%)	21 (5.3%)	60 (7.6%)
	Grade 1	3 (0.8%)	4 (1.0%)	7 (0.9%)
	Grade 2	16 (4.1%)	7 (1.8%)	23 (2.9%)
	Grade 3	20 (5.1%)	9 (2.3%)	29 (3.7%)
	Missing		1 (0.3%)	1 (0.1%)

MedDRA version 20.1
CTCAE Version 4.03
Radium-223: Radium-223 dichloride 55 kBq/kg(up to 6 doses)
CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = Treatment emergent adverse event
Source: Bayer: /by-sasp/patdb/projects/888223/15396_p/stat/test_interim03/pgms/t_ae_fracture_sag_o.sas emqsy 30MAY2018 22:06

Severity and nature of risk:

Patients with prostate cancer metastatic to bone face severe morbidity, including bone fractures. Presence of bone metastases and the occurrence of skeletal-related events such as bone fractures, is strongly associated with increased mortality in mCRPC.

The severity of bone fractures according to CTCAE in pooled populations is displayed in the section frequency in Table SVII.2. In clinical trial populations treated with Xofigo® (pool 1), 19 of 35 (54.3%) cases were of mild-to-moderate intensity, with the other 16 (45.7%) cases reported as Grade 3. The results were very similar in pool 2 patients, with 21 of 41 (51.2%) mild-to-moderate intensity cases, with the remaining 20 (48.8%) cases of Grade 3 severity. In pool 3 Xofigo® monotherapy studies, 30 out of 45 (66.7%) cases were of mild-to-moderate

intensity, with 15 (33.3%) additional Grade 3 cases. Overall, the severity of bone fractures across Xofigo® treated pools 1 and 2 was comparable to the placebo arms in pool 1, where 8 of 19 (42.1%) cases of mild-to-moderate intensity were reported, with additional 10 (52.6%) Grade 3 fracture cases. There were no Grade 4 or 5 fractures in any of the Xofigo®-treated populations, with one Grade 4 case reported in the placebo arms in pool 1.

The severity and nature of bone fractures in ERA-223 is displayed in Table SVII.4 by treatment arm after or on the first study medication date by MedDRA preferred term and worst CTCAE grade.

Risk factors and risk groups:

Patients receiving Xofigo® in combination with abiraterone plus prednisone/ prednisolone. Patients with a medical history of osteoporosis and <6 metastases.

Preventability:

Concurrent use of bone health agents (BHA), including bisphosphonates (etidronic acid, clodronic acid, pamidronic acid, alendronic acid, tiludronic acid, ibandronic acid, risedronic acid, and zoledronic acid) and denosumab.

Impact on the risk-benefit balance of the product:

The impact of the increased risk of bone fractures under treatment with Xofigo® is countered by an inclusion of a broad contraindication in the SmPC for combination of Xofigo® and abiraterone plus prednisone/ prednisolone. In addition, 5 studies to further characterise the risk are currently ongoing (refer to Section V.3 for more details).

Public health impact:

There is limited public health impact due to a broad contraindication in the SmPC for combination of Xofigo® and abiraterone plus prednisone/ prednisolone.

SVII.3.1.2. Important Identified Risk: Bone marrow toxicity leading to reduced formed elements in blood

MedDRA Labelling Group (MLG) Neutropenia, MLG Thrombocytopenia, MLG Pancytopenia, MLG Leukopenia. Refer to **Annex 7.1** for List of PTs included.

MedDRA Version 14.1 was used for coding of pools 1 and 2, MedDRA version 21.0 for pool 3, MedDRA Version 20.0 for study 16506.

Potential mechanisms:

Radiation to bone marrow.

Evidence source(s) and strength of evidence:

Pooled data from clinical studies with Xofigo®; re-treatment safety study 16506.

Characterisation of the risk:

In a recently completed re-treatment safety study 16506 in subjects with CRPC with bone metastases who received an initial course of six doses of Radium-223 dichloride 50 kBq/kg

every four weeks there was minimal haematologic toxicity during the treatment period and the 2-year follow-up period with no cumulative haematologic toxicity being reported.

Frequency with 95% confidence interval (CI):

Neutropenia

In the randomised, blinded trial population (pool 1), the MLG Neutropenia yielded 31 cases (4.9%) in the patient arms treated with Xofigo®, compared to 3 cases (0.9%) in the placebo treatment arms. In all clinical trial populations treated with Xofigo® (pool 2), a total of 40 cases were reported, corresponding to an incidence of 4.4%. A total of 41 (4.0%) cases were reported in the Xofigo® monotherapy studies (pool 3). In the re-treatment safety study 16506, a total of 2 cases of MLG neutropenia were reported (PT: neutrophil count decreased), corresponding to an incidence of 4.5% (see Table SVII.5).

Thrombocytopenia

In the randomised, blinded trial population (pool 1), thrombocytopenia was reported in 69 cases (10.9%) in the arms treated with Xofigo®, in comparison to 18 cases (5.4%) in the placebo treatment arm. Thrombocytopenia occurred in a total of 82 cases in all clinical trial populations treated with Xofigo® (pool 2), corresponding to an incidence of 9.1%. A total of 106 (10.3%) cases were reported in the Xofigo® monotherapy studies (pool 3). In the re-treatment safety study 16506, 1 case of thrombocytopenia was reported (PT: thrombocytopenia), corresponding to an incidence of 2.3% (see Table SVII.6).

Pancytopenia

Pancytopenia was reported in 12 cases (1.9%) in the arms treated with Xofigo® of the randomised, blinded trial population (pool 1), whereas no case occurred in the placebo treatment arms. A total of 13 cases, corresponding to an incidence of 1.4%, were observed in all clinical trial populations treated with Xofigo® (pool 2). A total of 10 (1.0%) cases were reported in the Xofigo® monotherapy studies (pool 3). In the re-treatment safety study 16506, no cases of pancytopenia were reported (see Table SVII.7).

Leukopenia

In the randomised, blinded trial population (pool 1), leukopenia was observed in 25 cases corresponding to an incidence of 3.9% in the arms treated with Xofigo®, whereas in the placebo arm, leukopenia was seen only in 1 case (0.3%). A total of 45 cases (5.0%) of leukopenia were reported in all clinical trial populations (pool 2) treated with Xofigo® (see Table SVII.8). A total of 64 (6.2%) cases were reported in the Xofigo® monotherapy studies (pool 3). In the re-treatment safety study 16506, a total of 4 cases of MLG leukopenia were reported (PT: leukopenia [1 case]; white blood cell count decreased [3 cases]), corresponding to an incidence of 9.1% (see Table SVII.8).

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Table SVII.5: Incidence rates of TEAE "neutropenia" by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: MLG Neutropenia

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]	Study 16506[c]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)	Xofigo® (N=44) n (rate in %)
Worst CTCAE Grade	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**
Grade 1	5 (0.8)	0 (0.0)	5 (0.6)	11 (1.07)	1 (2.3)
Grade 2	13 (2.1)	1 (0.3)	20 (2.2)	17 (1.65)	1 (2.3)
Grade 3	9 (1.4)	2 (0.6)	10 (1.1)	10 (0.97)	0 (0.0)
Grade 4	4 (0.6)	0 (0.0)	5 (0.6)	3 (0.29)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All [95% CI for rate (%)]	31 (4.9) [3.4, 6.9]	3 (0.9) [0.2, 2.6]	40 (4.4) [3.2, 6.0]	41 (3.99) [2.88, 5.37]	2 (4.5)
Risk difference [95% CI]		0.04 [0.02, 0.06]			
EAIR [95% CI]	31 (0.094) [0.064, 0.133]	3 (0.019) [0.004, 0.056]	40 (0.096) [0.068, 0.130]	41 (0.103) [0.074; 0.140]	
IRD for EAIR [95% CI]		0.07 [0.04, 0.11]			

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.

CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, EAIR = Exposure-adjusted incidence rate, IRD = Incidence rate difference, MedDRA = Medical Dictionary for Regulatory Activities, MLG = MedDRA Labelling Group, TEAE = Treatment emergent adverse event.

[a]MedDRA version 14.1. CTCAE Version 3
[b]MedDRA version 21.0. CTCAE Version 4.03
[c]MedDRA version 20.0. CTCAE Version 4.03

Sources: Integrated Analysis of Safety for Xofigo®, Table 1.3.1/9.24.1
Integrated Analysis of Safety for Xofigo®, Table 4.3.1/9.24.1
Global Integrated Analysis:
sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
20180612_bay888223_rmp_update - Data on file
Amended Clinical Study Report PH-38459, Table 14.3.1/4

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Table SVII.6: Incidence rates of TEAE "thrombocytopenia" by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: MLG Thrombocytopenia

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]	Study 16506[c]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)	Xofigo® (N=44) n (rate in %)
Worst CTCAE Grade	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**
Grade 1	11 (1.7)	4 (1.2)	18 (2.0)	34 (3.31)	0 (0.0)
Grade 2	19 (3.0)	7 (2.1)	22 (2.4)	24 (2.33)	0 (0.0)
Grade 3	20 (3.2)	6 (1.8)	22 (2.4)	30 (2.92)	1 (2.3)
Grade 4	18 (2.8)	1 (0.3)	19 (2.1)	18 (1.75)	0 (0.0)
Grade 5	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All [95% CI for rate (%)]	69 (10.9) [8.6, 13.6]	18 (5.4) [3.2, 8.4]	82 (9.1) [7.3, 11.1]	106 (10.31) [8.52; 12.33]	1 (2.3)
Risk difference [95% CI]		0.05 [0.02, 0.09]			
EAIR [95% CI]	69 (0.211) [0.164, 0.267]	18 (0.116) [0.069, 0.184]	82 (0.197) [0.157, 0.245]	106 (0.268) [0.219; 0.324]	
IRD for EAIR [95% CI]		0.09 [0.02, 0.17]			

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.

CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, EAIR = Exposure-adjusted incidence rate, IRD = Incidence rate difference, MedDRA = Medical Dictionary for Regulatory Activities, MLG = MedDRA Labelling Group, TEAE = Treatment emergent adverse event

[a]MedDRA version 14.1. CTCAE Version 3

[b]MedDRA version 21.0. CTCAE Version 4.03

[c]MedDRA version 20.0. CTCAE Version 4.03

Sources: Integrated Analysis of Safety for Xofigo®, Table 1.3.1/9.25.1
Integrated Analysis of Safety for Xofigo®, Table 4.3.1/9.25.1
Global Integrated Analysis:
sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
20180612_bay888223_rmp_update - Data on file
Amended Clinical Study Report PH-38459, Table 14.3.1/4

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Table SVII.7: Incidence rates of TEAE "pancytopenia" by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: MLG Pancytopenia

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]	Study 16506[c]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)	Xofigo® (N=44) n (rate in %)
Worst CTCAE Grade	Crude Incidence Rate	Crude Incidence Rate	Crude Incidence Rate	Crude Incidence Rate	Crude Incidence Rate
Grade 1	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Grade 2	4 (0.6)	0 (0.0)	4 (0.4)	3 (0.29)	0 (0.0)
Grade 3	4 (0.6)	0 (0.0)	4 (0.4)	5 (0.49)	0 (0.0)
Grade 4	3 (0.5)	0 (0.0)	3 (0.3)	2 (0.19)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
All [95% CI for rate (%)]	12 (1.9) [1.0, 3.3]	0 (0.0) [0 0, 1.1]	13 (1.4) [0.8, 2.4]	10 (0.97) [0.47. 1.78]	0 (0.0)
Risk difference [95% CI]		0.02 [0.01, 0.03]			
EAIR [95% CI]	12 (0.036) [0.018, 0.062]	0 (0.000) [0.000, 0.023]	13 (0.030) [0.016, 0.052]	10 (0.025) [0.012, 0.045]	
IRD for EAIR [95% CI]		0.04 [0.02, 0.06]			

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.

CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, EAIR = Exposure-adjusted incidence rate, IRD = Incidence rate difference, MedDRA = Medical Dictionary for Regulatory Activities, MLG = MedDRA Labelling Group, TEAE = Treatment emergent adverse event

[a]MedDRA version 14.1. CTCAE Version 3
[b]MedDRA version 21.0. CTCAE Version 4.03
[c]MedDRA version 20.0. CTCAE Version 4.03

Sources: Integrated Analysis of Safety for Xofigo®, Table 1.3.1/9.26.1
Integrated Analysis of Safety for Xofigo®, Table 4.3.1/9.26.1
Global Integrated Analysis:
sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
20180612_bay888223_rmp_update - Data on file
Amended Clinical Study Report PH-38459, Table 14.3.1/4

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Table SVII.8: Incidence rates of TEAE "leukopenia" by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: MLG Leukopenia

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]	Study 16506[c]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)	Xofigo® (N=44) n (rate in %)
Worst CTCAE Grade	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**
Grade 1	3 (0.5)	0 (0.0)	13 (1.4)	18 (1.75)	2 (4.5)
Grade 2	14 (2.2)	0 (0.0)	19 (2.1)	34 (3.31)	1 (2.3)
Grade 3	7 (1.1)	1 (0.3)	10 (1.1)	11 (1.07)	0 (0.0)
Grade 4	1 (0.2)	0 (0.0)	2 (0.2)	1 (0.10)	1 (2.3)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
All [95% CI for rate (%)]	25 (3.9) [2.6, 5.8]	1 (0.3) [0.0, 1.7]	45 (5.0) [3.7, 6.6]	64 (6.23) [4.83, 7.88]	4 (9.1)
Risk difference [95% CI]		0.04 [0.02, 0.05]			
EAIR [95% CI]	25 (0.075) [0.049, 0.111]	1 (0.006) [0.000, 0.035]	45 (0.107) [0.078, 0.144]	64 (0.162) [0.124, 0.206]	
IRD for EAIR [95% CI]		0.07 [0.04, 0.10]			

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.

CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, EAIR = Exposure-adjusted incidence rate, IRD = Incidence rate difference, MedDRA = Medical Dictionary for Regulatory Activities, MLG = MedDRA Labelling Group, TEAE = Treatment emergent adverse event

[a]MedDRA version 14.1. CTCAE Version 3
[b]MedDRA version 21.0. CTCAE Version 4.03
[c]MedDRA version 20.0. CTCAE Version 4.03

Sources: Integrated Analysis of Safety for Xofigo®, Table 1.3.1/9.27.1
Integrated Analysis of Safety for Xofigo®, Table 4.3.1/9.27.1
Global Integrated Analysis:
sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
20180612_bay888223_rmp_update - Data on file
Amended Clinical Study Report PH-38459, Table 14.3.1/4

Seriousness/outcomes:

Neutropenia

In the randomised, blinded trial population (pool 1), most cases of neutropenia were resolved (27 of 31 cases in the Xofigo® treatment arms and 2 of 3 cases in the placebo treatment arms). Serious neutropenia was reported in 3 cases in the Xofigo® treatment arm (0.5%) and in 1 case (0.3%) in the placebo arm. Hospitalisation was required or prolonged only in 1 case (0.2%) in the Xofigo® treatment arms. In the Xofigo® treatment arms, 3 cases (0.5%) had to permanently discontinue the study in comparison to 1 case (0.3%) in the placebo arms (see Table SVII.9).

In all clinical trial populations treated with Xofigo® (pool 2), 4 cases (0.4%) of neutropenia were reported as serious and 2 cases (0.2%) required hospitalisation. 36 of 40 cases were resolved, whereas in 3 cases, (0.3%) the patients had to discontinue the study.

In Xofigo® monotherapy studies (pool 3), a total of 4 cases were reported as serious (0.4%), with 1 case which required hospitalisation. 36 of 41 cases were resolved, whereas in 4 cases, (0.4%) the patients had to discontinue the study.

In the re-treatment safety study 16506, no cases of serious neutropenia were reported.

Thrombocytopenia

In the randomised, blinded trial population (pool 1), 14 cases (2.2%) of serious thrombocytopenia were reported in the arms who received Xofigo® compared to 3 cases (0.9%) in the placebo arms. In the Xofigo® treatment arms, 1 case was fatal and 10 cases (1.6%) required hospitalisation. Most of the cases (53 of 69 cases in the Xofigo® treatment arms and 13 of 18 cases in the placebo arms) did not recover. And in 10 cases (1.6%) in the Xofigo® treated arms and in 4 cases (1.2%) in the placebo arms, patients discontinued the study drug permanently (see Table SVII.10).

In all clinical trial populations treated with Xofigo® (pool 2), 16 cases (1.8%) of serious thrombocytopenia were reported and 55 (6.1%) cases did not resolve. Hospitalisation was required or prolonged in 11 cases (1.2%) and patients had to permanently discontinue the study drug in 11 cases (1.2%).

In Xofigo® monotherapy studies (pool 3), a total of 18 cases were reported as serious (1.8%), with 75 (7.3%) out of 106 total cases which did not resolve. Hospitalisation was required or prolonged in 13 cases (1.3%) and patients had to permanently discontinue the study drug in 17 cases (1.7%).

In the re-treatment safety study 16506, no cases of serious thrombocytopenia were reported.

Pancytopenia

In the Xofigo® treated patients of the randomised, blinded trial population (pool 1), 5 (0.8%) out of 12 total cases of pancytopenia were regarded as serious, 8 cases (1.3%) did not recover and 3 cases (0.5%) required hospitalisation. No cases of pancytopenia were reported in the placebo arms.

In all clinical trial populations treated with Xofigo®, most of the cases (9 of 13 cases) did not resolve and in 3 cases (0.3%), patients had to be hospitalised or prolong their hospital stay. Serious pancytopenia was reported in 5 cases (0.6%). One patient had to permanently discontinue the study drug (0.1%) (see Table SVII.11).

In Xofigo® monotherapy studies (pool 3), a total of 6 cases were reported as serious (0.6%), with 5 (0.5%) out of 10 total cases which did not resolve. Hospitalisation was required or prolonged in 4 cases (0.4%) and patients had to permanently discontinue the study drug in 2 cases (0.2%).

In the re-treatment safety study 16506, no cases of pancytopenia were reported.

Leukopenia

Events pertaining to the MLG “leukopenia” were considered serious in 3 cases (0.5%) in the Xofigo® arms of the randomised, blinded trial population. In the placebo arms, no serious cases were observed. Hospitalisation was necessary or prolonged in 2 cases of Xofigo®-treated arms (0.3%), and Xofigo® had to be discontinued in 2 cases (see Table SVII.12).

In all clinical trial populations treated with Xofigo®, over half of the patients recovered (32 of 45 cases), and 3 cases (0.3%) of serious leukopenia were reported. Hospitalisation and permanent discontinuation of the study drug were reported in 2 cases each (0.2%).

In Xofigo® monotherapy studies (pool 3), over half of the patients recovered (49 of 64 cases), and 4 (0.4%) reported cases of serious leukopenia. Hospitalisation was necessary or prolonged in 3 cases (0.3%), and Xofigo® had to be discontinued in 1 case (0.1%).

In the re-treatment safety study 16506, no cases of serious leukopenia were reported.

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Table SVII.9: Incidence rates of serious TEAE "neutropenia" and outcomes of all TEAEs by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: MLG Neutropenia

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]	Study 16506[c]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)	Xofigo® (N=44) n (rate in %)
Serious adverse event	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**
All (serious)	3 (0.5)	1 (0.3)	4 (0.4)	4 (0.39)	0 (0.0)
[95% CI for rate (%)]	[0.1, 1.4]	[0.0, 1.7]	[0.1, 1.1]	[0.11, 0.99]	
Worst outcome					
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Not recovered/ resolved	4 (0.6)	1 (0.3)	4 (0.4)	4 (0.39)	
Recovering/resolving	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Recovered/resolved with sequelae	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Recovered/resolved	27 (4.3)	2 (0.6)	36 (4.0)	36 (3.50)	
Missing/Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.10)	
Hospitalisation[d]	1 (0.2)	0 (0.0)	2 (0.2)	1 (0.10)	
[95% CI for rate (%)]	[0.0, 0.9]	[0.0, 1.1]	[0.0, 0.8]	[0.0, 0.54]	
Discontinuation[e]	3 (0.5)	1 (0.3)	3 (0.3)	4 (0.39)	
[95% CI for rate (%)]	[0.1, 1.4]	[0.0, 1.7]	[0.1, 1.0]		

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.
CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, MLG = MedDRA Labelling Group, TEAE = Treatment emergent adverse event
[a]MedDRA version 14.1. CTCAE Version 3
[b]MedDRA version 21.0. CTCAE Version 4.03
[c]MedDRA version 20.0. CTCAE Version 4.03
[d]Required or prolonged
[e]Adverse events leading to permanent study drug discontinuation
Sources: Integrated Analysis of Safety for Xofigo®, Table 1.3.1/9.24.1
Integrated Analysis of Safety for Xofigo®, Table 4.3.1/9.24.1
Global Integrated Analysis:
sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
20180612_bay888223_rmp_update - Data on file
Amended Clinical Study Report PH-38459, Table 14.3.1/4

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Table SVII.10: Incidence rates of serious TEAE "thrombocytopenia" and outcomes of all TEAEs by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: MLG Thrombocytopenia

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]	Study 16506[c]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)	Xofigo® (N=44) n (rate in %)
Serious adverse event	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**
All (serious)	14 (2.2)	3 (0.9)	16 (1.8)	18 (1.75)	0 (0.0)
[95% CI for rate (%)]	[1.2, 3.7]	[0.2, 2.6]	[1.0, 2.9]	[1.04, 2.75]	
Worst outcome					
Fatal	1 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	
Not recovered/ resolved	53 (8.4)	13 (3.9)	55 (6.1)	75 (7.30)	
Recovering/resolving	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.29)	
Recovered/resolved with sequelae	3 (0.5)	1 (0.3)	3 (0.3)	2 (0.19)	
Recovered/resolved	9 (1.4)	3 (0.9)	15 (1.7)	25 (2.43)	
Missing/Unknown	3 (0.5)	1 (0.3)	4 (0.4)	1 (0.10)	
Hospitalisation[d]	10 (1.6)	1 (0.3)	11 (1.2)	13 (1.26)	
[95% CI for rate (%)]	[0.8, 2.9]	[0.0, 1.7]	[0.6, 2.2]	[0.68, 2.15]	
Discontinuation[e]	10 (1.6)	4 (1.2)	11 (1.2)	17 (1.65)	
[95% CI for rate (%)]	[0.8, 2.9]	[0.3, 3.1]	[0.6, 2.2]		

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.
CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, MLG = MedDRA Labelling Group, TEAE = Treatment emergent adverse event
[a]MedDRA version 14.1. CTCAE Version 3
[b]MedDRA version 21.0. CTCAE Version 4.03
[c]MedDRA version 20.0. CTCAE Version 4.03
[d]Required or prolonged
[e]Adverse events leading to permanent study drug discontinuation
Sources: Integrated Analysis of Safety for Xofigo®, Table 1.3.1/9.25.1
Integrated Analysis of Safety for Xofigo®, Table 4.3.1/9.25.1
Global Integrated Analysis:
sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
20180612_bay888223_rmp_update - Data on file Amended Clinical Study Report PH-38459, Table 14.3.1/4

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Table SVII.11: Incidence rates of serious TEAE "pancytopenia" and outcomes of all TEAEs by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: MLG Pancytopenia

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]	Study 16506[c]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)	Xofigo® (N=44) n (rate in %)
Serious adverse event	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**
All (serious)	5 (0.8)	0 (0.0)	5 (0.6)	6 (0.58)	0 (0.0)
[95% CI for rate (%)]	[0.3, 1.8]	[0.0, 1.1]	[0.2, 1.3]	[0.21, 1.27]	
Worst outcome					
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Not recovered/ resolved	8 (1.3)	0 (0.0)	9 (1.0)	5 (0.49)	
Recovering/resolving	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Recovered/resolved with sequelae	3 (0.5)	0 (0.0)	3 (0.3)	3 (0.29)	
Recovered/resolved	1 (0.2)	0 (0.0)	1 (0.1)	2 (0.19)	
Missing/Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hospitalisation[d]	3 (0.5)	0 (0.0)	3 (0.3)	4 (0.39)	
[95% CI for rate (%)]	[0.1, 1.4]	[0.0, 1.1]	[0.1, 1.0]	[0.11, 0.99]	
Discontinuation[e]	1 (0.2)	0 (0.0)	1 (0.1)	2 (0.19)	
[95% CI for rate (%)]	[0.0, 0.9]	[0.0, 1.1]	[0.0, 0.6]		

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.
CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, MLG = MedDRA Labelling Group, TEAE = Treatment emergent adverse event
[a]MedDRA version 14.1. CTCAE Version 3
[b]MedDRA version 21.0. CTCAE Version 4.03
[c]MedDRA version 20.0. CTCAE Version 4.03
[d]Required or prolonged
[e]Adverse events leading to permanent study drug discontinuation
Sources: Integrated Analysis of Safety for Xofigo®, Table 1.3.1/9.26.1
Integrated Analysis of Safety for Xofigo®, Table 4.3.1/9.26.1
Global Integrated Analysis:
sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
20180612_bay888223_rmp_update - Data on file Amended Clinical Study Report PH-38459, Table 14.3.1/4

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Table SVII.12: Incidence rates of serious TEAE "leukopenia" and outcomes of all TEAEs by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: MLG Leukopenia

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]	Study 16506[c]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)	Xofigo® (N=44) n (rate in %)
Serious adverse event	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**
All (serious)	3 (0.5)	0 (0.0)	3 (0.3)	4 (0.39)	0 (0.0)
[95% CI for rate (%)]	[0.1, 1.4]	[0.0, 1.1]	[0.1, 1.0]	[0.11, 0.99]	
Worst outcome					
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Not recovered/ resolved	7 (1.1)	0 (0.0)	11 (1.2)	13 (1.26)	
Recovering/resolving	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.10)	
Recovered/resolved with sequelae	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Recovered/resolved	17 (2.7)	1 (0.3)	32 (3.5)	49 (4.77)	
Missing/Unknown	1 (0.2)	0 (0.0)	2 (0.2)	1 (0.10)	
Hospitalisation[d]	2 (0.3)	0 (0.0)	2 (0.2)	3 (0.29)	
[95% CI for rate (%)]	[0.0, 1.1]	[0.0, 1.1]	[0.0, 0.8]	[0.06, 0.85]	
Discontinuation[e]	2 (0.3)	0 (0.0)	2 (0.2)	1 (0.10)	
[95% CI for rate (%)]	[0.0, 1.1]	[0.0, 1.1]	[0.0, 0.8]		

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.
CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, MLG = MedDRA Labelling Group, TEAE = Treatment emergent adverse event
[a]MedDRA version 14.1. CTCAE Version 3
[b]MedDRA version 21.0. CTCAE Version 4.03
[c]MedDRA version 20.0. CTCAE Version 4.03
[d]Required or prolonged
[e]Adverse events leading to permanent study drug discontinuation
Sources: Integrated Analysis of Safety for Xofigo®, Table 1.3.1/9.27.1
Integrated Analysis of Safety for Xofigo®, Table 4.3.1/9.27.1
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Severity and nature of risk:

Bone marrow toxicity is very common side effect of chemotherapy used as treatment of metastatic CRPC (40, 41).

The majority of reported events were of mild-to-moderate severity. However, it can be life-threatening and may be fatal.

Neutropenia

The severity of neutropenia according to CTCAE is displayed in the section frequency in Table SVII.5. Most of the cases (27 of 42 cases) were of mild-to-moderate intensity in all clinical trial populations (pool 2 and study 16506) treated with Xofigo®. In Xofigo® monotherapy studies (pool 3), 28 of 41 cases were of mild-to-moderate intensity.

Thrombocytopenia

The severity of thrombocytopenia according to CTCAE is displayed in the section frequency in Table SVII.6. Half of the cases (41 of 83 cases) were of mild-to-moderate intensity in all clinical trial populations (pool 2 and study 16506) treated with Xofigo®. In Xofigo® monotherapy studies (pool 3), 58 of 106 cases were of mild-to-moderate intensity.

Pancytopenia

The severity of pancytopenia according to CTCAE is displayed in the section frequency in Table SVII.7. In all clinical trial populations (pool 2 and study 16506) treated with Xofigo®, 5 of 13 cases were of mild-to-moderate intensity and 7 cases were of Grade 3 to Grade 4 intensity. In Xofigo® monotherapy studies (pool 3), 3 of 10 cases were of mild-to-moderate intensity, and 7 cases of Grade 3 to Grade 4 intensity.

Leukopenia

The severity of leukopenia according to CTCAE is displayed in the section frequency in Table SVII.8. In all clinical trial populations (pool 2 and study 16506), most of the cases (35 of 49 cases) were of mild-to-moderate intensity. In Xofigo® monotherapy studies (pool 3), 52 of 64 cases were of mild-to-moderate intensity.

Risk factors and risk groups:

Patients with reduced bone marrow capacity e.g., following prior cytotoxic and/or radiation treatment.

Preventability:

Haematological evaluation of patients must be performed at baseline and prior to every dose of Xofigo®. Before the first administration of Xofigo®, the absolute neutrophil count (ANC) should be $\geq 1.5 \times 10^9$/L, the platelet count $\geq 100 \times 10^9$/L and haemoglobin ≥ 10.0 g/dL. Before subsequent administrations, the ANC should be $\geq 1.0 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L. In case there is no recovery in these values within 6 weeks after the last administration of Xofigo® despite receiving standard of care, further treatment with Xofigo® should only be continued after a careful benefit/risk evaluation.

Patients with evidence of compromised bone marrow reserve should be treated with caution.

Impact on the risk-benefit balance of the product:

The impact of bone marrow toxicity leading to reduced formed elements in blood under treatment with Xofigo® is countered by routine pharmacovigilance measures.

Public health impact:

Only a limited number of bone marrow toxicity cases result in hospitalisation of the affected patients. Therefore, the public health impact of this risk can be considered low.

SVII.3.1.3. Important Potential Risk: Late Bone Marrow Toxicity

Bayer MedDRA Query (BMQ): Late Bone marrow toxicity (Radium-223 dichloride). Refer to **Annex 7.1** for List of PTs included.

MedDRA Version 14.1 was used for coding of pools 1 and 2, MedDRA version 21.0 for pool 3, MedDRA Version 20.0 for study 16506.

Potential mechanisms**:**

Radiation induced bone marrow fibrosis and hypocellularity.

Evidence source(s) and strength of evidence:

Data from clinical studies with Xofigo®; Re-treatment safety study 16506.

Characterisation of the risk:

Re-treatment safety study 16506 in subjects with CRPC with bone metastases who received an initial course of six doses of Radium-223 dichloride 50 kBq/kg every four weeks was recently completed. There was minimal haematologic toxicity during the treatment period (see previous section SVII.3.1.2) and the 2-year follow-up period with no cumulative haematologic toxicity being reported. During the 2-year follow-up period following the last dose of Radium-223 dichloride, there were no occurrences of second primary malignancies, aplastic anaemia, or myelodysplastic syndrome.

Frequency with 95% confidence interval (CI):

Clinical trials

Randomised, blinded trial population only (pool 1):

As of 15 JUL 2011, one SAE report of aplastic anaemia was received in study BC1-06. Aplastic anaemia was diagnosed in JUN 2011, one year after last treatment with Xofigo®. The event was confounded by prior systemic radionuclide (samarium), external radiotherapy, and chemotherapy (docetaxel).

In placebo arm, there was one case of aplastic anaemia reported in a patient, diagnosed in NOV 2010. Aplastic anaemia was diagnosed 31 weeks after last injection of injection and this patient had also received prior docetaxel chemotherapy.

All clinical trial populations (pool 2):

There were no additional cases of late bone marrow toxicity reported in this analysis pool compared to pool 1.

Xofigo® monotherapy populations (pool 3):

There were no additional cases of late bone marrow toxicity reported in this analysis pool compared to pools 1 and 2.

Other clinical trial data

No additional cases of aplastic anaemia were reported during the 3-year follow-up of ALSYMPCA study, the long term follow-up of EAP 15995, EAP 16216, and in the re-treatment safety study 16506.

Seriousness/outcomes:

Clinical trials

Randomised, blinded trial population only (pool 1):

There was one SAE report of aplastic anaemia (confirmed by bone marrow biopsy) received in the Xofigo® arm of study BC1-06. This patient did not recover and required ongoing red cell transfusions.

There was one case of aplastic anaemia in the placebo arm of study BC1-06 (not confirmed by bone marrow biopsy). This patient was reported to have died subsequently of skeletal metastases from prostate cancer.

All clinical trial populations (pool 2):

There were no additional SAEs of aplastic anaemia reported in this analysis pool compared to pool 1.

Xofigo® monotherapy populations (pool 3):

There were no additional cases of late bone marrow toxicity reported in this analysis pool compared to pools 1 and 2.

There were no additional SAEs of aplastic anaemia in the re-treatment safety study 16506.

Severity and nature of risk:

Late bone marrow toxicity is life-threatening and potentially fatal.

Risk factors and risk groups:

Prior exposure to systemic radionuclide therapy, and/or chemotherapy.

Preventability:

No known preventive measures.

Impact on the risk-benefit balance of the product:

The impact of late bone marrow toxicity under treatment with Xofigo® is countered by routine pharmacovigilance activities.

Public health impact:

Long-term transfusion support, hospitalisation and mortality associated.

SVII.3.1.4. Important Potential Risk: Myelodysplastic syndrome (MDS); acute myeloid leukaemia (AML)

BMQ: Myelodysplastic Syndrome and Acute Myeloid Leukaemia (Radium-223 dichloride). Refer to **Annex 7.1** for List of PTs included.

MedDRA Version 14.1 was used for coding of pools 1 and 2, MedDRA version 21.0 for pool 3, MedDRA Version 20.0 for study 16506.

Potential mechanisms:

Radiation induced genetic damage in haematopoietic stem cells in the bone marrow and induction of MDS/AML.

Evidence source (s) and strength of evidence:

No cases have been reported in interventional clinical trials of Radium-223 dichloride. Information obtained from literature regarding risks from radiation.

Characterisation of the risk:

Frequency with 95% confidence interval (CI):

Clinical trials

No cases of MDS/AML reported in interventional clinical trials of Xofigo®.

Other clinical study data

There were no reported cases of myelodysplastic syndrome or AML in EAP 16216, 3-year follow-up of ALSYMPCA study (15245), the long-term follow-up in EAP 15995, or in the re-treatment safety study 16506.

Severity and nature of risk:

MDS/AML is potentially life threatening or fatal should it occur.

Risk factors and risk groups:

Patients who survive cancer treatment with alkylating agents, with or without radiotherapy, have a high risk of developing MDS or secondary acute leukaemia.

Preventability:

No known preventive measures.

Impact on the risk-benefit balance of the product:

The impact of the important potential risk of MDS/AML under treatment with Xofigo® is countered by routine pharmacovigilance activities.

Public health impact:

To date clinical data do not demonstrate an increased risk of MDS/AML as no cases have been reported in Radium-223 dichloride interventional clinical trials.

Any impact on public health is not expected to be significant considering the latency period for developing MDS/AML, and the limited life expectancy of the target population.

SVII.3.1.5. Important Potential Risk: Bone sarcoma

BMQ: Bone Sarcoma (Radium-223 dichloride). Refer to **Annex 7.1** for List of PTs included.

MedDRA Version 14.1 was used for coding of pools 1 and 2, MedDRA version 21.0 for pool 3, MedDRA Version 20.0 for study 16506.

Potential mechanisms:

Alpha particles recognised as carcinogen (42).

Evidence source (s) and strength of evidence:

No cases have been reported in clinical studies of Xofigo®. Information obtained from literature regarding risks from radiation.

Characterisation of the risk:

Frequency with 95% confidence interval (CI):

Clinical trials

No cases of bone sarcoma reported in clinical studies of Xofigo®.

Other clinical study data

No cases of bone sarcoma were reported from long term follow-up of EAP 15995, from 3-year follow-up of ALSYMPCA study (15245), and in the re-treatment study 16506.
One event of primary bone cancer was reported in the EAP 16216, diagnosed on the day of fifth dose of study drug by imaging, and was considered not related to Xofigo®. No other details, including whether bone metastasis was ruled out, were available regarding the event.

Severity and nature of risk:

Potentially life-threatening or fatal should it occur.

Risk factors and risk groups:

Prior external radiation therapy to bone and/ or systemic bone seeking radionuclide therapy.
Young age (growing skeleton) at the time of exposure.

Bone tumours, primarily osteogenic sarcomas, have appeared in the first arm of German patients injected with Radium-224; study of 899 persons who received multiple injections of

Radium-224, another alpha particle emitting isotope of Radium, between 1945 and 1955 for treatment of tuberculosis, ankylosing spondylitis. A total of 56 sarcomas have been found; the expected number is 0.2 to 0.3 (43). The lowest total dose associated with a bone tumour was 6.4 µCi/kg (237 kBq/kg) given over two months (44).

In the second group of German patients treated with Radium-224, at lower injected doses, three malignant tumours in the skeleton have been observed (versus 0.4 to 0.7 expected); two were tumours of the bone marrow (a reticulum cell sarcoma and a plasmocytoma) and one was a fibrosarcoma (45). One skeletal tumour, a plasmocytoma, was observed among the controls, a arm of 1,338 ankylosing spondylitis patients who were not treated with radiation (45).

Among 1,474 women employed in the US Radium industry before 1930, 61 osteosarcomas have been reported (42, 46).

Preventability:

No known preventive measures.

Impact on the risk-benefit balance of the product:

The impact of the important potential risk of bone sarcoma under treatment with Xofigo® is countered by routine pharmacovigilance activities.

Public health impact:

Unknown, as no cases have been reported in Xofigo® clinical studies to date. Target population consists of older age group at the time of exposure and the usual latency period is much longer (several years to decades) compared to the relatively short life expectancy in target population.

SVII.3.1.6. Important Potential Risk: Second primary malignancies (other than bone sarcoma and myelodysplastic syndrome, acute myeloid leukaemia)

Standardised MedDRA Query (SMQ): Malignant tumours excluding PTs from MTGs: SMQ: Prostate Malignant Tumours, Product specific Bayer MedDRA query (PBMQ): Bone sarcoma (Radium-223 dichloride), PBMQ: Late bone marrow toxicity (Radium-223 dichloride), PBMQ: Myelodysplastic syndrome and Acute myeloid leukaemia, excluding PTs from HLGT: Metastases; PT: Cancer in remission; PT: Neonatal leukaemia; PT: Neonatal neuroblastoma; Lowest Level Term (LLT): Progression of pre-existing cancer. Refer to **Annex 7.1** for List of PTs included.

MedDRA Version 14.1 was used for coding of pools 1 and 2, MedDRA version 21.0 for pool 3, MedDRA Version 20.0 for study 16506.

Potential mechanisms:

Radiation induced genetic mutation and induction of carcinogenesis.

Evidence source(s) and strength of evidence:

Data from clinical studies with Xofigo®; Re-treatment safety study 16506.

Characterisation of the risk:

Re-treatment safety study 16506 in subjects with CRPC with bone metastases who received an initial course of six doses of Radium-223 dichloride 50 kBq/kg every four weeks was recently completed. During the 2-year follow-up period following the last dose of Radium-223 dichloride, there were no occurrences of second primary malignancies, aplastic anaemia, or myelodysplastic syndrome. Long-term safety Study 16913 (REASSURE) in patients with CRPC with bone metastasis was recently completed. This observational, prospective, single-arm cohort study aimed to evaluate the short- and long-term safety profile of radium-223 dichloride in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving radium-223 in routine clinical practice. Twenty-four (24) patients (1.6%) experienced 25 second primary malignancies, which included skin cancers, lung-related malignancies, and gastrointestinal cancers. Notably, the incidence of second primary malignancies observed in REASSURE was lower than expected based on external reference studies with standardised morbidity ratios (SMRs).

Frequency with 95% confidence interval (CI):

Clinical trials

Randomised, blinded trial population only (pool 1):

There were seven second primary malignancies reported in patients treated with Xofigo®.

In placebo group – There were two second primary cancers reported.

All clinical trial populations (pool 2):

There were eight second primary malignancies reported in patients treated with Xofigo®.

Xofigo® monotherapy populations (pool 3):

There were 5 second primary malignancies reported in patients treated with Xofigo®.

Other clinical study data:

Second primary malignancies were reported in eight patients in the EAP 16216 and in five patients in the EAP 15995. None of the malignancies were considered related to Xofigo®. At the end of the 3-year follow-up of ALSYMPCA study, there were in total 0.8% (5/600) subjects in the Xofigo® arm and 1.33% (4/301) subjects in the placebo arm with confirmed new primary neoplasms reported. Second primary malignancies (squamous cell carcinoma of skin and meningioma) were reported in two patients who crossed over from placebo to Xofigo® arm.

Seriousness/outcomes:

Clinical trials

Randomised, blinded trial population only (pool 1):

In study BC1-02 – Xofigo® arm - There were 3 second primary cancers reported. These include 1 case of rectal cancer diagnosed at 6 months after first injection (Outcome: patient died 8 months after diagnosis, cause of death was progression of metastatic prostate cancer),

1 case of superficial papillary transitional cell carcinoma of bladder diagnosed 12 months after first injection (Outcome: Asymptomatic and removed on the same day as diagnosed), and 1 case of pancreatic cancer at 18 months after first injection.(Outcome: No treatment for pancreatic cancer, patient died one month later, due to metastatic prostate cancer/pancreas cancer).

In study BC1-06 – Xofigo® arm - there were 4 second primary cancers observed. These included 1 skin cancer (non-melanoma, CTCAE grade 1) at 4 weeks post 4 injections (Outcome: unknown, no action taken), 1 squamous cell carcinoma right wrist at 4 weeks post 5 injections (Outcome: recovered the same day as diagnosis, because of removal), 1 bladder cancer at 4 weeks post 6 injections (Outcome: no action taken to treat, patient died about 6 months later, cause of death was reported as unknown with event ongoing at the time of death), and 1 case of lymph node metastasis not from prostate cancer observed at follow-up visit 6 (84 weeks after post 6 injections).

None were reported as related to the study drug. None of these second primary cancers are considered as likely due to Xofigo® because of its biodistribution and as well as latency period of radiation-induced malignancies (solid tumours) which is much longer (47-49).

Placebo arm – There were 2 second primary cancers observed. These included 1 gastric carcinoma at 12 weeks post 5 injections (Outcome: the patient died soon afterwards and the cause of death was reported as due to gastric carcinoma) and 1 squamous cell carcinoma skin at 4 weeks post 5 injections (Outcome reported as recovered after removal). In addition there was 1 case reported as neoplasm (tumour left nates, CTCAE grade 2, and not confirmed as malignant). Outcome: Neoplasm treated with medication, not recovered but no changes expected, patient died of prostate cancer, skeletal metastases, unrelated to study drug.

All clinical trial populations (pool 2):

In addition to the cases reported in Pool 1, there was one case reported from study BC1-04 at 1 month post first injection of metastatic squamous cell carcinoma unknown primary. No action was taken to treat this and patient died about two month later, cause of death reported as metastatic squamous cell carcinoma unknown primary. The event was reported as unrelated to the study drug.

Xofigo® monotherapy populations (pool 3):

Of the 5 second primary malignancies reported in patients treated with Xofigo®, there was one reported Grade 2 SAE which was not recovered/resolved. In one case, permanent study drug discontinuation was required. Of the remaining 4 AEs, there was one case each of Grades 1, 2, 3, and 5. Two of these cases did not recover/resolve, one case was resolved, and one case was fatal.

Other clinical study data:

In EAP 16216, second primary malignancies were reported in eight patients: oral cavity cancer (diagnosed shortly after fourth [final] dose of study drug [exact date unknown]), squamous cell cancer (diagnosed on the day of sixth [final] dose of study drug), pseudomyxoma peritonei (diagnosed 71 days after sixth [final] dose of study drug), bladder

cancer (diagnosed 26 days after fifth [final] dose of study drug), soft tissue carcinoma (diagnosed 32 days after fourth dose of study drug; subject completed 6 cycles of treatment), kidney cancer (diagnosed 12 days after first dose of study drug; subject completed 6 cycles of treatment), basal cell carcinoma (diagnosed on day of fourth dose of study drug; subject received final dose at cycle 5), and malignant melanoma (diagnosed 13 days after fifth dose of study drug; subject completed 6 cycles of treatment). All events occurred in 1 subject each (0.1%). None of these malignancies were considered related to study drug. Outcome for squamous cell carcinoma of skin, basal cell carcinoma, melanoma, pseudomyxoma peritonei and soft tissue carcinoma was reported as recovered/resolved. No fatal outcomes were reported for any of the malignancies.

In EAP 15995, five subjects experienced second primary malignancies: squamous cell carcinoma (initially diagnosed approximately 3 years before starting Xofigo® but under control following surgery, radiation and chemotherapy and recurred after starting Xofigo®) basal cell carcinoma (diagnosed 6 weeks after sixth [final] dose of study drug), bronchial carcinoma (diagnosed 2 days after sixth [final] dose of study drug), meningioma (diagnosed 2 weeks after second [final] dose of study drug), and plasma cell myeloma (diagnosed 15 days after third [final] dose of study drug). All events occurred in 1 subject each (0.5%). None of these malignancies were considered related to study drug. For two of the patients (patients with squamous cell carcinoma skin and basal cell carcinoma) there was a history of similar prior malignancies. One event of bronchial carcinoma was reported in a patient with history of smoking. A biopsy report from the patient with meningioma observed that whether the tumour was meningothelial hyperplasia or meningioma could not fully be answered and carcinomatous invasion of the suspected meningioma by prostate cancer metastasis was observed. Outcomes for the basal cell carcinoma and meningioma were reported as recovered/resolved. The other three malignancies were reported with fatal outcomes.

Three-year follow-up of ALSYMPCA study BC1-06 – Xofigo® arm – there were 3 additional second primary malignancies: squamous cell carcinoma of skin (diagnosed 7 weeks post 6^{th} dose), neoplasm skin (diagnosed post first dose), and meningioma (diagnosed 23 weeks post 6^{th} dose). Medical history of the patient presenting with squamous cell carcinoma included superficial bladder cancer, malignant melanoma and docetaxel use. Patient with neoplasm skin had prior radiotherapy and presented with abnormal skin growth on face (Not otherwise specified [NOS]) which resolved following skin biopsy. Patient diagnosed with meningioma had a history of multiple exposures to EBRT and docetaxel use. No fatal outcomes were reported.

Placebo arm – there were 2 additional second primary malignancies: Adenocarcinoma of rectum (diagnosed 12 weeks post 6^{th} dose) and skin cancer (diagnosed 101 weeks post 6^{th} dose). Both patients had a history of radiotherapy. No fatal outcomes were reported.

Severity and nature of risk:

Second primary malignancies are life-threatening and potentially fatal.

Risk factors and risk groups:

No defined risk group in target population.

Preventability:

No known preventive measures.

Impact on the risk-benefit balance of the product:

The impact of the important potential risk of second primary malignancies under treatment with Xofigo® is countered by routine pharmacovigilance activities.

Public health impact:

At present public health impact is unknown.

SVII.3.1.7. Important Potential Risk: Osteonecrosis of the jaw

Refer to **Annex 7.1** for List of PTs for the topic 'Osteonecrosis of the jaw'.

MedDRA Version 14.1 was used for coding of pools 1 and 2, MedDRA version 21.0 for pool 3, MedDRA Version 20.0 for study 16506.

Potential mechanisms:

Radiation of the bone.

Evidence source and strength of evidence:

Data from clinical studies with Xofigo®. Re-treatment safety study 16506.

Characterisation of the risk:

Frequency with 95% confidence interval (CI):

ONJ was reported in 4 cases (0.6%) in patients receiving Xofigo® in the randomised, blinded trial population (pool 1), compared to 1 case (0.3%) in the placebo arms. In all clinical trial populations treated with Xofigo® (pool 2), 4 cases (0.4%) of ONJ were reported (see Table SVII.16). In the Xofigo® monotherapy studies (pool 3), a total of 7 (0.68%) ONJ cases were reported. In the re-treatment safety study 16506, a total of 4 cases of ONJ were reported (PT: osteonecrosis of the jaw [3 cases]; osteonecrosis [1 case]), corresponding to an incidence of 9.1%. The 4 subjects were receiving concomitant denosumab or zoledronic acid.

Seriousness/outcomes:

Apart from 1 case (0.3%) in the placebo arms of the randomised, blinded trial population (pool 1), no serious cases of ONJ were reported across treatment arms. Only in 1 case (0.3%) in the placebo arm hospitalisation was required or prolonged (see Table SVII.17). In the Xofigo® treated patients, 3 cases (0.5%) did not recover compared to 1 case (0.3%) in the placebo arm. In all clinical trial populations treated with Xofigo® (pool 2), 2 cases (0.2%) had to permanently discontinue the study drug and 3 of 4 cases were not resolved. Of the 7 cases in pool 3, two (0.19%) were serious (Grade 3). Hospitalisation was required or prolonged in 2 cases, and the Xofigo® treatment had to be permanently discontinued in 3 cases. Four cases were not recovered, and 3 cases were resolved. One case in the re-treatment safety study 16506 (2.3%) was serious.

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Table SVII.16: Incidence rates of TEAE "osteonecrosis of the jaw" by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: see Annex 7.1

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]	Study 16506[c]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)	Xofigo® (N=44) n (rate in %)
Worst CTCAE Grade	Crude Incidence Rate	Crude Incidence Rate	Crude Incidence Rate	Crude Incidence Rate	Crude Incidence Rate
Grade 1	1 (0.2)	0 (0.0)	1 (0.1)	1 (0.10)	0 (0.0)
Grade 2	2 (0.3)	0 (0.0)	2 (0.2)	3 (0.29)	3 (6.8)
Grade 3	1 (0.2)	1 (0.3)	1 (0.1)	3 (0.29)	1 (2.3)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All [95% CI for rate (%)]	4 (0.6) [0.2, 1.6]	1 (0.3) [0.0, 1.7]	4 (0.4) [0.1, 1.1]	7 (0.68) [0.27, 1.40]	4 (9.1)
Risk difference [95% CI]		0.00 [-0.01, 0.01]			
EAIR [95% CI]	4 (0.012) [0.003, 0.030]	1 (0.006) [0.000, 0.036]	4 (0.009) [0.003, 0.024]	7 (0.017) [0.007, 0.036]	
IRD for EAIR [95% CI]		0.01 (-0.01, 0.02)			

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.
CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, EAIR = Exposure-adjusted incidence rate, IRD = Incidence rate difference, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = Treatment emergent adverse event
[a]MedDRA version 14.1. CTCAE Version 3
[b]MedDRA version 21.0. CTCAE Version 4.03
[c]MedDRA version 20.0. CTCAE Version 4.03
Sources: Integrated Analysis of Safety for Xofigo®, Table 1.3.1/9.28.1
Integrated Analysis of Safety for Xofigo®, Table 4.3.1/9.28.1
Global Integrated Analysis:
sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
20180612_bay888223_rmp_update - Data on file
Amended Clinical Study Report PH-38459, Table 14.3.1/4

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Table SVII.17: Incidence rates of serious TEAE "osteonecrosis of the jaw" and outcomes of all TEAEs by integrated analysis pool, worst CTCAE grade and treatment group - MedDRA search strategy: see Annex 7.1

	Randomised, blinded trial population only (pool 1)[a]		All clinical trial populations (pool 2)[a]	Xofigo® monotherapy (pool 3)[b]	Study 16506[c]
	Xofigo® (N=633) n (rate in %)	Placebo (N=332) n (rate in %)	Xofigo® (N=904) n (rate in %)	Xofigo® (N=1,028) n (rate in %)	Xofigo® (N=44) n (rate in %)
Serious adverse event	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**	**Crude Incidence Rate**
All (serious)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.19)	1 (2.3)
[95% CI for rate (%)]	[0.0, 0.6]	[0.0, 1.7]	[0.0, 0.4]	[0.02, 0.70]	
Worst outcome					
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Not recovered/ resolved	3 (0.5)	1 (0.3)	3 (0.3)	4 (0.39)	
Recovering/resolving	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Recovered/resolved with sequelae	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Recovered/resolved	1 (0.2)	0 (0.0)	1 (0.1)	3 (0.29)	
Missing/Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hospitalisation[d]	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.19)	
[95% CI for rate (%)]	[0.0, 0.6]	[0.0, 1.7]	[0.0, 0.4]	[0.02, 0.70]	
Discontinuation[e]	2 (0.3)	0 (0.0)	2 (0.2)	3 (0.29)	
[95% CI for rate (%)]	[0.0, 1.1]	[0.0, 1.1]	[0.0, 0.8]		

EAIR is presented as patient-year. This table contains counts of subjects. If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term and for the episode with the maximum severity.
CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = Treatment emergent adverse event
[a]MedDRA version 14.1. CTCAE Version 3
[b]MedDRA version 21.0. CTCAE Version 4.03
[c]MedDRA version 20.0. CTCAE Version 4.03
[d]Required or prolonged
[e]Adverse events leading to permanent study drug discontinuation
Sources: Integrated Analysis of Safety for Xofigo®, Table 1.3.1/9.28.1
Integrated Analysis of Safety for Xofigo®, Table 4.3.1/9.28.1
Global Integrated Analysis:
sasp/patdb/ia/888223/stat/2018/prod_0523_rmp_msaf/pgms/t_durat_exposure.sas enaja 12JUN2018 18:08
20180612_bay888223_rmp_update - Data on file
Amended Clinical Study Report PH-38459, Table 14.3.1/4

Severity and nature of risk:

ONJ is a manageable and preventable condition. It may be debilitating condition requiring potentially hospitalisation especially when not diagnosed early and treated.

The severity of ONJ according to CTCAE is displayed in the section frequency in Table SVII.16 . In all clinical trial populations treated with Xofigo® (pool 2), three of 4 cases were of mild-to-moderate intensity. In pool 3 Xofigo® monotherapy studies, 4 out of 7 cases were of mild-to-moderate intensity, with three additional Grade 3 cases. In the re-treatment safety study 16506, 3 of 4 cases were of moderate intensity (Grade 2).

Risk factors and risk groups:

Bisphosphonate and/or denosumab use is a known risk factor for developing ONJ. Risk groups or risk factors for Xofigo® treatment are unknown.

Preventability:

Unknown for Xofigo® treatment.

Impact on the risk-benefit balance of the product:

The impact of the important potential risk of ONJ under treatment with Xofigo® is countered by routine pharmacovigilance activities.

Public health impact:

There is limited public health impact due to Xofigo® considering the reports received so far were all due to well-known causes of ONJ.

SVII.3.1.8. Important Potential Risks: Off-label use in women and children

Potential mechanisms

Off-label prescription by healthcare professionals.

Evidence source(s) and strength of evidence:

PASS 17399: The objective of this study was to evaluate the extent of potential off-label use of Xofigo®, in Sweden. Patients receiving Xofigo® with data recorded at nuclear medicine centres in Sweden between 01 JUL 2014 and 30 JUN 2016 were included in the study. Patients participating in clinical trials were excluded. Data from 12 out of 17 centres treating patients in Sweden during the time period was obtained. A total of 310 patients were included.

Characterisation of the risk:

Of the 310 recruited patients, 306 (98.7%) had metastatic CRPC. Four (1.29%) patients were treated for an indication other than metastatic CRPC, 2 with breast cancer, 1 with lung cancer, and 1 with osteosarcoma. All these patients had bone metastasis. One patient in the metastatic CRPC group had both skeletal and visceral metastasis at time of treatment. Two (0.64%) women were treated with Xofigo®, both with breast cancer. No children (under 18 years) were treated with Xofigo®. No patient was treated with more than 6 doses. 1.7 % of evaluable

doses were given either with less than 90% of planned dose or more than 110% of planned dose.

In this study of contemporary Xofigo® use in Sweden, a low rate of off-label use and no use of children (<18 yrs) were observed.

Risk factors and risk groups:

Breast cancer with bone metastases and children with osteosarcoma.

Preventability:

No known preventive measures.

Impact on the risk-benefit balance of the product:

Given the limited number of off-label use cases, the potential impact of off-label use in women and children remains uncertain.

Public health impact:

Limited, as the PASS has demonstrated low rates of off-label use.

SVII.3.1.9. Important Potential Risk: Off-label administration of repeated courses of treatment, or other administration of doses in excess of those recommended in the product information

Potential mechanisms:

Off-label prescription by healthcare professionals.

Evidence source(s) and strength of evidence:

PASS 17399: The objective of this study was to evaluate the extent of potential off-label use of Xofigo®, in Sweden. Patients receiving Xofigo® with data recorded at nuclear medicine centres in Sweden between 01 JUL 2014 and 30 JUN 2016 were included in the study. Patients participating in clinical trials were excluded. Data from 12 out of 17 centres treating patients in Sweden during the time period was obtained. A total of 310 patients were included.

Characterisation of the risk:

Of the 310 patients recruited in the PASS, no patient received an excess number of doses and a low percentage of doses was given in abnormal dosage.

A too low or too high dose was defined as a dose less than 90% or more than 110% of the expected, respectively. However, this data must be interpreted with some caution, because different nuclear medicine centres had different routines of recording the weight of the patient. Some had a new weight registered before each treatment and others just registered weight at the beginning of the treatment period. Of the given doses, 1.7 % were given with a too low or high dose from the definition.

The study has a high generalizability for Sweden and other countries with a similar health care system organised in a similar way.

Risk factors and risk groups:

Healthcare professionals administering higher doses than recommended and/or prescribing errors may increase potential for AEs, particularly increase the risk of bone marrow toxicity.

Preventability:

Not applicable.

Impact on the risk-benefit balance of the product:

Given the limited number of off-label use cases, the potential impact of off-label use remains uncertain.

Public health impact:

Limited, as the PASS has demonstrated low rates of off-label use.

SVII.3.2 Presentation of Missing Information

SVII.3.2.1 Safety in patients with insufficient wash-out period

Evidence source:

Wash-out period between the last injection of Radium-223 dichloride and abiraterone has not been studied.

Population in need of further characterisation:

Respective patients.

Anticipated risk/consequence:

Increased risk of AEs.

SVII.3.2.2 Safety of Radium-223 with other cancer therapy apart from therapy for maintenance of castration-level

Evidence source:

Benefits and risks of combination of Radium-223 dichloride with any other cancer therapies have not been established.

Population in need of further characterisation:

Respective patients.

Anticipated risk/consequence:

Increased risk of AEs.

SVII.3.2.3 Reproductive toxicity in men with metastatic CRPC

Evidence source:

Reproductive toxicity in men has not been studied.

Population in need of further characterisation:

Men who can father a child.

Anticipated risk/consequence:

Increased risk of infertility.

SVII.3.2.4 Reproductive toxicity due to off-label use in women

Evidence source:

Patient population has not been studied.

Population in need of further characterisation:

Women of childbearing potential.

Anticipated risk/consequence:

Radiation-induced reproductive toxicity.

SVII.3.2.5 Developmental toxicity due to off-label use in children

Evidence source:

Patient population has not been studied.

Population in need of further characterisation:

Respective patients.

Anticipated risk/consequence:

Increased risk of developmental abnormalities.

SVII.3.2.6 Clinical safety in patients with inflammatory bowel disease

Evidence source:

Patient population has not been studied.

Population in need of further characterisation:

Respective patients.

Anticipated risk/consequence:

Increased risk of aggravation of acute inflammatory bowel disease.

SVII.3.2.7 Clinical safety in non-white ethnic groups

Evidence source:

Patient population has not been studied.

Population in need of further characterisation:

Respective patients.

Anticipated risk/consequence:

Radium-223 is an isotope which decays and is not metabolised. Therefore no effect of ethnicity on pharmacokinetics/ pharmacodynamics of Radium-223 dichloride is expected.

SVII.3.2.8 Clinical safety in patients receiving chemotherapy

Evidence source:

Patient population has not been studied.

Population in need of further characterisation:

Respective patients.

Anticipated risk/consequence:

Increased risk of AEs and haematological toxicities.

SVII.3.2.9 Clinical safety in patients receiving calcium supplementation, phosphates or vitamin D

Evidence source:

Patient population has not been studied.

Population in need of further characterisation:

Respective patients.

Anticipated risk/consequence:

Potential competitive uptake in the bone.

SVII.3.2.10 Clinical safety in patients receiving external beam radiation therapy to bone or prostate

Evidence source:

Long-term follow-up of patients receiving concomitant EBRT.

Population in need of further characterisation:

Respective patients.

Anticipated risk/consequence:

Increased risk of AEs and haematological toxicities.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Bone fractures • Bone marrow toxicity leading to reduced formed elements in blood
Important potential risks	• Late bone marrow toxicity • Myelodysplastic syndrome/ Acute myeloid leukaemia (MDS/AML) • Bone sarcoma • Second primary malignancies (other than MDS/AML and bone sarcoma) • Osteonecrosis of the jaw • Off-label use in women or children • Off-label administration of repeated courses of treatment, or other administration of doses in excess of those recommended in the product information
Missing information	• Safety in patients with insufficient wash-out period • Safety of Radium-223 with other cancer therapy apart from therapy for maintenance of castration-level • Reproductive toxicity in men with metastatic CRPC • Reproductive toxicity due to off-label use in women • Developmental toxicity due to off-label use in children • Clinical safety in patients with inflammatory bowel disease • Clinical safety in non-white ethnic groups • Clinical safety in patients receiving chemotherapy • Clinical safety in patients receiving calcium supplementation, phosphates or vitamin D • Clinical safety in patients receiving external beam radiation therapy to bone or prostate

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance was and will be conducted for Xofigo® as detailed in corresponding pharmacovigilance procedures that are in place at Bayer. These routine activities include the collection, follow-up, evaluation and expedited reporting of individual case reports from all respective sources, ongoing monitoring and signal detection activities, preparation of Periodic Benefit-Risk Evaluation Reports (PBRERs)/ Periodic Safety Update Reports (PSURs), and initiation of label changes as required, and are described in applicable Standard Operating Procedures.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

III.1.1 Specific adverse reaction follow-up questionnaires for safety concerns

III.1.1.1 Questionnaire for “Haemorrhage with thrombocytopenia”

Increased bleeding may be indicative of bone marrow suppression. This questionnaire is designed for use following serious adverse event (SAE) reports of haemorrhage with thrombocytopenia. The requested data include detailed descriptions of the clinical symptoms and signs of the reported adverse event. The full questionnaire is provided in **Annex 4.1**.

III.1.1.2 Questionnaire for “Intracranial haemorrhage”

In PBRER/PSUR No. 12, Bayer proposed to stop close monitoring of cerebral haemorrhage events and continue routine pharmacovigilance. The event “cerebral haemorrhage” is unlisted in the current EU SmPC, and no changes are warranted to the label. The MAH assessment was endorsed by PRAC in the final PSUR assessment report (Procedure No.: EMEA/H/C/PSUSA/00010132/202105).

The follow-up questionnaire for intracranial haemorrhage was removed from the EU RMP but will continue to be used for routine pharmacovigilance.

III.1.1.3 Questionnaire for “Infection with neutropenia”

Neutropenia may be indicative of bone marrow suppression and may lead to an increased risk of developing infections. This questionnaire is designed for use following SAE reports of infection with neutropenia. The requested data include detailed descriptions of the clinical symptoms and signs of the reported adverse event, relevant concomitant medication and comorbidities, as well as detailed haematological analyses. The full questionnaire is provided in **Annex 4.2**.

III.1.1.4 Questionnaire for “Late bone marrow toxicity”

Late bone marrow toxicity is categorised as an important potential risk associated with Xofigo® treatment. This questionnaire is designed for use following reports of late bone marrow toxicity. The requested data include detailed descriptions of the clinical symptoms and signs of the late bone marrow toxicity, relevant medical history, histopathological

findings and the results of diagnostic investigations, and the query regarding prior exposure to risk factors known to be associated with bone marrow toxicity. The full questionnaire is provided in **Annex 4.3**.

III.1.1.5 Questionnaire for "New primary malignancy"

Myelodysplastic syndrome (MDS) / Acute myeloid leukaemia (AML) and bone sarcoma are categorised as important potential risks associated with Xofigo® treatment. This questionnaire is designed for use following reports of new primary malignancies and premalignant conditions. The requested data include detailed descriptions of the clinical symptoms and signs of the reported malignancy/premalignancy, relevant medical history, histopathological findings and the results of diagnostic investigations, query regarding prior exposure to risk factors known to be associated with the development of malignancy, as well details of the treatment undertaken. The full questionnaire is provided in **Annex 4.4**.

III.1.1.6 Questionnaire for "Osteonecrosis of the jaw"

Osteonecrosis of the jaw (ONJ) is categorised as an important potential risk associated with Xofigo® treatment. This questionnaire is designed for use following SAE reports of ONJ. The questionnaire specifically requests data on bisphospanate treatment, as ONJ events are a known class adverse reaction for the class of bisphosphonates. In addition, detailed descriptions of the clinical symptoms and signs of the reported SAE, relevant medical history, concomitant medications and diagnostic tests are also requested. The full questionnaire is provided in **Annex 4.5**.

III.1.1.7 Questionnaire for "Bone fractures"

Bone fractures are categorised as an important identified risk associated with Xofigo® treatment. This questionnaire is designed for use following SAE reports of bone fractures. In addition to requesting details on the reported SAE, the questionnaire specifically requests data on the existing glucocorticoid and systemic antiandrogen therapy, as the increased risk of fractures was observed in patients in ERA-223 trial who received the combination of Xofigo® and abiraterone plus predniso(lo)ne. The full questionnaire is provided in **Annex 4.6**.

III.1.2 Other forms of routine pharmacovigilance activities for safety concerns

Xofigo® might be expected to be used off-label by medical practitioners in indications authorised prior to PRAC Article 20 referral procedure. Routine Pharmacovigilance activities will consist of the review of reports of off-label use received from all sources during the respective period of PBRERs/PSURs.

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III.2 Additional pharmacovigilance activities

A total of two Category 1 studies and two Category 3 PASS are currently ongoing. The integrated study programme is summarised as follows:

Category 1 – 20510 – RADIANT – Phase IV randomised open-label multicentre study

Study short name and title:

A Phase 4, Randomized, Open-label, Multicenter Efficacy and Safety Study of Standard Dose of Radium-223 Dichloride *vs*. Standard Doses of Novel Anti-hormonal Therapy (NAH) in Patients with Bone Dominant Metastatic Castration Resistant Prostate Cancer (mCRPC) Progressing on/After One Line of NAH.

Rationale and study objectives:

The MAH was required to conduct and submit the results of a phase IV randomised open-label multicentre study according to an agreed protocol in order to further characterise the efficacy and safety, in particular the risk of fractures with Radium-223 dichloride in the authorised indication.

The protocol should foresee a stratified randomisation of patients according to total ALP levels.

This study will specifically address the important identified risk of bone fractures. The study also includes bone biomarker assessments (markers of bone formation and bone resorption) in the control arm.

Milestones:

Protocol submission to PRAC: Within 6 months of the EC decision

Final CSR submission: Q2 2026

Category 1 – 20511 – Phase I biodistribution study

Study short name and title:

Open-label, Non-randomized Phase 1, Multicenter Study to Assess Radium- 223 Biodistribution in Participants with Bone Metastatic Castration Resistant Prostate Cancer (CRPC) Receiving Radium-223 Dichloride Treatment.

Rationale and study objectives:

The MAH was required to conduct and submit the results of a phase I biodistribution study according to an agreed protocol in order to further characterise correlation between the extent of the disease, the dose and the distribution of Radium-223 dichloride in bone metastases versus sites of impaired bone health (e.g., osteoporosis) versus normal bone structure.

The study will specifically address the important identified risk of bone fractures.

Milestones:

Protocol submission to PRAC: 6 months after EC decision

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FPFV: AUG 2020

Final CSR submission: Q1 2026

Category 3 – 17739 – PEACE-3 – EORTC-sponsored Phase III study

Study short name and title:

A Randomised multicentre phase III trial comparing enzalutamide *vs*. a combination of Radium-223 dichloride and enzalutamide in asymptomatic or mildly symptomatic castration resistant prostate cancer patients metastatic to bone.

Rationale and study objectives:

The study sponsored by the European Organisation for Research and Treatment of Cancer (EORTC) is investigating the combination use with enzalutamide in asymptomatic and mildly symptomatic CRPC patients. The study will specifically address the important identified risk of bone fractures.

The primary objective of this study is:

- To assess if upfront combination of enzalutamide and Radium-223 dichloride improves radiological progression-free survival (rPFS1) compared to enzalutamide single agent in CRPC patients metastatic to bone

The secondary objective of this study is:

- To assess if upfront combination of enzalutamide with Radium-223 dichloride (experimental arm) offers further benefits over enzalutamide alone in terms of the secondary efficacy endpoints, to compare the safety profile of the approaches and to document their impact on patient reported outcomes (pain and QoL)

Study design:

A randomised phase III parallel assignment open label interventional trial.

Study population:

The study population will consist of asymptomatic or mildly symptomatic castration resistant prostate cancer patients metastatic to bone. The estimated recruitment will be 560 participants.

Milestones:

Study start date: OCT 2015

Interim status update: APR 2020

Primary completion: FEB 2024

Final CSR submission: Q4 2025

PEACE-3 Data Monitoring Committee (DMC) reports are provided by EORTC for every 50 newly enrolled patients and will be provided to EMA upon request.

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Category 3 – 19263 – DoRa – PCCTC-sponsored Phase III study

Study short name and title:

Phase III Trial of Docetaxel *vs*. Docetaxel and Radium-223 dichloride for Metastatic Castration-Resistant Prostate Cancer.

Rationale and study objectives:

The study sponsored by the Prostate Cancer Clinical Trials Consortium (PCCTC) is investigating the combination use of Xofigo® with docetaxel in CRPC patients.

The study will specifically address the important identified risk of bone fractures.

The primary objective of this study is:

- To compare overall survival for subjects treated with docetaxel versus subjects treated with docetaxel plus Radium-223 dichloride

The secondary objectives of this study are to compare:

- Radiographic progression-free survival as defined in PCWG3 (Prostate Cancer Clinical Trials Working Group 3) criteria
- Symptomatic Skeletal event free survival
- Time to total alkaline phosphatase (ALP) progression
- On-treatment alterations in quality of life as assessed by FACT-P (The Functional Assessment of Cancer Therapy-Prostate), BPI (Brief Pain Inventory), and BFI (Brief Fatigue Inventory) measures between subjects who receive docetaxel with those who receive docetaxel and Radium-223 dichloride.

Study design:

An open-label, 1:1 randomised, phase III study of docetaxel versus docetaxel in combination with Radium-223 dichloride in subjects with mCRPC.

Study population:

The study population will consist of chemo-naive castration resistant prostate cancer patients metastatic to bone with progressive disease and ≥ 2 bone lesions and who have received up to three prior treatments for mCRPC. The estimated recruitment will be up to a maximum of 738 participants.

Milestones:

Study start date: 20 JUN 2018

Interim status update: 30 APR 2021

Primary completion: NOV 2025

Final CSR submission: Q3 2026

DMC reports will be provided and discussed in PBRERs/PSURs.

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III.3 Summary table of additional pharmacovigilance activities

Table Part III.1: Ongoing and planned additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
20510 – RADIANT Phase IV randomised open-label multicentre study Ongoing	The MAH was required to conduct and submit the results of a phase IV randomised open-label multicentre study according to an agreed protocol in order to further characterise the efficacy and safety, in particular the risk of fractures, with Radium-223 dichloride in the authorised indication. The protocol should foresee a stratified randomisation of patients according to total ALP levels. The study also includes bone biomarker assessments (markers of bone formation and bone resorption) in the control arm.	Important identified risk: • Bone fractures	Protocol submission to PRAC Final CSR submission	Within 6 months of the EC decision Q2 2026
20511 Phase I biodistribution study	The MAH was required to conduct and submit the results of a phase I biodistribution study according to an agreed	Important identified risk: • Bone fractures	Protocol submission to PRAC FPFV	6 months after EC decision AUG 2020

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Table Part III.1: Ongoing and planned additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Final CSR submission	Q1 2026
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
17739 – PEACE-3 EORTC-sponsored Phase III study Ongoing	To investigate the combination use of Radium-223 dichloride with enzalutamide in asymptomatic and mildly symptomatic CRPC patients.	<u>Important identified risk:</u> • Bone fractures	Study start date Interim status update Primary completion Final CSR submission	OCT 2015 APR 2020 FEB 2024 Q4 2025
19263 – DoRa PCCTC-sponsored Phase III study Ongoing	To investigate the combination use of Radium-223 dichloride with docetaxel in CRPC patients.	<u>Important identified risk:</u> • Bone fractures	Study start date Interim status update Primary completion Final CSR submission to PRAC DMC reports will be provided and discussed in PBRERs/PSURs	20 JUN 2018 30 APR 2021 NOV 2025 Q3 2026

Part IV: Plans for post-authorisation efficacy studies

IV.1 Applicability of efficacy to all patients in the target population Indication: CRPC with bone metastases

Subgroup survival analysis showed a consistent survival benefit for treatment with Xofigo®, independent of levels of total ALP, current use of bisphosphonates, prior use of docetaxel and Eastern Cooperative Oncology Group (ECOG) status at baseline. A post-hoc analysis showed that the beneficial effect of Xofigo® on survival was independent of steroid use at baseline.

In clinical studies in the Radium-223 dichloride development program excluded patients with known visceral metastases, lymph node disease up to 3 cm was acceptable. In these patients, bone disease is often dominant (up to 90% of cases) and visceral lesions can be clinically inconsequential. As the bone disease dominates the clinical picture, Radium-223 dichloride is likely to be of benefit for patients with bone metastases and visceral metastases.

Nearly all patients in study BC1-06 were symptomatic (World Health Organisation [WHO] ladder of pain 2-3) or minimally symptomatic (WHO ladder of pain 1). However, there is no rationale why Xofigo® would be less effective in asymptomatic patients with bone metastases.

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IV.2 List of the Planned and Ongoing Imposed Post-authorisation Efficacy Studies

Overall survival was used to demonstrate the efficacy of Xofigo® in the main study BC1-06.

Bayer has obtained confirmation from the European Medicines Agency that the class waiver for paediatric investigational plan with respect to prostate cancer is applicable to Xofigo® for the treatment of castration-resistant prostate cancer with bone metastases.

Table Part IV.1: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study Status	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones** (planned, started)	**Due Date**
20510 – RADIANT Phase IV randomised open-label clinical trial Ongoing	The MAH was required to conduct and submit the results of a phase IV randomised open-label multicentre study according to an agreed protocol in order to further characterise the efficacy and safety, in particular the risk of fractures, with Radium-223 dichloride in the authorised indication. The protocol should foresee a stratified randomisation of patients according to bone ALP levels. The study also includes bone biomarker assessments (markers of bone formation and bone resorption) in the control arm.	<u>Important identified risk:</u> • Bone fractures	Study protocol submission to PRAC Final CSR submission	6 months of the EC decision Q2 2026

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Risk minimisation plan

The Risk Minimisation Plan for Xofigo® comprises routine risk minimisation measures for the safety concerns as detailed in Section V.1.

V.1 Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important Identified risks	
Bone fractures	**Routine risk communication:** SmPCs: Section 4.1 (Therapeutic indication) Section 4.8 (Undesirable effects) Section 5.1 (Pharmacodynamic properties) Section 5.3 (Preclinical safety data) Package leaflets (PLs): Section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Sections 4.3 (Contraindications), 4.4. (Special warnings and precautions for use), and PL Section 2 (“Xofigo® must not be given”; Warnings and precautions; Other medicines and Xofigo®) Instructions that Xofigo® must not be given in combination with abiraterone and prednisone/prednisolone. The combination of Xofigo® with other systemic cancer therapies other than luteinising hormone-releasing hormone (LHRH) analogues is not recommended. Subsequent treatment with Xofigo® should not be initiated for at least 5 days after the last administration of abiraterone acetate in combination with prednisone/prednisolone. Subsequent systemic cancer treatment should not be initiated for at least 30 days after the last administration of Xofigo®. Patients are instructed to inform their healthcare practitioner if they are already taking any of the above mentioned medicines or other second generation androgen receptors antagonists. Patients are instructed to inform their healthcare practitioner if they have osteoporosis or a known increased risk for fractures (e.g. recent bone fracture, fragility). The use of Xofigo® is not recommended for treatment of adults with castration-resistant prostate cancer and asymptomatic or mildly symptomatic bone metastases. Prior to starting Xofigo® therapy, bone status (e.g. by scintigraphy, bone mineral density measurement) and baseline risk of fractures of patients (e.g.

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Safety concern	Routine risk minimisation measures
	osteoporosis, medication increasing fracture risk, low body mass index) should be carefully assessed, and closely monitored for at least 24 months. Preventive measures such as the use of bisphosphonate or other comparable bone protective agents (e.g. denosumab) should be considered before starting or resuming treatment with Xofigo®. In patients with a high baseline risk of fracture, the benefit of treatment should be carefully assessed to outweigh the risk. In patients with bone fractures, orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with Xofigo®. **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Bone marrow toxicity leading to reduced formed elements in blood	**Routine risk communication:** SmPCs: Section 4.5 (Interaction with other medicinal products and other forms of interaction) Section 4.8 (Undesirable effects) Section 5.3 (Preclinical safety data) PLs: Section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4 (Special warnings and precautions for use) and PL Section 2 (Warnings and precautions) Instructions that haematological evaluation of patients must be performed at baseline and prior to every dose of Xofigo®. Patients with evidence of compromised bone marrow reserve or prostate cancer patients with advanced diffuse infiltration of the bone (extent of disease 4 [EOD4]; “superscan”) should be treated with caution. **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.

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Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important potential risk	
Late bone marrow toxicity	**Routine risk communication:** SmPCs: Section 4.8 (Undesirable effects) PLs: Section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4 (Special warnings and precautions for use) and PL Section 2 (Warnings and precautions) Instructions that haematological evaluation of patients must be performed at baseline and prior to every dose of Xofigo®. Patients with evidence of compromised bone marrow reserve or prostate cancer patients with advanced diffuse infiltration of the bone (EOD4; “superscan”) should be treated with caution. **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Myelodysplastic syndrome/ Acute myeloid leukaemia (MDS/AML)	**Routine risk communication:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Bone sarcoma	**Routine risk communication:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Section 5.3 (Preclinical safety data) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.

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Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Second primary malignancies (other than MDS/AML and bone sarcoma)	**Routine risk communication:** SmPCs: Section 4.8 (Undesirable effect) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Osteonecrosis of the jaw	**Routine risk communication:** SmPC: SmPC Section 4.4 (Special warnings and precautions for use PLs: Section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • PL Section 2 (Warnings and precautions) Instructions for patients who take or have taken bisphosphonates or have received chemotherapy prior to treatment with Xofigo® to inform their healthcare practitioner. **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Off-label use in women or children	**Routine risk communication:** SmPCs: Section 4.1 (Therapeutic indications) Section 4.2 (Posology and method of administration) Section 4.6 (Fertility, pregnancy and lactation) PLs: Section 2 (Children and adolescents) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Off-label administration of repeated courses	**Routine risk communication:** SmPCs: Section 4.2 (Posology and method of administration)

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Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
of treatment, or other administration of doses in excess of those recommended in the product information	**Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.9 (Overdose) and PL Section 3 (How Xofigo is used) Instructions that in the event of an inadvertent overdose, general supportive measures, including monitoring for potential haematological and gastrointestinal toxicity should be undertaken. **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Missing information	
Safety in patients with insufficient wash-out period	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4. (Special warnings and precautions for use), and PL Section 2 (Warnings and precautions) Subsequent treatment with Xofigo® should not be initiated for at least 5 days after the last administration of abiraterone acetate in combination with prednisone/prednisolone. Subsequent systemic cancer treatment should not be initiated for at least 30 days after the last administration of Xofigo®. **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Safety of Radium-223 with other cancer therapy apart from therapy for maintenance of castration-level	**Routine risk communication:** SmPCs: Section 4.1 (Therapeutic indication) Section 4.5 (Interaction with other medicinal products and other forms of interaction) Section 5.1 (Pharmacodynamic properties) Package leaflets (PLs): Section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Sections 4.3 (Contraindications), 4.4. (Special warnings and precautions for use), and PL Section 2 (“Xofigo® must not be given”; Warnings and precautions; Other medicines and Xofigo®) Instructions that Xofigo® must not be given in combination with abiraterone and prednisone/prednisolone. The combination of Xofigo® with other systemic cancer therapies other than luteinising hormone-releasing hormone (LHRH) analogues is not recommended.

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Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
	Patients are instructed to inform their healthcare practitioner if they are already taking any of the above mentioned medicines or other second generation androgen receptors antagonists. **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Reproductive toxicity in men with metastatic castration-resistant prostate cancer (CRPC)	**Routine risk communication:** SmPCs: Section 4.6 (Fertility, pregnancy and lactation) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Reproductive toxicity due to off-label use in women	**Routine risk communication:** SmPCs: Section 4.6 (Fertility, pregnancy and lactation) PLs: Section 2 (Pregnancy and breast feeding; Contraception in males and females; Fertility) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Developmental toxicity due to off-label use in children	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) PLs: Section 2 (Children and adolescents) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.

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Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Clinical safety in patients with inflammatory bowel disease	**Routine risk communication:** None proposed **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4 (Special warnings and precautions for use) and PL Section 2 (Warnings and precautions) Instructions for careful case-by-case assessment of the benefit risk in patients with inflammatory bowel disease by healthcare practitioners. **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Clinical safety in patients receiving chemotherapy	**Routine risk communication:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) PLs: Section 2 (Other medicines and Xofigo®) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Clinical safety in patients receiving calcium supplementation, phosphates or vitamin D	**Routine risk communication:** SmPCs: Section 4.5 (Interaction with other medicinal products and other forms of interaction) PLs: Section 2 (Other medicines and Xofigo®) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.
Clinical safety in patients receiving	**Routine risk communication:** None proposed **Routine risk minimisation activities recommending specific clinical**

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Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
external beam radiation therapy to bone or prostate	**measures to address the risk:** SmPC Section 4.4 (Special warnings and precautions for use) and PL Section 2 (Warnings and precautions) Instructions that the respective patient population should be treated with caution. **Other routine risk minimisation measures beyond the Product Information:** Xofigo® is to be prescribed and used only by physicians trained in the handling of radiopharmaceuticals and familiar with potential radiation effects.

V.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Bone fractures	**Routine risk minimisation measures:** SmPCs: Section 4.1 (Therapeutic indication) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Section 5.1 (Pharmacodynamic properties) Section 5.3 (Preclinical safety data) PLs: Section 2 (“Xofigo® must not be given”; Warnings and precautions, Other medicines and Xofigo®) Section 4 (Possible side effects) SmPC sections 4.3, 4.4 and PL section 2: The use of Xofigo® is not	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up questionnaire for bone fractures **Additional pharmacovigilance activities:** 20510 – RADIANT – Phase IV randomised open-label multicentre study (ongoing) 20511 – Phase I biodistribution study ongoing) 17739 – PEACE-3 – EORTC-sponsored Phase III study (ongoing) 19263 – DoRa – PCCTC-sponsored Phase III study (ongoing)

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	recommended for treatment of adults with castration-resistant prostate cancer and asymptomatic or mildly symptomatic bone metastases. Xofigo® is contraindicated in combination with abiraterone and predniso(lo)ne The combination of Xofigo® with other systemic cancer therapies other than LHRH analogues is not recommended. Physicians are advised to carefully assess bone status and baseline risk of fractures in patients prior to initiating the therapy. Patients should be closely monitored for at least 24 months. Administration of bone protective agents is recommended as a preventive measure before starting or resuming treatment with Xofigo®. In patients with a high baseline risk of fracture, the benefit of treatment should be carefully assessed to outweigh the risk. Sufficient treatment wash-out period is recommended before and/or after treatment with Xofigo® and other cancer therapies. In patients with bone fractures, orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with Xofigo®. Patients are instructed to inform their healthcare practitioner if they have osteoporosis or a known increased risk for fractures. Patients are instructed to inform their healthcare practitioner if they taking any systemic cancer therapies and/or second generation androgen receptors antagonists. Prescription-only medicine.	

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Trained physicians. **Additional risk minimisation measures:** None.	
Important identified risk: Bone marrow toxicity leading to reduced formed elements in blood	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) Section 4.8 (Undesirable effects) Section 5.3 (Preclinical safety data) PLs: Section 2 (Warnings and precautions) Section 4 (Possible side effects) SmPC section 4.4 and PL section 2: Instructions on monitoring haematological parameters. Patients with evidence of compromised bone marrow reserve or prostate cancer patients with advanced diffuse infiltration of the bone should be treated with caution. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up questionnaire for haemorrhage with thrombocytopenia AE follow-up questionnaire for infection with neutropenia **Additional pharmacovigilance activities:** None.
Important potential risk: Late bone marrow toxicity	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effect) PLs:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up questionnaire for haemorrhage with thrombocytopenia AE follow-up questionnaire for infection with neutropenia AE follow-up questionnaire for late

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Section 2 (Warnings and precautions) Section 4 (Possible side effects) SmPC section 4.4 and PL section 2: Instructions on monitoring haematological parameters. Patients with evidence of compromised bone marrow reserve or prostate cancer patients with advanced diffuse infiltration of the bone should be treated with caution. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None	bone marrow toxicity **Additional pharmacovigilance activities:** None.
Important potential risk: Myelodysplastic syndrome/ Acute myeloid leukaemia (MDS/AML)	**Routine risk minimisation measures:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up questionnaire for new primary malignancy **Additional pharmacovigilance activities:** None.
Important potential risk: Bone sarcoma	**Routine risk minimisation measures:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Section 5.3 (Preclinical safety data) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up questionnaire for new primary malignancy **Additional pharmacovigilance activities:** None.

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: Second primary malignancies (other than MDS/AML and bone sarcoma)	**Routine risk minimisation measures:** SmPC: Section 4.8 (Undesirable effect) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important potential risk: Osteonecrosis of the jaw	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) PLs: Section 2 (Warnings and precautions) Section 4 (Possible side effects) Instructions for the patient to inform the healthcare practitioner of any existing bisphosphonate treatment. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up questionnaire for osteonecrosis of the jaw **Additional pharmacovigilance activities:** None.

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: Off-label use in women or children	**Routine risk minimisation measures:** SmPCs: Section 4.1 (Therapeutic indications) Section 4.2 (Posology and method of administration) Section 4.6 (Fertility, pregnancy and lactation) PLs: Section 2 (Children and adolescents) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important potential risk: Off-label administration of repeated courses of treatment, or other administration of doses in excess of those recommended in the product information	**Routine risk minimisation measures:** SmPCs: Section 4.2 (Posology and method of administration) SmPC Section 4.9 (Overdose) and PL Section 3 (How Xofigo is used) Instructions that in the event of an inadvertent overdose, general supportive measures, including monitoring for potential haematological and gastrointestinal toxicity should be undertaken. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing information: Safety in patients with insufficient	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
wash-out period	precautions for use) PLs: Section 2 (Warnings and precautions) Sufficient treatment wash-out period is recommended before and/or after treatment with Xofigo® and other cancer therapies. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities:** None.
Missing information: Safety of Radium-223 with other cancer therapy apart from therapy for maintenance of castration-level	**Routine risk minimisation measures:** SmPCs: Section 4.1 (Therapeutic indication) Section 4.5 (Interaction with other medicinal products and other forms of interaction) Section 5.1 (Pharmacodynamic properties) Package leaflets (PLs): Section 4 (Possible side effects) SmPC sections 4.3, 4.4 and PL section 2: Xofigo® is contraindicated in combination with abiraterone and predniso(lo)ne. The combination of Xofigo® with other systemic cancer therapies other than LHRH analogues is not recommended. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing information: Reproductive toxicity in men with	**Routine risk minimisation measures:** SmPCs: Section 4.6 (Fertility, pregnancy	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
metastatic CRPC	and lactation) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities:** None.
Missing information: Reproductive toxicity due to off-label use in women	**Routine risk minimisation measures:** SmPCs: Section 4.6 (Fertility, pregnancy and lactation) PLs: Section 2 (Pregnancy and breast feeding; Contraception in males and females; Fertility) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing information: Developmental toxicity due to off-label use in children	**Routine risk minimisation measures:** SmPC: Section 4.2 (Posology and method of administration) PLs: Section 2 (Children and adolescents) Prescription-only medicine Trained physicians **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing information: Clinical safety in patients with inflammatory bowel disease	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) PLs: Section 2 (Warnings and precautions) Case-by-case benefit risk	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	assessment in respective patient population. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None.	
Missing information: Clinical safety in patients receiving chemotherapy	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) PLs: Section 2 (Warnings and precautions) Respective patients should be treated with caution. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. Additional pharmacovigilance activities: None.
Missing information: Clinical safety in patients receiving calcium supplementation, phosphates or vitamin D	**Routine risk minimisation measures:** SmPCs: Section 4.5 (Interaction with other medicinal products and other forms of interaction) PLs: Section 2 (Other medicines and Xofigo®) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing information: Clinical safety in	**Routine risk minimisation measures:** SmPC:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
patients receiving external beam radiation therapy to bone or prostate	Section 4.4 (Special warnings and precautions for use) PL: Section 2 (Warnings and precautions) Instructions that the respective patient population should be treated with caution. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None	None. **Additional pharmacovigilance activities:** None.

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Part VI: Summary of the risk management plan

Part VI: Summary of the risk management plan

Summary of risk management plan for Xofigo® (Radium-223 dichloride)

This is a summary of the risk management plan (RMP) for Xofigo®. The RMP details important risks of Xofigo®, how these risks can be minimised, and how more information will be obtained about Xofigo®'s risks and uncertainties (missing information).

Xofigo®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Xofigo® should be used.

This summary of the RMP for Xofigo® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xofigo®'s RMP.

I. The medicine and what it is used for

Xofigo®, as monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue, is authorised for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment (see SmPC for the full indication). It contains Radium-223 dichloride as the active substance and it is administered by intravenous injection.

Further information about the evaluation of Xofigo®'s benefits can be found in Xofigo®'s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage found on the following link: https://www.ema.europa.eu/en/medicines/human/EPAR/xofigo.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Xofigo®, together with measures to minimise such risks and the proposed studies for learning more about Xofigo®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

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Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PBRER/PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Xofigo® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Xofigo® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Xofigo®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table Part VI.1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	• Bone fractures • Bone marrow toxicity leading to reduced formed elements in blood
Important potential risks	• Late bone marrow toxicity • Myelodysplastic syndrome/ Acute myeloid leukaemia (MDS/AML) • Bone sarcoma • Second primary malignancies (other than MDS/AML and bone sarcoma) • Osteonecrosis of the jaw • Off-label use in women or children • Off-label administration of repeated courses of treatment, or other administration of doses in excess of those recommended in the product information

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Table Part VI.1: Summary of safety concerns

List of important risks and missing information	
Missing information	• Safety in patients with insufficient wash-out period • Safety of Radium-223 with other cancer therapy apart from therapy for maintenance of castration-level • Reproductive toxicity in men with metastatic CRPC (mCRPC) • Reproductive toxicity due to off-label use in women • Developmental toxicity due to off-label use in children • Clinical safety in patients with inflammatory bowel disease • Clinical safety in non-white ethnic groups • Clinical safety in patients receiving chemotherapy • Clinical safety in patients receiving calcium supplementation, phosphates or vitamin D • Clinical safety in patients receiving external beam radiation therapy (EBRT) to bone or prostate

II.B Summary of Important Risks

Important identified risk: Bone fractures	
Evidence for linking the risk to the medicine	Data from Bayer Global Pharmacovigilance database and clinical studies with Xofigo®.
Risk factors and risk groups	Patients receiving Xofigo® in combination with abiraterone plus prednisone/ prednisolone. Patients with a medical history of osteoporosis and <6 metastases.

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Important identified risk: Bone fractures	
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.1 (Therapeutic indication) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Section 5.1 (Pharmacodynamic properties) Section 5.3 (Preclinical safety data) PLs: Section 2 ("Xofigo® must not be given"; Warnings and precautions, Other medicines and Xofigo®) Section 4 (Possible side effects) SmPC sections 4.3, 4.4 and PL section 2: Xofigo® is contraindicated in combination with abiraterone and predniso(lo)ne. The combination of Xofigo® with other systemic cancer therapies other than LHRH analogues is not recommended. Physicians are advised to carefully assess bone status and baseline risk of fractures in patients prior to initiating the therapy. Patients should be closely monitored for at least 24 months. Administration of bone protective agents is recommended as a preventive measure before starting or resuming treatment with Xofigo®. In patients with a high baseline risk of fracture, the benefit of treatment should be carefully assessed to outweigh the risk. Sufficient treatment wash-out period is recommended before and/or after treatment with Xofigo® and other cancer therapies. In patients with bone fractures, orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with Xofigo®. Patients are instructed to inform their healthcare practitioner if they have osteoporosis or a known increased risk for fractures. Patients are instructed to inform their healthcare practitioner if they taking any systemic cancer therapies and/or second generation androgen receptors antagonists. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	20510 – RADIANT – Phase IV randomised open-label multicentre study (ongoing) 20511 – Phase I biodistribution study (ongoing) 17739 – PEACE-3 – EORTC-sponsored Phase III study (ongoing) 19263 – DoRa – PCCTC-sponsored Phase III study (ongoing)

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Important identified risk: Bone marrow toxicity leading to reduced formed elements in blood	
Evidence for linking the risk to the medicine	Pooled data from clinical studies with Xofigo® Re-treatment safety study 16506
Risk factors and risk groups	Patients with reduced bone marrow capacity e.g., following prior cytotoxic and/or radiation treatment
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) Section 4.8 (Undesirable effects) Section 5.3 (Preclinical safety data) PLs: Section 2 (Warnings and precautions) Section 4 (Possible side effects) SmPC section 4.4 and PL section 2: Instructions on monitoring haematological parameters. Patients with evidence of compromised bone marrow reserve or prostate cancer patients with advanced diffuse infiltration of the bone should be treated with caution. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Important potential risk: Late bone marrow toxicity	
Evidence for linking the risk to the medicine	Data from clinical studies with Xofigo® Re-treatment safety study 16506
Risk factors and risk groups	Prior exposure to systemic radionuclide therapy, and/or chemotherapy
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effect) PLs: Section 2 (Warnings and precautions) Section 4 (Possible side effects) SmPC section 4.4 and PL section 2: Instructions on monitoring haematological parameters. Patients with evidence of compromised bone marrow reserve or prostate cancer patients with advanced diffuse infiltration of the bone

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Important potential risk: Late bone marrow toxicity	
	should be treated with caution. Prescription-only medicine Trained physicians **Additional risk minimisation measures:** None

Important potential risk: Myelodysplastic syndrome/ Acute myeloid leukaemia (MDS/AML)	
Evidence for linking the risk to the medicine	No cases have been reported in interventional clinical trials of Radium-223 dichloride. Information obtained from literature regarding risks from radiation.
Risk factors and risk groups	Patients who survive cancer treatment with alkylating agents, with or without radiotherapy, have a high risk of developing MDS or secondary acute leukaemia.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Important potential risk: Bone sarcoma	
Evidence for linking the risk to the medicine	No cases have been reported in clinical studies of Xofigo®. Information obtained from literature regarding risks from radiation.
Risk factors and risk groups	Prior external radiation therapy to bone and /or systemic bone seeking radionuclide therapy. Young age (growing skeleton) at the time of exposure.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Section 5.3 (preclinical safety data) Prescription-only medicine Trained physicians **Additional risk minimisation measures:** None

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Important potential risk: Second primary malignancies (other than MDS/AML and bone sarcoma)	
Evidence for linking the risk to the medicine	Data from clinical studies with Xofigo® Re-treatment safety study 16506.
Risk factors and risk groups	No defined risk group in target population
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.8 (Undesirable effects) Prescription-only medicine Trained physicians **Additional risk minimisation measures:** None

Important potential risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	Data from clinical studies with Xofigo®.
Risk factors and risk groups	Bisphosphonate and/or denosumab use is a known risk factor for developing osteonecrosis of the jaw. Risk groups or risk factors for Xofigo® treatment are unknown.
Risk minimisation measures	**Routine risk minimisation measures:** PLs: Section 4 (Possible side effects) SmPC section 4.4 and PL section 2 where instructions are given for patients who take or have taken bisphosphonates or have received chemotherapy prior to treatment with Xofigo® to inform their healthcare practitioner. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Important potential risk: Off-label use in women and children	
Evidence for linking the risk to the medicine	PASS 17399
Risk factors and risk groups	Breast cancer with bone metastases and children with osteosarcoma

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Important potential risk: Off-label use in women and children	
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.1 (Therapeutic indications) Section 4.2 (Posology and method of administration) Section 4.6 (Fertility, pregnancy and lactation) PLs: Section 2 (Children and adolescents) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Important potential risk: Off-label administration of repeated courses of treatment, or other administration of doses in excess of those recommended in the product information	
Evidence for linking the risk to the medicine	PASS 17399
Risk factors and risk groups	Unknown
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.2 (Posology and method of administration) Posology SmPC Section 4.9 (Overdose) and PL Section 3 (How Xofigo is used) Instructions that in the event of an inadvertent overdose, general supportive measures, including monitoring for potential haematological and gastrointestinal toxicity should be undertaken. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Missing information: Safety in patients with insufficient wash-out period	
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) PLs: Section 2 (Warnings and precautions) Sufficient treatment wash-out period is recommended before and/or after treatment with Xofigo® and other cancer therapies.

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Missing information: Safety in patients with insufficient wash-out period	
	Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Missing information: Safety of Radium-223 with other cancer therapy apart from therapy for maintenance of castration-level	
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.1 (Therapeutic indication) Section 4.5 (Interaction with other medicinal products and other forms of interaction) Section 5.1 (Pharmacodynamic properties) Package leaflets (PLs): Section 4 (Possible side effects) SmPC sections 4.3, 4.4 and PL section 2: Xofigo® is contraindicated in combination with abiraterone and predniso(lo)ne. The combination of Xofigo® with other systemic cancer therapies other than LHRH analogues is not recommended. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Missing information: Reproductive toxicity in men with metastatic CRPC	
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.6 (Fertility, pregnancy and lactation) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

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Missing information: Reproductive toxicity due to off-label use in women/Missing information: Reproductive toxicity in men with metastatic CRPC	
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.6 (Fertility, pregnancy and lactation) PLs: Section 2 (Pregnancy and breast feeding; Contraception in males and females; Fertility) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Missing information: Developmental toxicity due to off-label use in children	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.2 (Posology and method of administration) PLs: Section 2 (Children and adolescents) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Missing information: Clinical safety in patients with inflammatory bowel disease/Missing information: Developmental toxicity due to off label use in children	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 and PL section 2 where instructions are given for careful case-by-case assessment of the benefit risk in patients with inflammatory bowel disease by healthcare practitioners. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

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Missing information: Clinical safety in patients receiving chemotherapy	
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) PLs: Section 2 (Warnings and precautions) Respective patients should be treated with caution. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Missing information: Clinical safety in patients receiving calcium supplementation, phosphates or vitamin D	
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.5 (Interaction with other medicinal products and other forms of interaction) PLs: Section 2 (Other medicines and Xofigo®) Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

Missing information: Clinical safety in patients receiving external beam radiation therapy (EBRT) to bone or prostate	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.4 (Special warnings and precautions for use) PL: Section 2 (Warnings and precautions) Instructions that the respective patient population should be treated with caution. Prescription-only medicine. Trained physicians. **Additional risk minimisation measures:** None

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II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation (refer to Table Part VI.2 for a tabulated summary):

20510 – RADIANT - Phase IV randomised open-label multicentre study

Study short name and title:

Phase IV randomised open-label multicentre study.

Purpose of the study:

The MAH was required to conduct and submit the results of a phase IV randomised open-label multicentre study according to an agreed protocol in order to further characterise the efficacy and safety, in particular the risk of fractures with Radium-223 dichloride in the authorised indication.

The protocol should foresee a stratified randomisation of patients according to total ALP levels.

This study will specifically address the important identified risk of bone fractures. The study also includes bone biomarker assessments (markers of bone formation and bone resorption) in the control arm.

20511 – Phase I biodistribution study

Study short name and title:

Phase I biodistribution study.

Purpose of the study:

The MAH was required to conduct and submit the results of a phase I biodistribution study according to an agreed protocol in order to further characterise correlation between the extent of the disease, the dose and the distribution of Radium-223 dichloride in bone metastases versus sites of impaired bone health (e.g., osteoporosis) versus normal bone structure.

The study will specifically address the important identified risk of bone fractures.

Table Part VI.2: Summary of studies which are Conditions of the Marketing Authorisation

Study Status	Summary of objectives	Safety concerns/ efficacy issue addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
20510 –	The MAH was required to conduct and submit the results of a phase IV	Important	Protocol submission	Within 6 months of

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Table Part VI.2: Summary of studies which are Conditions of the Marketing Authorisation

Study Status	Summary of objectives	Safety concerns/ efficacy issue addressed	Milestones	Due dates
RADIANT Phase IV randomised open-label multicentre study Ongoing	randomised open-label multicentre study according to an agreed protocol in order to further characterise the efficacy and safety, in particular the risk of fractures, with Radium-223 dichloride in the authorised indication. The protocol should foresee a stratified randomisation of patients according to total ALP levels. The study also includes bone biomarker assessments (markers of bone formation and bone resorption) in the control arm.	identified risk: Bone fractures	to PRAC Final CSR submission	the EC decision Q2 2026
20511 Phase I biodistribution study Ongoing	The MAH was required to conduct and submit the results of a phase I biodistribution study according to an agreed protocol in order to further characterise correlation between the extent of the disease, the dose and the distribution of Radium-223 dichloride in bone metastases versus sites of impaired bone health (e.g., osteoporosis) versus normal bone structure.	Important identified risk: Bone fractures	Protocol submission to PRAC FPFV Final CSR submission	6 months after EC decision AUG 2020 Q1 2026

II.C.2 Other studies in post-authorisation development plan

The following studies are required additional pharmacovigilance activities (refer to Table Part VI.3 for a tabulated summary):

17739 – PEACE-3 – EORTC-sponsored Phase III study

Study short name and title:

A Randomised multicentre phase III trial comparing enzalutamide *vs*. a combination of Radium-223 dichloride and enzalutamide in asymptomatic or mildly symptomatic castration resistant prostate cancer patients metastatic to bone.

Purpose of the study:

The study sponsored by the European Organisation for Research and Treatment of Cancer (EORTC) is investigating the combination use with enzalutamide in asymptomatic and mildly symptomatic CRPC patients. The study will specifically address the important identified risk of bone fractures.

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19263 – DoRa – PCCTC-sponsored Phase III study

Study short name and title:

Phase III Trial of Docetaxel *vs*. Docetaxel and Radium-223 dichloride for Metastatic Castration-Resistant Prostate Cancer.

Purpose of the study:

The study sponsored by the Prostate Cancer Clinical Trials Consortium (PCCTC) is investigating the combination use of Xofigo® with docetaxel in CRPC patients.

The study will specifically address the important identified risk of bone fractures.

Table Part VI.3: Summary of other studies in post-authorisation development plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
17739 – **PEACE-3** EORTC-sponsored Phase III study Ongoing	To investigate the combination use of Radium-223 dichloride with enzalutamide in asymptomatic and mildly symptomatic CRPC patients.	Important identified risk: Bone fractures	Study start date Interim status update Primary completion Final CSR submission	OCT 2015 APR 2020 FEB 2024 Q4 2025
19263 – DoRa PCCTC-sponsored Phase III study Ongoing	To investigate the combination use of Radium-223 dichloride with docetaxel in CRPC patients.	Important identified risk: Bone fractures	Study start date Interim status update Primary completion Final CSR submission to PRAC DMC reports will be provided and discussed in PBRERs/PSURs	20 JUN 2018 30 APR 2021 NOV 2025 Q3 2026

AML: Acute Myeloid Leukaemia, CRPC: Castration-resistant prostate cancer, CSR: Clinical study report, DMC: Data Monitoring Committee, EC: European Committee, FPFV: First patient first visit, LPLV: Last patient last visit, MDS: Myelodysplastic Syndrome, PBRER: Periodic Risk Evaluation Report, PRAC: Pharmacovigilance Risk Assessment Committee, PSUR: Periodic Safety Update Report, Q: Quarter.

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

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Radium-223 dichloride Questionnaire Hemorrhage with Thrombocytopenia

SECTION I - REFERENCE ID		
BAYER CASE ID:	**STUDY / PROJECT ID:**	**PATIENT ID:**

SECTION II - REPORTER/PATIENT INFORMATION
REPORTER: ○ Physician ○ Nurse ○ Patient ○ Other *(specify)*:

REPORTER CONTACT INFORMATION		
Name:	**Institution/Practice Name:**	
Address:		
ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**

PATIENT INFORMATION			
Age [years]: *(at onset of event)*	**Gender:** ○ Male ○ Female	**Weight** [kg]:	**Height** [cm]:
Cancer staging (TNM):	**Number of bone metastases:**	**Confirm indication tumor type:**	

SECTION III - PRODUCT INFORMATION (Radium-223)	
Indication:	**Diagnosed on:**

Radium-223 injection	Date *(dd/mm/yyyy)*	Comments
#1		
#2		
#3		
#4		
#5		

SECTION IV - ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Outcome** *(if fatal, see SECTION VII)*:
Bleeding site:			

SUSPECTED CAUSE OF EVENT
Do you think that the event was caused by Radium-223 treatment?
○ Yes ○ No *(specify alternative explanation/other contributing factor e.g., underlying disease / condition predisposing to the events)*:

Radium-223 dichloride Questionnaire Hemorrhage with Thrombocytopenia

TREATMENT PROVIDED FOR _____		
Treatments such as anticoagulation or invasive procedure or surgery?	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*
☐ Surgery		
☐ Intensive blood pressure control		
☐ Factor VIIa (Dosage_____U/kg)		
☐ Fresh frozen Plasma		
☐ Blood transfusion (how many packs/units) _____		
☐ Prothrombin complex concentrate		
☐ Other, specify		

Action taken with Radium-223 dichloride		
○ Dose not changed		
○ Dose reduced		New dose:
○ Interrupted	From:	To:
○ Drug withdrawn		
○ Unknown		

SECTION IV A – RELEVANT CLINICAL SYMPTOMS *(to AE of interest, which were not reported at time of first report)*	
Signs or symptoms	**Details** *(e.g. provide values or frequency if available)*
☐ Haematuria	
☐ Haematemesis	
☐ Hemoptysis	
☐ Hematochezia	
☐ Gastrointestinal bleeding	
☐ Hemorrhoidal hemorrhage	
☐ Heavy menstrual bleeding	
☐ Easy bruising	
☐ Excessive bruising	
☐ Petechiae	
☐ Prolonged bleeding	
☐ Subcutaneous bleeding	
☐ Fatigue	
☐ Epistaxis	
☐ Ecchymosis	
☐ Enlarged spleen	
☐ Gingival bleeding	
☐ Other, specify:	

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SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS							
Laboratory Data	**Units / reference range**	**Before initiation of drug**	**Last values before event**	**After onset of event** (values can also be provided via attachment of Lab report)			
		Date *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*
PT							
INR							
aPTT							
Anti-factor Xa activity							
CBC: Platelets							
Hemoglobin (Hb)							
Hematocrit							
RBC							
WBC							
MCV							
Reticulocytes							
ANC							
Albumin							
Creatinine							
Creatinine clearance							
GFR							
D-dimer							
Anti-Thrombine III							
Other, specify							

Further investigations	**Test date** *(dd/mm/yyyy)*	**Short summary of the result**
☐ Imaging study (specify technique, organ):		
☐ Endoscopy *(specify technique, organ)*:		
☐ Bone marrow aspiration and biopsy		
☐ Other *(specify technique, organ)*:		

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SECTION V - RELEVANT CONCOMITANT MEDICATION						
Concomitantly administered medications given up to *1 month prior to* the reported bleeding event.						
Concomitant product name	**Route**	**Indication for use**	**Dose / Frequency**	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Possible cause for the event?**
☐ NSAIDs *(specify)*:						☐
☐ Vitamin K antagonists (e.g. Warfarin, Coumadin, Phenprocumin, Acenocoumarol, specify):						☐
☐ Low molecular weight Heparin *(specify)*:						☐
☐ Heparin						☐
☐ Acetylsalicylic acid						☐
☐ Ticlopidine						☐
☐ Clopidogrel						☐
☐ Prasugrel						☐
☐ Ticagrelor						☐
☐ Thrombin inhibitors (e.g. dabigatran)						☐
☐ Factor Xa inhibitors (e.g. , apixaban, betrixaban, edoxaban, fondaparinux, rivaroxaban specify):						☐
☐ Other specify:						☐

Radium-223 dichloride Questionnaire Hemorrhage with Thrombocytopenia

SYSTEMIC ANTI-CANCER THERAPY OTHER THAN Radium-223 *If the event reported occurred during a Radium-223 clinical study, you do not need to enter the agents used to treat cancer as part of the study protocol.*				
Product name	**Start date** *(dd/mm/yyyy)*	**Duration** *[days]*	**Indication for use**	**Comment**
☐ Hormonal therapy				
Anti-androgen				
☐ Nilutamide				
☐ Bicalutamide				
☐ Flutamide				
☐ Abiraterone				
☐ Enzalutamide				
☐ Apalutamide				
☐ Darolutamide				
LHRH Agonist / Antagonist				
☐ Goserelin				
☐ Buserelin				
☐ Leuprolide / Leuporelin				
☐ Triptorelin				
☐ Degarelix				
Radiation Therapy				
☐ External beam radiotherapy *site:* *site:* *site:*				
☐ Systemic radionuclide therapy *(e.g. Lu-177-PSMA)*				
☐ Other *(specify)*:				

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Product name	Start date *(dd/mm/yyyy)*	Duration *(days)*	Indication for use	Comment
Chemotherapy				
☐ Docetaxel				
☐ Cabacitaxel				
☐ PARP-Inhibitors *(e.g. olaparib and rucaparib)*				
☐ Mitoxantrone				
☐ Other *(specify)*:				

SECTION VI - MEDICAL HISTORY / RISK FACTORS				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Hereditary clotting disorder (specify):		☐		
☐ Other clotting factor deficiency (specify):		☐		
☐ Chronic renal impairment		☐		
☐ Chronic liver disease / cirrhosis ☐ Child-Pugh Class:		☐		*Aetiology of cirrhosis:*
☐ Haematological malignancy *(specify)*:		☐		
☐ Vasculitis *(e.g. Scleroderma, Systemic lupus erythematosus, Polyarteritis nodosa)*		☐		
☐ Immune thrombocytopenia (ITP)		☐		
☐ Arteriovenous malformation		☐		
☐ Intracranial/Cerebral hemorrhage		☐		
☐ Brain/Subdural metastases		☐		
☐ Head trauma		☐		
☐ Other *(specify)*:		☐		

Radium-223 dichloride Questionnaire Hemorrhage with Thrombocytopenia

Acute conditions *within 2 weeks* of the onset of hemorrhage				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Trauma *(specify body site)*:		☐		
☐ Disseminated intravascular coagulation (DIC)		☐		
Intercurrent infection, specify		☐		
☐ Surgery *(specify type of intervention)*:		N/A	N/A	
☐ Other *(specify)*:		☐		

SECTION VII - ADDITIONAL INFORMATION / COMMENTS *(if any):*
This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death *(If selected outcome was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *(Continue with SECTION IV)*
		☐	

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document, if available.

Please sign electronically:
If your signature is not configured yet on your device, please follow the instruction when you click into the signature field.

Radium-223 dichloride Questionnaire Infection with Neutropenia

SECTION I - REFERENCE ID		
BAYER CASE ID:	**STUDY / PROJECT ID:**	**PATIENT ID:**

SECTION II - REPORTER/PATIENT INFORMATION
REPORTER: Physician Nurse Patient Other *(specify)*:

REPORTER CONTACT INFORMATION		
Name:	**Institution/Practice Name:**	
Address:		
ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**

PATIENT INFORMATION			
Age [years]: *(At onset of event)*	**Gender:** Male Female	**Weight** kg	**Height** cm
Cancer staging (TNM):		**Number of bone metastases:**	
Anatomical site of the infection:		**Primary tumor growth or metastases at this site** ☐	

SECTION III - PRODUCT INFORMATION (Radium-223)		
Indication:		
Radium-223 injection	**Date** *(dd/mm/yyyy)*	**Comments**
#1		
#2		
#3		
#4		
#5		
#6		

SECTION IV - ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Outcome** *(if fatal, see SECTION VII)*:

TREATMENT PROVIDED FOR INFECTION		
Treatment such as any antibiotics, corticosteroids, Colony-stimulating factors (CSF)?	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*

SUSPECTED CAUSE OF EVENT
Related to Radium-223 treatment?
Yes No *(specify alternative explanation/other contributing factors)*:

Radium-223 dichloride Questionnaire Infection with Neutropenia

Action taken with product		
○ Dose not changed		
○ Dose reduced		New dose:
○ Interrupted	From:	To:
○ Withdrawn		
○ Unknown		

Did the event abate/ stop after treatment was stopped?	Did the event reoccur upon resuming treatment:
☐ Yes ☐ No ☐ Unk ☐ not applicable	☐ Yes ☐ No ☐ Unk ☐ not applicable

SECTION IV A – RELEVANT CLINICAL SYMPTOMS *(to AE (Adverse Event) of interest, which were not reported at time of first report)*

Signs or symptoms	Details *(e.g., provide values or frequency if available)*
☐ Fever > 100.4° F or 38° C	
☐ Sores, please specify site _____	
☐ Swelling, please specify site _____	
☐ Sweating	
☐ Chills	
☐ Cough	
☐ Pain, please specify site _____	
☐ Pain, burning sensation during urination	
☐ Stiff neck	
☐ Confusion	
☐ Splenomegaly	
☐ Cervical lymphadenopathy	
☐ Rapid pulse	
☐ Rapid respiration	
☐ Skin abscess	
☐ Other *(specify)*:	

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS

Laboratory Data	Units / reference range	Before initiation of drug	Last values before event	After onset of event (further values can be provided via Laboratory report as attachment. See Section VII)			
		Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*
☐ RBC							
☐ MCV							
☐ WBC							
☐ Neutrophils							
☐ ANC							

Radium-223 dichloride Questionnaire Infection with Neutropenia

Laboratory Data	Units / reference range	Before initiation of drug	Last values before event	After onset of event (further values can be provided via Laboratory report as attachment. See Section VII)			
		Date (dd/mm/yyyy)	Date (dd/mm/yyyy)	Date (dd/mm/yyyy)	Date (dd/mm/yyyy)	Date (dd/mm/yyyy)	Date (dd/mm/yyyy)
☐ Hemoglobin							
☐ Hematocrit							
☐ Creatinine							
☐ BUN							
☐ Bilirubin							
☐ ALT							
☐ AST							

Further investigations	Test date (dd/mm/yyyy)	Short summary of the result
☐ Imaging study (specify technique, organ):		
☐ Endoscopy *(specify technique, organ)*:		
☐ Bone marrow biopsy		
☐ Blood culture		Negative Positive for:
☐ Other *(specify technique, organ)*:		

SECTION V - RELEVANT CONCOMITANT MEDICATION

Concomitantly administered medications given up to *1 month prior to* the Infection with Neutropenia.

Concomitant product name	Route of administration	Indication for use	Dose / Frequency	Start date (dd/mm/yyyy)	Stop date (dd/mm/yyyy)	Possible ause for the event?
☐ Aminopyrine						☐
☐ Quinidine						☐
☐ Cephalosporins						☐
☐ Penicillin						☐
☐ Sulfonamides						☐
☐ Phenothiazines						☐
☐ Hydralazine						☐
☐ Thyrostatic drugs						☐
☐ Thiouracil						☐
☐ Propylthio-uracil						☐
☐ Carbimazole						☐
☐ Methimazole						☐

Radium-223 dichloride Questionnaire Infection with Neutropenia

SYSTEMIC ANTI-CANCER THERAPY OTHER THAN Radium-223 *If the event reported occurred during a Radium-223 clinical study, you do not need to enter the agents used to treat cancer as part of the study protocol.*				
Product name	**Start date** *(dd/mm/yyyy)*	**Duration** *[days]*	**Indication for use**	**Comment**
☐ Hormonal Therapy				
Anti-androgen				
☐ Nilutamide				
☐ Bicalutamide				
☐ Flutamide				
☐ Enzalutamide				
☐ Abiraterone				
☐ Apalutamide				
☐ Darolutamide				
LHRH Agonist / Antagonist				
☐ Goserelin				
☐ Buserelin				
☐ Leuprolide / Leuporelin				
☐ Triptorelin				
☐ Degarelix				
Radiation Therapy				
☐ External beam radiotherapy *site:*				
site:				
☐ Systemic radionuclide therapy *(e.g., Lu-177-PSMA)*				
Chemotherapy				
☐ Docetaxel				
☐ Cabazitaxel				
☐ PARP-Inhibitors *(e.g., Olaparib and rucaparib)*				
☐ Mitoxantrone				
☐ Other, specify: _____				

SECTION VI - MEDICAL HISTORY / RISK FACTORS				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**Ongoing**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Toxoplasmosis		☐		
☐ Brucellosis		☐		
☐ Typhoid		☐		
☐ Malaria		☐		
☐ Dengue fever		☐		
☐ Rickettsia infection		☐		
☐ Babesiosis		☐		
☐ Influenza		☐		

Radium-223 dichloride Questionnaire Infection with Neutropenia

SECTION VI - MEDICAL HISTORY / RISK FACTORS				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Measles		☐		
☐ Epstein Barr virus		☐		
☐ Cytomegaly virus		☐		
☐ Viral hepatitis		☐		
☐ HIV		☐		
☐ Tuberculosis		☐		
☐ Sepsis		☐		
☐ Lyme disease		☐		
☐ Diabetes mellitus		☐		
☐ Immune deficiency		☐		
☐ Renal impairment		☐		
☐ Intravenous catheterization		☐		
☐ Urinary catheterization		☐		
☐ Other, specify:		☐		

Acute conditions *within 2 weeks* of the onset of infection				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Trauma *(specify body site)*:		☐		
☐ Disseminated intravascular coagulation (DIC)		☐		
☐ Intercurrent infection		☐		
☐ Surgery *(specify type of intervention)*:		N/A	N/A	
☐ Blood or bone marrow disorder, please specify:		☐		
☐ Vitamin B 12 deficiency		☐		
☐ Folate deficiency		☐		
☐ Copper deficiency		☐		
☐ Crohn's disease		☐		
☐ Lupus		☐		
☐ Rheumatoid arthritis		☐		
☐ Other *(specify)*:		☐		

Radium-223 dichloride Questionnaire Infection with Neutropenia

SECTION VII - ADDITIONAL INFORMATION / COMMENTS *(if any):*
This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death *(If selected outcome was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *(Continue with SECTION IV)*
		☐	

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document like hospital discharge letters, if available.

Radium-223 dichloride Questionnaire Late Bone Marrow Toxicity

SECTION I - REFERENCE ID		
BAYER CASE ID:	**STUDY / PROJECT ID:**	**PATIENT ID:**

SECTION II - REPORTER/PATIENT INFORMATION
REPORTER: ○ Physician ○ Nurse ○ Patient ○ Other *(specify)*:

REPORTER CONTACT INFORMATION		
Name:	**Institution/Practice Name:**	
Address:		
ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**

PATIENT INFORMATION			
Age [years]: *(at onset of event)*	**Gender:** ○ Male ○ Female	**Weight** [kg	**Height** [cm :
Confirm indication tumor type:		**Number of metastases:**	
Cancer staging (TNM):		**Signs for diffuse tumor infiltration within the bones?**	

SECTION III - PRODUCT INFORMATION (Radium-223)		
Underlying malignancy /Indication:		
Radium-223 injection	**Date** *(dd/mm/yyyy)*	**Comments**
#1		
#2		
#3		
#4		
#5		
#6		

SECTION IV - ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Outcome** *(if fatal, see section VII)* :

TREATMENT PROVIDED FOR THE EVENT		
Treatment such as any blood or platelet transfusion or platelet grow factors...	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*
☐ Transfusion		
☐ Granulocyte colony-stimulating factor (G-CSF)		
☐ Granulocyte-macrophage colony-stimulating factor (GM-CSF)		
☐ Other (please specify)		

Radium-223 dichloride Questionnaire Late Bone Marrow Toxicity

SUSPECTED CAUSE OF EVENT

Related to Radium-223 treatment?

☐ Yes ☐ No *(specify alternative explanation/other contributing factors)*:

Action taken with Radium-223 dichloride

	Date *(dd/mm/yyyy)*		
○ Dose reduced			New dose:
○ Interrupted	From:	To:	
○ Withdrawn			
○ Dose not changed			
○ Unknown			

Did the event abate/stop after treatment stopped?	Did the event reoccur upon resuming treatment :
☐ Yes ☐ No ☐ Unk	☐ Yes ☐ No ☐ Unk

SECTION IV A – RELEVANT CLINICAL SYMPTOMS *(to AE of interest, which were not reported at time of first report)*

Clinical signs e.g. of anemia, neutropenia or thrombocytopenia?	Details *(e.g. provide values or frequency if available)*
☐ Yes, specify	
☐ Yes, specify	
☐ Yes, specify	

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS

Laboratory Data	Units / reference range	Before initiation of drug	Last values before event	After onset of event			
		Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*
☐ RBC							
☐ Hemoglobin							
☐ Hematocrit							
☐ MCV							
☐ Reticulocytes							
☐ WBC							
☐ Neutrophils							
☐ Eosinophils							
☐ Basophils							

Radium-223 dichloride Questionnaire Late Bone Marrow Toxicity

Laboratory Data	Units / reference range	Before initiation of drug	Last values before event	After onset of event			
		Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*
☐ ANC							
☐ Folate							
☐ Vit B12							

Further investigations	Test date *(dd/mm/yyyy)*	Short summary of the result
☐ Imaging study (specify technique, organ):		
☐ Bone marrow aspirate and biopsy		
☐ Endoscopy (specify technique and body system)		
☐ Other *(specify technique, site)*:		

SECTION V - RELEVANT CONCOMITANT MEDICATION

Concomitantly administered medications given up to *1 month prior to* the reported Late Bone Marrow Toxicity.

Concomitant product name	Route of administration	Indication for use	Dose/Frequency	Start date *(dd/mm/yyyy)*	Stop date *(dd/mm/yyyy)*	Possible cause for the event?
☐ Proton pump inhibitors						☐
☐ Other, specify:						☐

Radium-223 dichloride Questionnaire Late Bone Marrow Toxicity

SYSTEMIC ANTI-CANCER THERAPY OTHER THAN Radium-223 dichloride *If the event reported occurred during a Radium-223 clinical study, you do not need to enter the agents used to treat cancer as part of the study protocol.*				
Product name	**Start date** *(dd/mm/yyyy)*	**Duration** *[days]*	**Indication for use**	**Comment**
☐ Hormonal therapy				
Anti-androgen				
☐ Nilutamide				
☐ Bicalutamide				
☐ Flutamide				
☐ Abiraterone				
☐ Enzalutamide				
☐ Apalutamide				
☐ Darolutamide				
LHRH Agonist / Antagonist				
☐ Goserelin				
☐ Buserelin				
☐ Leuprolide / Leuporelin				
☐ Triptorelin				
☐ Degarelix				
☐ Other therapy specify				
Radiation Therapy				
☐ External beam radiotherapy *site:* *site:* *site:*				
☐ Systemic radionuclide therapy *(e.g. Lu-177-PSMA)*				
☐ Other *(specify)*:				
Chemotherapy				
☐ Docetaxel				
☐ Cabazitaxel				

Radium-223 dichloride Questionnaire Late Bone Marrow Toxicity

Product name	Start date *(dd/mm/yyyy)*	Duration *[days]*	Indication for use	Comment
PARP-Inhibitors				
☐ Olaparib				
☐ Rucoparib				
☐ Nilaparib				
☐ Talazoparib				
☐ Mitoxantrone				
☐ Other *(specify)*:				
Did the patient receive any growth factors? ☐ Yes ☐ No If yes, specify below				
☐ G-CSF				
☐ GM-CSF				
☐ Romiplostim (thrompopoietin agonist)				
☐ Eltrombopag (thrombopoietin agonist)				
Transfusions	**Start date** *(dd/mm/yyyy)*	**Duration** *(days)*	**Indication for use**	**Comment**
☐ Packed RBC				
☐ Platelets				
☐ Other, please specify: _____				

SECTION VI - MEDICAL HISTORY / RISK				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Smoking		☐		
☐ Alcohol abuse (>3 drinks/d)		☐		
☐ Low body mass (<19 kg/m2)		☐		
☐ Exposure to ionizing radiation?		☐		Please specify:
☐ Exposure to hazardous chemicals that are considered associated to the toxicity?		☐		Please specify:
☐ Chronic liver disease		☐		
☐ Viral infection		☐		Please specify:
☐ Known DNA repair defects		☐		Please specify:

Radium-223 dichloride QuestionnaireLate Bone Marrow Toxicity

Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Cancer		☐		Please specify:
☐ Family history of cancer		☐		Please specify:
☐ HIV infection		☐		
☐ Signs of Myelodysplastic syndrome		☐		
☐ Signs of myelofibrosis		☐		
☐ Other *(specify)*:		☐		

SECTION VII - ADDITIONAL INFORMATION / COMMENTS *(if any):*
This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death *(If selected outcome was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *(Continue with SECTION IV)*
		☐	

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document, like hospital discharge letters, if available.

Please sign electronically: **If your signature is not yet configured on your computer, please follow the instruction when you click in the signature field**	**Signature:**

Radium-223 dichloride Questionnaire New Primary Malignancy

SECTION I - REFERENCE ID		
BAYER CASE ID:	**STUDY / PROJECT ID:**	**PATIENT ID:**

SECTION II - REPORTER/PATIENT INFORMATION
REPORTER: Physician Nurse Patient Other *(specify)*:

REPORTER CONTACT INFORMATION	
Name:	**Institution/Practice Name:**
Address:	

ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**

PATIENT INFORMATION			
Age [years]: *(at onset of event)*	**Gender at birth:** Male Female	**Weight**: kg	**Height:** cm
Confirm indication tumor type:			
Cancer staging (TNM):			

SECTION III - PRODUCT INFORMATION (Radium-223)		
Underlying malignancy /Indication:		
Radium-223 injection	**Date** *(dd/mm/yyyy)*	**Comments**
#1		
#2		
#3		
#4		
#5		
#6		

SECTION IV - ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Outcome** *(if fatal, see Section VII)*

TREATMENT PROVIDED FOR		
Treatment such as any surgery, radiation therapy, immunotherapy etc.	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*

Radium-223 dichloride Questionnaire New Primary Malignancy

SUSPECTED CAUSE OF EVENT
Related to Radium-223 treatment? ☐ Yes ☐ No *(specify alternative explanation/other contributing factors)*:
Alternative explanation (e.g. underlying disease / condition predisposing to the event):

Action taken with Radium-223 dichloride		
○ Dose not change		
○ Dose reduced		New dose:
○ Interrupted	From:	To:
○ Withdrawn		
○ Unknown		

Did the event abate/stop after treatment stopped?	Did the event reoccur upon resuming treatment :
☐ Yes ☐ No ☐ Unk	☐ Yes ☐ No ☐ Unk

SECTION IV A – RELEVANT CLINICAL SYMPTOMS *(to AE of interest, which were not reported at time of first report)*

Signs or symptoms	Details *(e.g. provide values or frequency if available)*
☐	
☐	
☐	

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS

Laboratory Data	Units / reference range	Before initiation of drug	Last values before event	After onset of event			
		Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*

Further investigations	Test date *(dd/mm/yyyy)*	Short summary of the result
☐ Imaging study (specify technique, organ):		
☐ Endoscopy (specify technique and body system)		
☐ Bone marrow aspiration and biopsy		
☐ Other *(specify technique, site)*:		

Radium-223 dichloride Questionnaire New Primary Malignancy

SECTION V - RELEVANT CONCOMITANT MEDICATION

Concomitantly administered medications given up to *1 month prior to* the reported New Primary malignancy.

Concomitant product name	Route of administration	Indication for use	Dose / Frequency	Start date *(dd/mm/yyyy)*	Stop date *(dd/mm/yyyy)*	Possible cause for the event?
						☐
						☐
						☐

SYSTEMIC ANTI-CANCER THERAPY OTHER THAN Radium-223

If the event reported occurred during a Radium-223 clinical study, you do not need to enter the agents used to treat cancer as part of the study protocol.

Product name	Start date *(dd/mm/yyyy)*	Duration *[days]*	Indication for use	Comment
☐ Hormonal therapy				
Anti-androgen				
☐ Nilutamide				
☐ Bicalutamide				
☐ Flutamide				
☐ Abiraterone				
☐ Enzalutamide				
☐ Apalutamide				
☐ Darolutamide				
LHRH Agonist / Antagonist				
☐ Goserelin				
☐ Buserelin				
☐ Leuprolide / Leuporelin				
☐ Triptorelin				
☐ Degarelix				
☐ Other therapy specify				
Radiation Therapy				
☐ External beam radiotherapy *site:* _____				
site: _____				
site: _____				
☐ Systemic radionuclide therapy *(e.g. Lu-177-PSMA)*				
☐ Other *(specify:)*				

Radium-223 dichloride Questionnaire New Primary Malignancy

Chemotherapy				
Product name	**Start date** *(dd/mm/yyyy)*	**Duration** *[days]*	**Indication for use**	**Comment**
☐ Docetaxel				
☐ Cabazitaxel				
☐ PARP-Inhibitors *(e.g. olaparib and rucaparib)*				
☐ Mitoxantrone				
☐ Other *(specify)*:				
Did the patient receive any adjuvant/concomitant therapy ?				
☐ Steroids, specify:				
Did the patient receive any growth factors? ☐ Yes ☐ No If yes, specify below				
☐ G-CSF				
☐ GM-CSF				
☐ Romiplostim (thrompopoietin agonist)				
☐ Eltrombopag (thrombopoietin agonist)				

SECTION VI - MEDICAL HISTORY / RISK				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Smoking		☐		
☐ Alcohol abuse (>3 drinks/d)		☐		
☐ Obesity		☐		
☐ Exposure to ionizing radiation		☐		
☐ Exposure to hazardous chemicals that are considered associated to the malignancy		☐		
☐ Chronic liver disease		☐		
☐ Known DNA repair defects		☐		
☐ Family history of cancer		☐		
☐ HIV infection		☐		
☐ History of any other cancer (besides prostate cancer) diagnosed before Radium-223 therapy		☐		
☐ Other *(specify, such as heavy sunlight and UV exposure)*:		☐		

Radium-223 dichloride Questionnaire New Primary Malignancy

Acute conditions *within 2 weeks* of the onset of the NEW PRIMARY MALIGNANCY				
Relevant medical history /Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐		☐		
☐		☐		
☐		☐		
☐		☐		
☐		☐		

SECTION VII - ADDITIONAL INFORMATION / COMMENTS *(if any):*
This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death *(If selected outcome was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *(Continue with SECTION IV)*
		☐	

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document like hospital discharge letters, if available.

Radium-223 dichloride Questionnaire Osteonecrosis Of Jaw (ONJ)

SECTION I - REFERENCE ID		
BAYER CASE ID:	**STUDY / PROJECT ID:**	**PATIENT ID:**

SECTION II - REPORTER/PATIENT INFORMATION
REPORTER: ○ Physician ○ Nurse ○ Patient ○ Other *(specify)*:

REPORTER CONTACT INFORMATION		
Name:	**Institution/Practice Name:**	
Address:		
ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**

PATIENT INFORMATION			
Age [years]: *(at onset of event)*	**Gender:** Male Female	**Weight** kg	**Height** cm
Cancer staging (TNM):	**Number of bone metastases:**	**Tumor metastases at this site**	

SECTION III - PRODUCT INFORMATION (Radium-223)		
Underlying malignancy /Indication:		
Radium-223 injection	**Date** *(dd/mm/yyyy)*	**Comments**
#1		
#2		
#3		
#4		
#5		
#6		

SECTION IV - ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Outcome** *(if fatal, see Section VII)*

TREATMENT PROVIDED FOR OSTEONECROSIS OF JAW		
Treatment such as any invasive procedure or surgery?	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*
☐ Optimization of oral hygiene		
☐ Elimination of active dental or periodontal disease		
☐ Treatment of osteoporosis		
☐ Ostectomy of affected areas		

SUSPECTED CAUSE OF EVENT

Do you think that_____is related to Radium-223 treatment?

☐ Yes

☐ No *(specify alternative explanation/other contributing factors* on next page)

Radium-223 dichloride Questionnaire Osteonecrosis Of Jaw (ONJ)

If the event is not related to Radium-223 dichloride, please provide an alternative explanation (e.g., underlying disease / condition predisposing to the event, concomitant medication):		
Action taken with prodcut		
○ Dose not changed		
○ Dose reduced		New dose:
○ Interrupted	From: To:	
○ Withdrawn		
○ Unknown		

Did the event abate/stop after Radium-223 treatment stopped?	Did the event reoccur upon resuming Radium-223 treatment:
☐ Yes ☐ No ☐ Unk ☐ N/A	☐ Yes ☐ No ☐ Unk ☐ N/A

SECTION IV A – RELEVANT CLINICAL SYMPTOMS *(to AE of interest, which were not reported at time of first report)*

Signs or symptoms	**Details** *(e.g. provide values or frequency if available)*
☐ Affected jaw(s):	
☐ Multiple sites of necrosis (if yes, please specify site(s))	
☐ Association with trauma ☐ Repeated dental procedures	
☐ Other *(specify)*:	

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS

Laboratory Data	**Units / reference range**	**Before initiation of drug**	**Last values before event**	**After onset of event**			
		Date *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*
☐ WBC							
☐ RBC							
☐ Hemoglobin							
☐ Neutrophils							
☐ Basophils							
☐ Eosinophils							
☐ Monocytes							
☐ Lymphocytes							
☐ Thrombocytes							

Radium-223 dichloride Questionnaire Osteonecrosis Of Jaw (ONJ)

Laboratory Data	Units / reference range	Before initiation of drug	Last values before event	After onset of event			
		Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*
☐ MCV							
☐ MCH							
☐ MCHC							
☐ PCV							
☐ ESR							
☐ Factor V							
☐ Factor VII							
☐ Factor X							
☐ Fibrinogen							
☐ aPTT							
☐ PT							
☐ Thrombin time							
☐ Bleeding time							

Further investigations	Test date *(dd/mm/yyyy)*	Short summary of the result
☐ Imaging study (specify technique, organ):		
☐ Bone mineral density (e.g. DEXA):		
☐ Other *(specify technique, site)*:		

SECTION V - RELEVANT CONCOMITANT MEDICATION

Concomitantly administered medications given up to *1 month prior to* the reported ONJ.

History and concomitant treatment with known risk to decrease BMD and induce osteoporosis (radiation therapy, drugs like e.g. corticoids, some cytostatic drugs, proton pump inhibitors)

Concomitant product name	Route of administration	Indication for use	Dose / Frequency	Start date *(dd/mm/yyyy)*	Stop date *(dd/mm/yyyy)*	Possible cause for the event?
☐ Glucocorticoids						☐
☐ Corticoids						☐
☐ Bone health agents						☐
☐ Biphosphonates						☐
☐ Denosumab						☐
☐ Other, specify:						☐
☐ Teriparatide						☐

Radium-223 dichloride Questionnaire Osteonecrosis Of Jaw (ONJ)

Concomitant product name	Route of administration	Indication	Dose /Frequency	Start date *(dd/mm/yyyy)*	Stop date *(dd/mm/yyyy)*	Possible cause for the event
☐ Abaloparatide						☐
☐ Other, specify:						☐

SYSTEMIC ANTI-CANCER THERAPY OTHER THAN Radium-223

If the event reported occurred during a Radium-223 clinical study, you do not need to enter the agents used to treat cancer as part of the study protocol.

Product name	Start date *(dd/mm/yyyy)*	Duration *[days]*	Indication for use	Comment
☐ Hormonal Therapy				
Anti-androgen				
☐ Nilutamide				
☐ Bicalutamide				
☐ Flutamide				
☐ Enzalutamide				
☐ Abiraterone				
☐ Apalutamide				
☐ Darolutamide				
LHRH Agonist Antagonist				
☐ Goserelin				
☐ Buserelin				
☐ Leuprolide / Leuporelin				
☐ Triptorelin				
☐ Degarelix				
Radiation Therapy				
☐ External beam radiotherapy *site:* *site:*				
☐ Systemic radionuclide therapy *(e.g. Lu-177-PSMA)*				
☐ Other *(specify)*:				
Chemotherapy				
☐ Docetaxel				
☐ Cabazitaxel				
☐ PARP-Inhibitors *(e.g. olaparib and rucaparib)*				
☐ Mitoxantrone				
☐ Other *(specify)*:				

Radium-223 dichloride Questionnaire Osteonecrosis Of Jaw (ONJ)

ECTION VI - MEDICAL HISTORY / RISK				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Dry mouth		☐		
☐ Poor oral hygiene		☐		
☐ Any dental procedure done during or prior to starting Radium-223? (Specify site):		☐		
☐ Radiation therapy to head and neck? (specify):		☐		
☐ Comorbid conditions affecting bone (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia)		☐		Specify:
☐ Smoking		☐		
☐ Alcohol abuse (>3 drinks/d)		☐		
☐ Obesity		☐		
☐ Cachexia/sarcopenia		☐		BMI:
☐ Rheumatoid arthritis		☐		
☐ Hyperthyroidism		☐		
☐ Chronic liver disease		☐		
☐ Diabetes		☐		
☐ Inflammatory disease		☐		
☐ Endocrine disease		☐		
☐ Muscle disease		☐		
☐ Nutritional deficiencies		☐		
☐ HIV infection		☐		
☐ Systemic or oral infection		☐		
☐ Multiple myeloma		☐		
☐ Periodontal disease		☐		
☐ Dental surgery		☐		Specify:
☐ Cancer, specify:_____		☐		
☐ Sickle-cell disease		☐		
☐ Vascular disorders		☐		Specify:
☐ Renal dialysis		☐		
☐ Osteoporosis		☐		
☐ Hypothyroidism		☐		
☐ **Other** *(specify)*:		☐		
☐ **Coagulation abnormalities**		☐		
☐ **Edentulous regions**		☐		
☐ **Systemic lupus erythematosus**		☐		

Radium-223 dichloride Questionnaire Osteonecrosis Of Jaw (ONJ)

☐ Atmospheric pressure variations		☐		
☐ Hemodialysis		☐		
☐ Hypersensitivity reactions		☐		
☐ Storage diseases		☐		
☐ Hypertension		☐		
☐ Blood dyscrasias		☐		
☐ Malnutrition		☐		
☐ Gaucher's disease		☐		
☐ Physical inactivity		☐		
☐ Hyperlipidemia		☐		
☐ Fat embolism		☐		
☐ Neurologic damage		☐		

Acute conditions *within 2 weeks* of the onset of ONJ

Relevant medical history /Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Trauma *(specify body site)*:				
☐ Intercurrent infection				
☐ Surgery *(specify type of intervention)*:		N/A	N/A	
☐ Other *(specify)*:				

SECTION VII - ADDITIONAL INFORMATION / COMMENTS *(if any):*
This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death *(If selected outcome was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *(Continue with SECTION IV)*
		☐	

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document like hospital discharge letters, if available.

Please sign electronically: **If your signature is not yet configured on your computer, please follow the instruction when you click in the signature field**	**Signature:**

Radium-223 dichloride Questionnaire Bone Fracture

SECTION I - REFERENCE ID		
BAYER CASE ID:	**STUDY / PROJECT ID:**	**PATIENT ID:**

SECTION II - REPORTER/PATIENT INFORMATION
REPORTER: ○ Physician ○ Nurse ○ Patient ○ Other *(specify)*:

REPORTER CONTACT INFORMATION	
Name:	**Institution/Practice Name:**
Address:	

ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**

PATIENT INFORMATION			
Age [years]: *(at onset of event)*	**Gender:** ○ Male ○ Female	**Weight** [kg]:	**Height** [cm]:

Cancer staging (TNM):	**Number of bone metastases:**	**Local tumor infiltration or metastases at fracture site?**

SECTION III - PRODUCT INFORMATION (Radium-223)		
Underlying malignancy / Indication:		
Radium-223 injection	**Date** *(dd/mm/yyyy)*	**Comments**
#1		
#2		
#3		
#4		
#5		
#6		

SECTION IV - ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Outcome** *(if fatal, see SECTION VII)*:

SUSPECTED CAUSE OF EVENT
Do you think that the event was caused by Radium-223 treatment?
○ Yes ○ No *(specify alternative explanation/other contributing factor e.g., underlying disease / condition predisposing to the events)*:

Radium-223 dichloride Questionnaire Bone Fracture

TREATMENT PROVIDED FOR _____		
Treatments such as invasive procedure e.g., external beam radiation therapy or surgery?	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*
Surgery, specify:		
External beam radiation, specify:		
Other, specify:		

Action taken with Radium-223 dichloride		
○ Dose not changed		
○ Dose reduced		New dose:
○ Interrupted	From: To:	
○ Withdrawn		
○ Unknown		

Did the event abate/ stop after treatment was stopped?	Did the event reoccurr upon resuming treatment?
○ Yes ○ No Unk	○ Yes ○ No ○ Unk

SECTION IV A – RELEVANT CLINICAL SYMPTOMS *(to AE of interest, which were not reported at time of first report)*	
Signs or symptoms	**Details** *(e.g. provide values or frequency if available)*
☐ Affected bones	
☐ Multiple sites of fracture, specify sites	
☐ Association with trauma	
☐ major (car accident, fall from height	
☐ minor, e.g., fall from standing hight or less	
☐ Other, specify:	

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS

Laboratory Data	**Units / reference range**	**Before initiation of drug**	**Last values before event**	**After onset of event** (values can also be provided via attachment of Lab report)			
		Date *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*

Radium-223 dichloride Questionnaire Bone Fracture

Further investigations	Test date *(dd/mm/yyyy)*	Short summary of the result
☐ Imaging study (specify technique, organ):		
Bone mineral density and other relevant Test results (e.g., DEXA)		
☐ Other *(specify technique, organ)*:		

SECTION V - RELEVANT CONCOMITANT MEDICATION

Concomitantly administered medications *within the last year before* the reported bone fracture History and concomitant treatment with known risk to decrease BMD and induce osteoporosis (radiation therapy, drugs like e.g., corticoids, some cytostatic drugs, proton pump inhibitors)

Concomitant product name	Route of administration	Indication for use	Dose / Frequency	Start date *(dd/mm/yyyy)*	Stop date *(dd/mm/yyyy)*	Possible cause for the event?
☐ Glucocorticoids						☐
☐ Proton pump inhibitors						☐
Bone health agents						
☐ Biphosphonates ☐ Denosumab						☐ ☐
☐ Other, specify						☐

SYSTEMIC ANTI-CANCER THERAPY OTHER THAN Radium-223 dichloride

If the reported event occurred during a Radium-223 clinical study, you do not need to enter the agents used to treat cancer as part of the study protocol.

Product name	Start date *(dd/mm/yyyy)*	Duration *[days]*	Indication for use	Comment
☐ Hormonal therapy				
Anti-androgen				
☐ Nilutamide				
☐ Bicalutamide				
☐ Flutamide				
☐ Enzalutamide				
☐ Abiraterone				
☐ Apalutamide				
☐ Darolutamide				
LHRH Agonist / Antagonist				
☐ Goserelin				
☐ Buserelin				
☐ Leuprolide / Leuporelin				

Radium-223 dichloride Questionnaire Late Bone Marrow Toxicity

Radium-223 dichloride Questionnaire Bone Fracture

Product name	Start date *(dd/mm/yyyy)*	Duration *[days]*	Indication for use	Comment
☐ Triptorelin				
☐ Degarelix				

Radiation Therapy				
☐ External beam radiotherapy *site:* *site:* *site:*				
☐ Systemic radionuclide therapy *(e.g. Lu-177-PSMA)*				
☐ Other *(specify)*:				

Product name	Start date *(dd/mm/yyyy)*	Duration *(days)*	Indication for use	Comment
Chemotherapy				
☐ Docetaxel				
☐ Cabacitaxel				
PARP-Inhibitors ☐ Olaparib ☐ Rucoparib ☐ Nilaparib ☐ Talazoparib				
☐ Mitoxantrone				
☐ Other *(specify)*:				

SECTION VI - MEDICAL HISTORY / RISK FACTORS

e.g., life style behavior which may increase the risk of osteoporosis according to NOGG guidelines 2017

Relevant medical history / Concomitant conditions	Start date *(dd/mm/yyyy)*	On-going	Stop date *(dd/mm/yyyy)*	Details (e.g., specify condition)
☐ Previous fragility fractures (specify site):		☐		
☐ Metastatic involvement of bone by malignant disease at fracture site (specify):		☐		
☐ Osteoporosis		☐		
☐ Cachexia/sarcopenia		☐		
☐ Low body mass (<19 kg/m2)		☐		

Radium-223 dichloride Questionnaire Late Bone Marrow Toxicity

Radium-223 dichloride Questionnaire Bone Fracture

Relevant medical history / Concomitant conditions	Start date *(dd/mm/yyyy)*	On-going	Stop date *(dd/mm/yyyy)*	Details (e.g., specify condition)
☐ Osteopenia		☐		
☐ Vitamin D deficiency		☐		
☐ Hypophosphatasia		☐		
☐ Smoking		☐		
☐ Alcohol abuse (>3 drinks/d)		☐		
☐ Obesity		☐		
☐ HIV infection		☐		
☐ Rheumatoid arthritis		☐		
☐ Hyperthyroidism		☐		
☐ Chronic liver disease		☐		
☐ Diabetes		☐		
☐ History of falls		☐		
☐ Asthma/COPD		☐		
☐ Inflammatory disease		☐		
☐ Endocrine disease		☐		
☐ Muscle disease		☐		
☐ Nutritional deficiencies		☐		
☐ Neurological condition		☐		
☐ Psychiatric condition		☐		
☐ Other *(specify)*:		☐		

Radium-223 dichloride Questionnaire Bone Fracture

Acute conditions *within 2 weeks* of the onset of hemorrhage				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Trauma *(specify body site)*:		☐		
☐ Surgery *(specify type of intervention)*:		N/A	N/A	
☐ Other *(specify)*:		☐		

SECTION VII - ADDITIONAL INFORMATION / COMMENTS *(if any):*
This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death *(If selected outcome was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *(Continue with SECTION IV)*
		☐	

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document, if available.

Please sign electronically:
If your signature is not configured yet on your device, please follow the instruction when you click into the signature field.

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not applicable.