19 September 2013
EMA/CHMP/578779/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xofigo

Common name: RADIUM-223 DICHLORIDE

Procedure No. EMEA/H/C/002653/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Product information

Name of the medicinal product:	Xofigo
Applicant:	Bayer Pharma AG Muellerstrasse 178 13353 Berlin GERMANY
Active substance:	radium Ra223 dichloride
Common Name:	radium Ra223 dichloride
Pharmaco-therapeutic group (ATC Code):	V10XX03
Therapeutic indication:	Xofigo is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases
Pharmaceutical form:	Solution for injection
Strength:	1000 kBq/mL
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALAT	alanine aminotransferase
ALP	alkaline phosphatase
Alpharadin	former, now obsolete, interim name of Xofigo
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
ASAT	aspartate aminotransferase
AUC	area under the curve
BA	Barium
Bq	Becquerel
BSoC	best standard of care
BW	body weight
Ca	Calcium
CI	confidence interval
CL	Clearance
C_{max}	maximum concentration
CNS	Central nervous system
CHMP	Committee for Human Medicinal Products
CRPC	castration-resistant prostate cancer [Used interchangeably with hormone-refractory prostate cancer (HRPC)]
CT	Computed tomography
CTC	common toxicity criteria
DLT	Dose-limiting toxicity
EBRT	external beam radiation therapy
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG performance status
EDTMP	ethylenediamine tetra(methylene phosphonic acid)
EMA	European Medicines Agency
EOD	extent of disease
EOT	End of treatment
EQ-5D	European Quality of Life – 5 Dimensions
EWB	Emotional well-being
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy - PC patients
FAS	Full Analysis Set
FOB	Functional observational battery
FWB	Functional well-being
GIT	gastrointestinal (tract)
GLP	Good laboratory practice
GMP	Good manufacturing practice
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
IA	Interim analysis
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
ITT	intent to treat
IV, iv, i.v.	intravenous
kBq	kilobequerel
kg	kilogram
LDH	lactate dehydrogenase
LET	linear energy transfer
LHRH	luteinizing-hormone releasing hormone
MAA	marketing authorisation application
MDS	myodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Mg	Magnesium

mL	milliliter
MRI	Magnetic Resonance Imaging
NSCLC	Non-small cell lung cancer
No., no., n	number
ONJ	Osteonecrosis of the jaw
OS	overall survival
PC	prostate cancer
PFS	progression free survival
PK	pharmacokinetic(s)
PR	PR interval of the electrocardiogram
PRAC	Pharmacovigilance Risk Assessment Committee
PS	performance status
PSA	prostate-specific antigen
PWB	Physical well-being
q4w	once every 4 weeks
QoL	quality of life
QRS	QRS complex of the electrocardiogram
QT	QT interval of the electrocardiogram
QTcF	QT interval corrected for heart rate(using the Fridericia formula)
RR	RR interval of the electrocardiogram
SAE	serious adverse event
SmPC	Summary of Product Characteristics
Sr	Strontium
SRE	skeletal-related events
SWB	Social/Family well-being
TEAE	treatment-emergent adverse event
TTS	Time to sacrifice
ULN	upper limit of normal
VAS	visual analogue scale
Vss	volume of distribution at steady state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer Pharma AG submitted on 12 December 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Xofigo, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 October 2011.

The applicant applied for the following indication: Xofigo is indicated for the treatment of castration-resistant prostate cancer patients with bone metastases.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/345/2010 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance radium-223 chloride contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 October 2007 and follow-up advice on 18 February 2010. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Xofigo has been given a Marketing Authorisation in the USA on 15 May 2013.

1.2. Manufacturers

Manufacturer responsible for batch release

Algeta ASA
Kjelsåsveien 172 A
NO-0884, OSLO
Norway

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Harald Enzmann Co-Rapporteur: Daniela Melchiorri

The application was received by the EMA on 12 December 2012.

- Accelerated Assessment procedure was agreed-upon by CHMP on 17 January 2013.
- The procedure started on 30 January 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 23 April 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 April 2013.
- During the PRAC meeting on 16 May 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 30 May 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 31 May 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 June 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 July 2013.
- During the PRAC meeting on 11 July 2013, the PRAC adopted an RMP Advice and assessment overview.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 July 2013.
- During the meeting on 25 July 2013, the CHMP agreed on the consolidated List of Outstanding Issues to be sent to the applicant. The final consolidated List of Outstanding Issues was sent to the applicant on 26 July 2013.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 16 August 2013
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 September 2013.
- During the PRAC meeting on 5 September 2013, the PRAC adopted an RMP Advice and assessment overview.

- During the meeting on 19 September 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Xofigo.

2. Scientific discussion

2.1. Introduction

Problem statement

Prostate cancer is the most common non-cutaneous malignancy in men, affecting approximately 323,000 men in the EU including 71,000 fatalities from the disease. The incidence rate of about 135 cases per 100,000 men increases sharply with age, and is peaking at ≥75 years (781 per 100,000). Bone is the dominant site of metastases in prostate cancer. Depending on its location (e.g. spine) or bone marrow involvement, bone metastases result in potentially severe morbidity including bone pain, bone fractures, compression of the spinal cord and haematological consequences of bone marrow involvement such as anaemia. Nearly all treatments are directed toward eradicating or limiting osseous metastases or palliating the side effects. Once prostate cancer becomes metastatic, the survival of the patient is correlated with the extent of the disease.

As prostate cancer cells are stimulated by testosterone, conventional androgen deprivation therapy aims to reach castration levels of testosterone which can be effective initially to control the bone metastases. However, most patients eventually become castration-resistant. Approximately 50% of patients with bone-metastatic prostate cancer die of prostate cancer within 30 months, and 80% within 5 years. Early stages of castration-resistant prostate cancer (CRPC) with bone metastases are associated with substantial pain (35% of patients) and rising levels of prostate-specific antigen (PSA) in 90% of patients.

Current treatment options in metastatic CRPC include abiraterone in combination with prednisone or prednisolone for patients with asymptomatic or mildly symptomatic disease who are not yet eligible for chemotherapy, based on an overall survival benefit compared to placebo, and docetaxel in combination with prednisone, based on an overall survival benefit observed in a direct comparison with mitoxantrone. However, the potential haematological toxicity as well as clinical status of patients preclude a considerable proportion of patients from receiving this treatment: an estimated 40-60% of those who die of prostate cancer had never received docetaxel either because they were not considered eligible to tolerate the toxicity of docetaxel chemotherapy, or because they declined therapy due to concern about adverse events.

Cabazitaxel in combination with prednisone has been approved for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen on the basis of improved median OS compared to mitoxantrone. Furthermore, abiraterone acetate in combination with prednisone or prednisolone has also been approved for the treatment of metastatic castration resistant prostate cancer in adult men who have failed a docetaxel-based chemotherapy regimen, based on an OS benefit compared to placebo.

For palliation of bone pain from metastases the bone-targeting radionuclides strontium-89 and samarium-153 EDTMP are currently available. Both, however, are emitters of beta radiation which due to the long range of beta particles exerts toxicity to the haematopoietic cells of the bone marrow thereby restricting their clinical use mainly to pain palliation. The impact on survival of these palliative treatment options for CRPC patients with bone metastases has not been studied. Bone metastases are currently

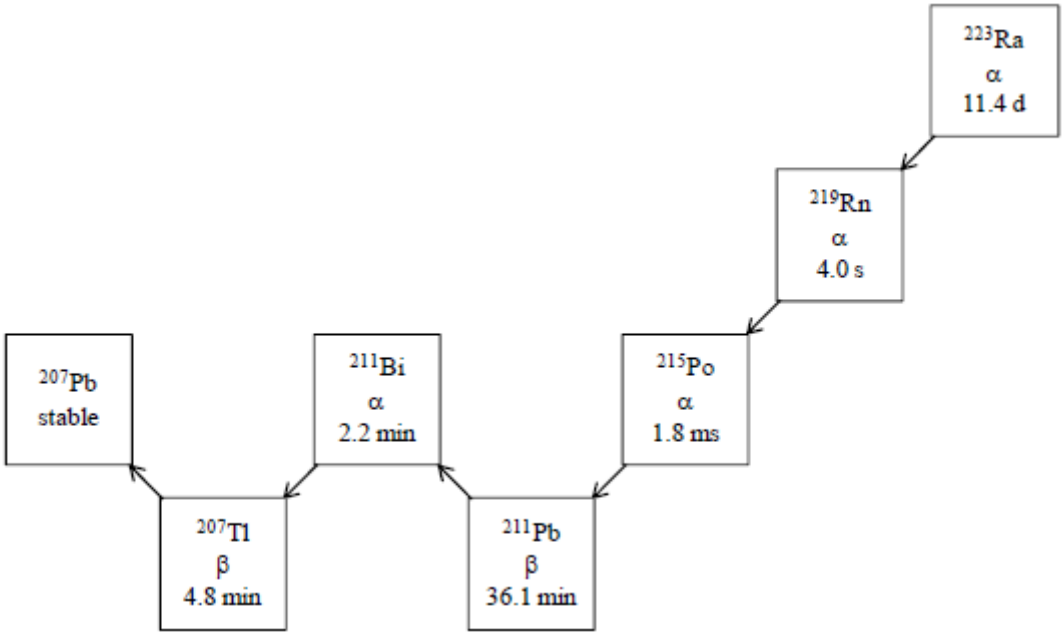
treated mainly with either bisphosphonates or anti-RANKL antibodies, both interfering with bone turnover without cytotoxic action. The main benefit of these treatments is delay of skeletal-related events.

About the product

Xofigo is a therapeutic alpha particle-emitting pharmaceutical. The active ingredient is radium-223 with a half-life of 11.4 days. The specific activity of radium-223 is 1.9 MBq/ng.

The six-stage-decay of radium-223 to lead-207 occurs via short-lived daughters, and is accompanied by a number of alpha, beta and gamma emissions with different energies and emission probabilities. The fraction of energy emitted from radium-223 and its daughters as alpha-particles is 95.3% (energy range of 5.0 7.5 MeV). The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), and the fraction emitted as gamma-radiation is 1.1% (energy range of 0.01 - 1.27 MeV).

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



Radium-223 (as radium-223 dichloride) mimics calcium and selectively targets bone, specifically areas of bone metastases associated with high bone turnover, by forming complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 keV/µm) is considered to lead to a high frequency of double-strand DNA breaks in adjacent tumour cells, resulting in a cytotoxic effect. Moreover, an inhibition of osteoclast differentiation and osteoblast activity which was seen *in vitro* may also account to the *in vivo* efficacy. The alpha particle range from radium-223 is less than 100 µm (less than 10 cell diameters) which minimises damage to the surrounding normal tissue.

The Applicant applied for the indication: Xofigo is indicated for the treatment of castration-resistant prostate cancer patients with bone metastases.

The finally approved indication is the following: Xofigo is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

The dose regimen of Xofigo is 50 kBq per kg body weight, given at 4 week intervals for 6 injections. Xofigo is for intravenous use. It must be administered by slow injection (generally up to 1 minute). The

intravenous access line or cannula must be flushed with isotonic sodium chloride 9 mg/ml (0.9%) solution for injection before and after injection of Xofigo.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection. Each ml of solution contains 1000 kBq radium Ra 223 chloride (radium-223 dichloride), corresponding to 0.53 ng radium-223 at the reference date as active substance.

Other ingredients are: water for injection, sodium citrate, sodium chloride, and hydrochloric acid.

The product is available in colourless Type I glass vial, closed with a grey chlorobutyl rubber stopper and aluminium seal.

2.2.2. Active Substance

The chemical name of active substance is Radium-223 dichloride (Radium-223 chloride can also be used). The active moiety of the Radium-223 dichloride active substance is the divalent cation of Radium-223, $^{223}Ra^{2+}$.

The active substance solution is a radioactive, clear and colourless aqueous solution of radium-223 dichloride with divalent carrier free radium-223 cations as the active moiety. Radium-223 is an alpha particle emitter (alpha emitter) with a physical half-life of 11.4 days. The active substance solution has identical composition as the finished product with the exception of radium-223 dichloride concentration.

Manufacture

Radium-223 is generated by natural decay of a mother nuclide. Data and discussion on the presence of potential chemical and radionuclidic impurities in the starting material was provided.

The radionuclide purity as the main quality feature of this type of active substance is assured by high resolution gamma spectroscopy. However, based on the currently proposed specification for the radionuclidic purity of the starting material, a definite radionuclidic purity value cannot be drawn since only the limit for two specified radionuclidic impurities and a limit for any unknown gamma impurities are included. Therefore, the CHMP recommends that the applicant should include a limit for 'Total unspecified gamma peaks' or a limit for radionuclidic purity of the actinium-227 activity in the starting material specification.

The active substance is synthesized in 8 main steps.

Adequate in-process controls are applied during the synthesis. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for appearance, radionuclidic identity (Gamma spectroscopy), pH (Ph Eur), osmolality (Ph Eur), citrate (UV/VIS spectroscopy), radionuclidic purity (Gamma spectroscopy).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Based on the presented data the radionuclidic purity in view of the potential impurities from the mother nuclides is sufficiently assured.

Batch analysis data of 3 production batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability studies were performed to generate holding time data for three representative batches of the radium - 223 chloride active substance solution in pilot scale and in production scale.

In the production setting the active substance solution will be stored in the proposed compounding container at ambient room temperature and humidity within the dedicated production hot cell until production of the finished product. These conditions are not in accordance with the ICH guidelines. This is justified because the active substance solution is never stored outside a dedicated hot cell.

The studies were performed under the same conditions as the production, i.e. ambient room temperature and humidity. The glass bottles were only tested in upright position as the active substance container is not subject to any shipment, and will always be stored in this fixed position prior to production of the finished product.

All stability indicating parameters (appearance, pH, osmolality, citrate and assay) were tested according to the test procedure and evaluated against the specification.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container. However, for new stability studies with higher radioactive concentrations, the CHMP recommends to take the trend in chemical stability (citrate and pH changes in relation to radioactive concentration) into consideration

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The finished product was developed as a ready-to-use, aqueous solution of radium-223 chloride for intravenous injection. With the exception of the radium-223 concentration and calcium chloride concentration, the composition of the finished product is the same as for the active substance solution. This allows for manufacturing of the finished product by dilution of the active substance solution with the premixed excipient solution (sodium citrate solution in sodium chloride) to achieve the claimed radium-223 radioactivity concentration and maintaining isotonicity and physiological pH

The finished product is obtained by dilution of the active substance solution. The manufacturing process development is adequate for a sterile solution for injection which contains a chemically stable active

substance, well known simple excipients and which can be sterilised according standard conditions by heat.

In view to the microbiological attributes it is evident that the alpha irradiation generates an antimicrobial environment. Taking into account that the finished product is terminally sterilized by heat using standard conditions the sterile status of the finished product is assured.

Sodium chloride is added to achieve isotonicity. The concentration of sodium citrate and hydrochloric acid was found sufficient to maintain the pH of the final finished product in the range of 6.0 - 8.0 throughout the shelf life.

Calcium chloride is added to the active substance solution to prevent adhesion of radium-223 ions to components in contact with the active substance. The amount of calcium chloride added to the active substance batch is constant, independent from the radioactivity concentration of the active substance batch. The amount of calcium chloride in the finished product will vary since the active substance is diluted depending on its radioactivity concentration, and the solution used for dilution contains no further calcium chloride. Since the total concentration of calcium carried over into the finished product is very low and will vary between batches, calcium is not declared as a component in the finished product.

The CHMP recommends to perform analytical tests towards the influence of calcium ions to the prevention of radium-223 absorption to the surfaces of the primary packaging components and typical administration syringe/kits if the radioactive concentration of the active substance solution is increased above the current approved specification limit.Xofigo is a ready-to-use solution and should not be diluted or mixed with any solutions.

Towards convenient use in the case of radiopharmaceuticals as solution for injections always the question occurs if the finished product can be solved with physiological saline or other solutions which facilitates the use. For Xofigo dilution is generally excluded but recognising the chemical character of radium ions dilution, at least with aqueous solution containing the excipients including some amount of calcium, will be possible. Therefore the CHMP recommends further development studies in view to the solubility / compatibility of the finished product

The process modifications and scale up of the active substance purification process during development had a minor impact on the finished product composition.

The finished product formulation from early development through clinical phases and to production scale have been the same, with the exception of some specific batches produced at lower radioactivity concentration to accommodate suitable injection volumes during studies with a wide range of dose levels.

The primary packaging is Type I glass vial. The suitability of this container closure system for packaging of radium-223 chloride solution for injection is demonstrated in stability studies, leachable/migration studies, and container closure integrity studies. There is no indication of any incompatibility between the primary packaging material and the components of the solution. The bioburden and bacterial endotoxin tests on the packaging materials are carried out by the supplier of the glass vials and stoppers and are included in the packaging specifications.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

Radium-223 chloride solution for injection is produced by dilution of radium-223 chloride active substance solution to achieve the target radioactivity concentration, followed by filling and terminal sterilization by autoclaving. The finished product manufacturing process consists of the following main steps: dilution and mixing (to obtain target radioactivity concentration), filling and sterilization (autoclaving).

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, radionuclidic identity (gamma spectroscopy), particulate matter (Ph Eur), pH (Ph Eur), osmolality (Ph Eur), assay citrate (UV/VIS spectroscopy), assay chloride (ion chromatography, chemical impurities (ICP-MS and FIMS), radionuclidic purity (gamma spectroscopy – not tested on the finished product, the results are carried forward from radium-223 chloride drug substance to be included in the Certificate of Analysis), assay (dose calibrator), bacterial endotoxins (Ph Eur), sterility (Ph Eur).

In cases when testing procedures are performed by radiation protection reasons retrospectively it is recommended to minimize the delay towards the technically necessary period. Without delays triggered by organizational reasons. In the case of the sterility testing this is fulfilled but in the case of the determination of the chloride assay and the testing of the chemical impurities a delay of 3 months additionally to the decay period of 10 months is not justified. Therefore, the CHMP recommends reducing the maximum delay of 13 months to not much more than the technically necessary 10 months of the decay time. . Furthermore the verification of the adequate performance of the analytical testing belongs also in the field of GMP and belongs by this in the competence of the local GMP authority

Batch analysis results are provided for 3 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of four pilot scale batches and three production scale batches under normal (25 °C/60 % RH) and accelerated (40 °C/75 % RH) conditions according to the ICH guidelines are presented. The storage period was four weeks, which is the intended shelf life of the finished product.

The production scale batches and one of the pilot scale batches were stored in the commercial container closure system. The other three pilot scale batches were stored in a 20 mL glass vial with rubber stopper, as it was used for clinical samples.

A thermal stress test was conducted over a period of four weeks at 60 °C, and a freeze/thaw study covering three cycles of -20 °C / room temperature (approx. 24 hours per cycle).

The results demonstrate that the finished product remains stable under long-term, accelerated, and thermal stress conditions for the tested period of four weeks, and after three freeze/thaw cycles.

All stability indicating parameters (appearance, particulate matter, pH, osmolality, assay citrate, assay chloride, chemical impurities, assay, bacterial endotoxins, and sterility) were tested according to the test procedures and evaluated against the specification.

The finished product is therefore evaluated to be stable in all climatic zones. The stability profiles of the pilot scale batches and production scale batches are comparable. Based on the results of the stability studies, a shelf life of 28 days in all climatic zones is justified. The finished product needs no specific storage conditions.

Based on available stability data, the shelf-life as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To include a limit for 'Total unspecified gamma peaks' or a limit for radionuclidic purity of the starting material activity (e.g.>99.5% or other) in the starting material specification.- new stability studies with higher radioactive concentrations the trend in chemical stability (citrate and pH changes in relation to radioactive concentration) should be taken into consideration.
- To perform analytical tests towards the influence of calcium ions to the prevention of radium-223 absorption on surfaces in the case if the radioactive concentration of the active substance solution is increased above the current approved specification limit.
- In view to user compliance further development studies in view to the solubility / compatibility of the finished product should be provided.
- In cases when testing procedures are performed retrospectively it is recommended to minimize the delay towards the technically necessary period without delays triggered by organizational reasons. In the case of the sterility testing this is fulfilled but in the case of the determination of the chloride assay and the testing of the chemical impurities a delay of 3 months additionally to the decay period of 10 months is not justified. Therefore, it is recommended to reduce the maximum delay of 13 months to not much more than the technically necessary 10 months of the decay time. Furthermore the verification of the adequate performance of the analytical testing belongs also in the field of GMP and belongs by this in the competence of the local GMP authority.

2.3. Non-clinical aspects

2.3.1. Introduction

The anti-tumour activity was assessed in two different experimental models of skeletal metastases in nude rats and nude mice. Additional experiments addressed the mechanism of action and potential interactions with bisphosphonates and doxorubicin. The effects of radium-223 chloride administration on vital organ systems were investigated in several safety pharmacology studies.

All pivotal non-clinical studies were conducted in accordance with current testing guidelines and in compliance with the principles of Good Laboratory Practice (GLP) with the exception of the radio-analytical part of the single dose mouse and rat toxicity studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Summaries of the overall radium-223 chloride effects *in vitro* and *in vivo*, based on submitted studies and information from the scientific literature, are presented in the following Tables 1 and 2.

Table 1. Summary of the in vitro activity of radium-223 chloride

Assay	Outcome
Effects on NHIK 3025, NSCLC A549 and multi drug resistant NHIK 3025 and A549 cells	• Reduction of the surviving fraction of NHIK 3025 at dose rates from 0.008 - 0.196 Gy/h • Similar effects in A549 cells and 2 multidrug resistant NHIK 3025 and A549 cells • Similar efficacy in exponentially growing and non-cycling cells • Induction of DNA double strand breaks • Induction of permanent G2 cell cycle arrest at doses > 0.35 Gy • Efficacy independent of the cell cycle distribution
Effects on osteoclast differentiation and activity	• Dose dependent inhibition of differentiation starting at 50 Bq/ml • No effects on osteoclast activity up to 1600 Bq/ml
Effects on osteoblast differentiation and activity	• Moderate inhibition of differentiation starting at 400 Bq/ml • Moderate induction of osteoblast activity induced at 100 and 200 Bq/ml • Strong inhibition at 800 and 1600 Bq/ml

Table 2. Summary of the in vivo activity of radium-223 chloride

Model	Outcome
Bone metastasis model (MT-1 cells) in nude rats	• Significant prolongation of the symptom free survival with single agent radium-223 chloride (60 kBq/kg and 110 kBq/kg) • Similar efficacy data after co-administration of pamidronic acid
Bone metastasis model (MDA-MB-231 (SA) GFP) in nude mice – First experiment (Dose finding study)	• Efficacy at 300, 600 and 1200 kBq/kg • Reduction of total tumour burden, the total osteolytic area and the lesion count at 300 kBq/kg
Second experiment (Efficacy and MoA at 300 kBq/kg)	• Reduction of the total osteolytic area and the total tumour burden • Prevention of the development of cachexia • Necrosis of bone metastases • Reduction of osteoclast number at the tumour/bone interface[3]
Third experiment (Survival at 300 kBq/kg)	• Prolongation of the TTS / survival • Lower relative change of the serum TRACP 5b
Fourth experiment (Combo study)	• Prolongation of the TTS / survival in combination with zoledronic acid • Prolongation of the TTS / survival in combination with doxorubicin
Bone and soft tissue uptake of radium-223 in comparison to beta emitting strontium-89 in mice	• Selective uptake of strontium-89 and radium-223 into the bone • No reduction of bone uptake of radium-223 during the 14 days follow up period • Little redistribution of radium-223 daughter products

Secondary pharmacodynamic studies

No studies were submitted (see discussion on non-clinical aspects).

Safety pharmacology programme

Effects of radium-223 chloride on vital organ functions [central nervous system, cardiovascular system (including ECG) and respiratory system] were investigated in several *in vivo* studies (rats, dogs). Clinical, gross and histopathology investigations were also included in the dog cardiovascular study. No blood or tissue levels of radioactivity levels were measured in the rat and dog safety pharmacology studies.

Doses administered were chosen to cover sufficient safety margins of up to 20-fold in the rat studies and up to 9-fold in the dog study; the clinical dose for radium-223 chloride is 50 kBq per kg body weight.

Radium-223 dichloride [i.v. (50, 250 or 1,000 kBq/kg (0.0014, 0.0068 or 0.027 mCi/kg, respectively)] did not induce treatment related, toxicologically significant effects on mortality, body temperatures, body weights, body weight gains, functional observational battery (FOB) and locomotor activity in male Sprague-Dawley rats. Statistically significant but sporadic changes in FOB were not considered biologically significant or treatment related.

Radium-223 dichloride [i.v. 50, 150 and 450 kBq/kg (0,0.0014, 0.0040 and 0.012 mCi/kg, respectively)] did not induce mortalities, treatment related statistically significant differences in mean body weights or total body weight gains, body temperature, locomotor activity, clinical chemistry changes, gross lesions or histologic findings in telemetered conscious Beagle dogs (n=4). Several haematology parameters (white blood cells, platelets, eosinophils, reticulocytes, monocytes and lymphocytes) showed apparent dose-related increases or decreases that were considered related to radium-223 dichloride

administration. None of the administered doses of radium-223 affected electrocardiogram (ECG) measurements (PR, QRS, RR and QT duration) or heart rate in any significant manner.

Radium-223 dichloride [i.v. 50, 150 and 1000 kBq/kg (0,0.0014, 0.0068 or 0.027 mCi/kg, respectively)] did not induce treatment related findings in in-life parameters, including clinical observations, body weights and total body weight gains, absolute values of respiratory rate, tidal volume and minute volume comparing to the mean of the 1st, 2nd, 3rd, and 4th hours after dosing to the mean of baseline measured prior to administration in male Sprague-Dawley rats.

Pharmacodynamic drug interactions

The potential additive efficacy of administration of radium-223 chloride with the subsequent (next day) administration of the bisphosphonate pamidronic acid (bone resorption inhibitor) has been investigated in a breast cancer bone metastasis model in nude rats (Henriksen et al. 2002). Efficacy (as percent symptom-free survival) of radium-223 chloride in this model was not modified by subsequent administration of pamidronic acid.

In a second model, radium-223 chloride treatment (300 kBq/kg) was combined with the administration of the bisphosphonate zoledronic acid (bone resorption inhibitor) or the administration of the cytotoxic agent doxorubicin in a breast cancer bone metastasis model in nude mice (R-8698) (n=10 per group). Primary endpoint of this study was the median time to sacrifice (TTS). While neither doxorubicin nor zoledronic acid prolonged the median TTS (24 days vs. 23 days vs. 25 days for the vehicle control) both combination treatment groups showed a significant increase of this parameter (30 days for the radium 223 chloride/doxorubicin combination vs. 33 days for the radium-223 chloride/zoledronic acid combination vs. 28 days for the radium-223 chloride single agent group). Additionally, the most pronounced reduction of the mean osteolytic lesion area at sacrifice was seen in mice which received the combination of radium-223 chloride and zoledronic acid.

2.3.3. Pharmacokinetics

The pharmacokinetics of radium-223 has been investigated *in vivo* in Wistar rats, Balb/c mice and Beagle dogs, using the same formulation as the clinically intended.

Blood pharmacokinetics of radium-223 has been determined in mice (only half-life) (R-8646, R-8649) and dogs (R-8668, R-8668A; R-8670; R-8670A) after single dose intravenous administration.

One hour after intravenous administration, less than 1% and 12% of the radioactive dose was present in plasma of mice and dogs, respectively. The values of radioactivity in blood decreased below 0.1% in mice and 2% in dogs 24h after administration. The blood elimination appeared to be biphasic in mice and triphasic in dogs. In the single dose study in dogs, where three different doses (50, 150 and 450 kBq/kg) were investigated, distribution and elimination from blood appeared to be independent of dose.

In mice administered 625 kBq/kg, calculation of the biological half-life of radium-223 in blood established the initial half-life ($t_{1/2\alpha}$) to be about 0.1 hours (about 5-10 minutes), and a last measured half-life ($t_{1/2ß}$) to be about 13 hours.

In dogs administered single doses of 50, 150 or 450 kBq/kg radium-223, the pharmacokinetic data indicate a triphasic elimination from blood with an initial half-life ($t_{1/2\alpha}$) calculated to be 0.2 hours (about 10 minutes), an intermediate half-life ($t_{1/2ß}$) of about 2 hours, and last measured half-life ($t_{1/2\gamma}$) of about 50 hours.

No separate studies on pharmacokinetics after repeat administration of radium-223 were performed. Pharmacokinetic data after repeat administration were performed in the 6-month repeat dose toxicity study in dogs (R-8670; R-8670A). Data were obtained after the 3rd and the 6th injection.

No plasma protein binding and plasma/blood cell partitioning investigation were submitted. Single dose biodistribution has been investigated in mice, rats and dogs, and after repeat dose intravenous administration in dogs.

In mice the biodistribution of radium-223 was followed up to 14 and 56 days after a single injection of 625 kBq/kg in two different studies. In the first study, over a period of 14 days, the greatest accumulation of activity occurred in bone. Levels of radium-223 decreased rapidly from the kidneys and large intestine. In addition, radium-223 was taken up in the spleen but appeared to clear from this organ over time. Radium-223 was essentially absent in soft tissue, with the exception of the spleen where a small amount could be detected. In the second study radium-223 remained within the bone at least up to approximately 5 half-lives and probably for the entire decay period.

As part of a single dose toxicology study in rats (R-8661), a non-GLP biodistribution assessment was performed. Thirty days after radium-223 chloride administration at a dose of 1,250 kBq/kg, the highest level of radioactivity was found in the bone and cartilage tissues. Low levels of radioactivity were measured in soft tissues such as urethra, salivary gland, thyroid, sciatic nerve and pituitary.

In dogs, after single or repeat dose of radium-223 biodistribution was assessed after 30 days following administration. Radium-223 was preferentially retained in bone samples compared to soft tissue organs. The liver and spleen were the only two soft tissue organs that showed measurable amount of retained radioactivity in the single dose study and then only in the highest dose group.

In Henriksen et al. (2003), uptake of radium-223 in organs and tissues of mice in comparison to the beta-emitter strontium-89 was evaluated. Both radionuclides reached an activity level equivalent to maximum only 1 h after injection and the radioactivity levels in bone did not change significantly up to 14 days. The highest absorbed dose of radium-223 occurred in bone with little absorbed dose occurring in soft tissue. Brain and heart samples contained insignificant amounts of radioactivity at all time-points (up to 14 days after dosing).

No studies investigating potential metabolism of radium-223 were submitted (see discussion on non-clinical aspects).

Urinary and faecal excretion was studied in two mice studies receiving a single injection of 625 kBq/kg radium-223 chloride (R-8647, R-8650). Radium-223 was seen in both urine and faeces as early as 1 hour after dosing. Maximum urinary and faecal excretion occurred at 6 hours or 12 hours after dosing. Five days after administration on average 16% (14-18%) of the administered dose was recovered. Little or no radium-223 was detected in urine and faeces 4 days after radium-223 chloride- administration. The cumulative urine to faeces ratios in these studies were found to be 1:1 or 1:3, respectively.

In another long term study in mice, small but detectable amounts of radium-223 were excreted in the urine and faeces over the entire time course of the study (56 days). The elimination of radium-223 in faeces and urine was even detectable after 56 days after injection, however on a continuously decreasing course. The ratio of urine and faeces excretion is considered unchanged during the course of excretion with a factor of about 1:5.

In the dog studies, total urine and faeces output was not measured, and a full mass balance was not available. However, data of Lloyd et al. (1982), showed retention of about 50% of injected radioactivity after intravenous radium-224 administration.

No relevant difference in blood pharmacokinetics or tissue biodistribution was observed between radium-223 given alone or 2 hours after zoledronic acid.

2.3.4. Toxicology

Single dose toxicity

Results of single dose toxicity studies with radium-223 chloride are summarised in Table 3.

Table 3. Single dose toxicity studies with radium-223 chloride

Study ID	**Species / Sex / Number / Group / Study outline**	**Dose [kBq/kg] / Route**	**Observed max non-lethal dose / NOAEL [kBq/kg]**
R-8660	Mouse/Balb/C Dose finding study: 8/sex/group Biodistribution study: 6 M Main study: 20/sex/group Necropsy: 28/29 days after administration	Dose finding study: 1250, 1875, 2188, 2500 Biodistribution study: 1250 Main study: 0, 1250, 2500, 3750 IV, Vehicle: 0.9 % saline	1250/ <1250
Major findings **Dose finding study:** No adverse clinical findings **Biodistribution study:** Ra-223 had pronounced affinity to calcified tissues, e.g. bone, cartilage (time points, 1 and 14 days post dose) **Main study: Died / sacrificed moribund:** 1 animal at 2500 and 2 animals at 3570 kBq/kg after showing clinical signs (piloerection, hunched posture and passive behaviour), **Body weight gain:** ≥ 1250 kBq/kg ↓, **Haematology:** ≥ 1250 kBq/kg: RBC ↓, WBC ↓, LYMPHO ↓, EOSIN ↓, **Clinical chemistry:** ≥ 1250 kBq/kg: ALP↓, **Organ weight:** ≥ 1250 kBq/kg: Spleen ↑, **Histopathology:** ≥ 1250 kBq/kg: Depletion of osteocytes/ osteoblasts (bone), Depletion of hematopoietic cells (bone marrow), Increase of extramedullary haematopoiesis (spleen); ≥ 2500 kBq/kg: Fibro-osseous lesions (bone); **Decedent animals:** marked atrophy of hematopoietic cells in bone marrow diffuse atrophy of spleen and thymus			
Study ID	**Species / Sex / Number / Group / Study outline**	**Dose [kBq/kg] / Route**	**Observed max non-lethal dose / NOAEL [kBq/kg]**
R-8661	Rats/Wistar Dose finding study: 2/sex/group Main study: 5/sex/group Necropsy: 28/29 days after administration	Dose finding study: 1258, 2202, 3145, 3774 Main study: 0, 1027, 2054, 3081 IV, Vehicle: 0.9 % saline	3081/ < 1027
Major findings **Dose finding study: Body weight gain:** ≥ 1258 kBq/kg ↓; **Biodistribution (only 1258 Bq/kg group sampled, final necropsy):** Radium-223 adhered to bone tissues, with little or no adhesion to other tissues **Main Study: Body weight gain:** ≥ 1027 kBq/kg ↓ (M); ≥ 2054 kBq/kg ↓ (F); **Food consumption:** ≥ 1027 kBq/kg ↓ (M); **Haematology:** ≥ 1027 kBq/kg: WBC ↓, NEUTRO ↓, LYMPHO ↓, MCV ↑, MCH ↑, Plt (M) ↓; ≥ 2054 kBq/kg: Plt ↓ (F), Pt ↓ (M); **Clinical chemistry:** ≥ 1027 kBq/kg: ALP ↓, G↑ (F); ≥ 2054 kBq/kg: P ↑ (F); 3081kBq/kg: GGT ↑, P ↑ (M); **Organ weight:** ≥ 1027 kBq/kg: Adrenal, relative ↑, Spleen, relative ↑, Kidney, absolute ↓ (M), Liver, absolute ↓ (M), thymus, absolute ↓ (M); ≥ 2054 kBq/kg: Ovary, absolute ↓ (F); **Histopathology:** ≥ 1027 kBq/kg: Depletion of osteocytes and osteoblasts (bone), Increase of fibro-osseous lesions (bone), Increase in extramedullary haematopoiesis (spleen), ≥ 2054 kBq/kg, Atrophy and/or increased lymphocytolysis (M) (thymus), Alveolar oedema (F) (lung), Giant cell formation (testes) (M); 3081 kBq/kg: Atrophy and/or increased lymphocytolysis (F) (thymus), Alveolar oedema (M) (lung)			
Study ID	**Species / Sex / Number / Group / Study outline**	**Dose [kBq/kg] / Route**	**Observed max non-lethal dose / NOAEL [kBq/kg]**
R-8668, R-8669, R-8668A	Dog/Beagle 2/sex/group Necropsy: 30 days after administration	0, 50, 150, 450 IV, Vehicle: 0.9 % saline	450/ < 50

Major findings **Died/sacrificed moribund:** 1 dog at 450 kBq/kg sacrificed on day 12 due to aspiration pneumonia; **Clinical signs:** 450 kBq/kg: Transient elevation in body temperature corresponding to granulocyte nadir days 7-14; **Haematology:** ≥ 50 kBq/kg WBC ↓, GRANU ↓, Plt ↓, RBC parameter ↓; **Histopathology:** ≥ 50 kBq/kg: Bone marrow cellularity ↓, M:E ratio ↓; 150 kBq/kg: Segmented retinal detachment with hypertrophy of the retinal unpigmented epithelium in 1 dog; 450 kBq/kg: Retinal detachment with hypertrophy of the retinal unpigmented and pigmented epithelium in 3/3 surviving dogs

Repeat dose toxicity

Results of repeat dose toxicity studies with radium-223 chloride are summarised in Table 4. The first study R-8662 was really a single dose study, but animals were followed up for a year.

Table 4. Repeat dose toxicity studies with radium-223 chloride

Study ID/ GLP	Species/ Sex/ Number/Group	Dose [kBq/kg]/Route	Duration	NOAEL [kBq/kg]
R-8662 GLP: yes	Rat/Wistar 8/sex/group	Single dose: Control: 0, LD: 20, MD: 80, HD: 325, VHD: 1300 IV, Vehicle: Sodium citrate buffer	single dose + 12 months postdose	< 20 kBq/kg
Major findings **Died/sacrificed moribund:** LD: 1M, MD: 1F, HD: 3M/4F, VHD: 3M/2F; **Body weight:** ≥ HD: ↓ **Food consumption:** ≥ HD: ↓; **Clinical observations:** ≥ LD: red secretion around nostril and eyes, piloerection ≥ HD: teeth worn down, paralytic hind-legs; VHD: abnormal neurologic behaviour (1 animal); **Haematology:** ***Day 15 (2 weeks after 1 dose):*** ≥ LD: WBC ↓, NEUTRO ↓, LYMPHO ↓; ≥ MD: EOS ↓,Plt ↓; ≥ HD: Hb ↓ (F), RBC ↓, HCT ↓; ***During recovery:*** ≥ HD: RBC ↓, MCV ↑, MCH ↑; VHD: (F), WBC ↓, LYMPHO ↓, APTT ↑ (F); ***End of study (week 52):*** ≥ LD: WBC ↓ (M), LYMPHO ↓ (M); ≥ MD: Lympho % ↓ (F), NEUTRO % ↑ (F); VHD: MCV ↑ (F); **Clinical chemistry:** ***Day 15 (2 weeks after 1 dose):*** ≥ LD: Mg ↓; ≥ MD: ALP ↓ (F); ≥ HD: ALP ↓ (M); VHD: Cl ↑ (F); ***During recovery:*** ≥ HD: CREA ↑, P ↑; VHD: ALT ↑ (F), AST ↑ (F), TRIG ↓ (M), Urea ↑, K ↓ (M); ***End of study (week 52):*** ≥ HD: ALT ↑, AST ↑ (M), K ↓ (F), P ↑; **Urinanalysis:** ***Day 15 (2 weeks after 1 dose):*** None; ***During recovery:*** ≥ HD: CREA ↑ (F), GGT ↓; VHD: Na ↑ (F); ***End of study (week 52):*** ≥ MD: CREA ↓ (M); VHD: Epithelial cells ↑ (F); **Organ weights:** ≥ HD: Liver ↓; **Gross pathology:** ***Early deaths:*** *Teeth:* Broken: (HD: 1F), *Jaw:* Upper jaw, broken (HD: 1F), Mandible, short, misshapen (VHD: 1M), *Skin:* Lip, thickened area (HD: 1F); Subcutis, mass, right arm (HD: 1M), *Hindleg:* Nodule (HD: 1M), *Vertebrae:* Thoracic, nodules (HD: 1F); Lumbar, masses (VHD: 1M), *Scapula:* Masses (VHD: 1M); **Histopathology:** ***Early deaths: Non-neoplastic findings:*** *Liver:* Karyomegaly (MD: 1F, HD: 1M/3F, VHD: 1M/2F), *Kidneys:* Karyomegaly (VHD: 1M), *Spleen:* Increased extramedullary haematopoiesis (MD: 1F, HD: 2M/3F, VHD: 3M/1F), *Uterus:* Polyp, endometrial stroma (VHD: 2F), *Bone, femur:* Bone marrow, decreased cellularity (HD: 3M/3F, VHD: 2M/1F), Depletion osteocytes, osteoblasts (HD: 3M/4F, VHD: 2M/1F), Hyperostosis (HD: 2M/3F, VHD: 2M/1F), Physis, abnormal/disorganized (HD: 2M/2F, VHD: 2M/1F), *Sternum:* Bone marrow, decreased cellularity (HD: 3M/3F, VHD: 3M/1F), Depletion osteocytes, osteoblasts (HD: 2M/1F, VHD: 2M/2F), Fibro-osseous lesion (VHD: 1M); ***Neoplastic findings:*** *Lung:* Osteosarcoma (VHD: 1M), *Adrenal Glands:* Adenoma, cortex (HD: 1M), *Epididymes:* Mononuclear cell leukaemia, bilateral (LD: 1M), *Muscle, skeletal:* Osteosarcoma (HD: 1M), *Vertebrae:* Osteosarcoma (HD: 2F, VHD: 1M), *Bones:* Osteosarcoma, front leg (HD: 1M); Osteosarcoma, scapuöa (VHD: 1M), *Systemic tumours:* Large glandular lymphocyte lymphoma (LD: 1M); Lymphoma (VHD: 1F) ***Scheduled termination: Non-neoplastic findings:*** *Teeth:* Bone socket, fibrous-osseous lesion (VHD: 1M/1F), *Liver:* Karyomegaly (Control: 6F, LD: 4F, MD: 6F, HD: 3F, VHD: 5F); Bile duct hyperplasia (Control: 1F, LD: 2F, MD: 1M/1F, HD: 1M/1F, VHD: 1M), *Kidneys:* Karyomegaly (VHD: 4M), *Spleen:* Increased extramedullary haematopoiesis (Control: 3M/3F, LD: 6M/4F, MD: 5M/4F, HD: 4M/3F, VHD: 5M/6F), *Uterus:* Polyp, endometrial stroma (HD: 1F, VHD: 3F), *Vagina:* Polyp (VHD: 1F), *Bone, femur:* Bone marrow, decreased cellularity (Control: 6M/1F, LD: 6M/1F, MD: 8M/4F, HD: 5M/3F, VHD: 5M/4F), Depletion osteocytes, osteoblasts (HD: 5M/4F, VHD: 5M, 6F), Hyperostosis (Control: 1F, HD: 4M/3F, VHD: 5M/6F), Physis, abnormal/ disorganized (MD: 1M, HD: 2M/2F, VHD: 5M/6F), *Sternum:* Bone marrow, decreased cellularity (Control: 1M/3F, LD: 1M/3F, MD: 7M/2F, HD: 5M/2F, VHD: 5M/6F); Depletion osteocytes, osteoblasts (LD: 5M, MD: 2M, HD: 2M/1F, VHD: 5M/6F); Fibro-osseous lesion (VHD: 1M), ***Neoplastic findings:*** *Brain:* Astrocytoma (LD:IM) *Thyroid gland:* Adenoma, C-cell (MD: 1F); Adenocarcinoma (MD: 1M), *Bones:* Osteosarcoma, tibia (HD: 1M) *Injection site:* Carcinoma, squamous cell (HD: 1F)				
Study ID/ GLP	**Species/ Sex/ Number/Group**	**Dose [kBq/kg]/Route**	**Duration**	**NOAEL [kBq/kg]**
R-8662/	Rat/Wistar	Control: 0, LD: 20,	Repeat dose: once every 4	< 20 kBq/kg

GLP: yes	8/sex/group	MD: 325, HD: 650	weeks x 4 + 12 months post-dose	

Major findings
Died/sacrificed moribund: Control: 1M, LD. 1M/1F, MD: 5M/5F, HD: 6M/6F; **Body weight:** ≥ MD: ↓; **Food consumption:** ≥ MD: ↓; **Clinical observations:** ≥ LD: passive/less active, paralytic hind-legs; ≥ MD: red secretion around eyes, piloerection, nodules/swelling, limping of hind-or forelegs, teeth worn down; HD: noisy respiration, forced respiration, convulsions;
Haematology: ***Day 15 (2 weeks after 1 dose):*** ≥ LD: WBC ↓, NEUTRO ↓, LYMPHO ↓, EOS ↓; ≥ MD: Hb ↓, RBC ↓, HCT ↓, MCV ↑, Plt ↓; ***During recovery:*** ≥ LD: WBC ↓, NEUTRO ↓, LYMPHO ↓, EOS ↓, Plt ↓ (F); ≥ MD: RBC ↓, MCV ↑, MCH ↑, Pt ↓ (F); HD: Hb ↓, HCT ↓; ***End of recovery (week 64):*** ≥ MD: MCV ↑, MCH ↑;
Clinical chemistry: ***Day 15 (2 weeks after 1 dose):*** ≥ MD:Cl ↑ (M), G ↑, Alb/G ratio ↓; HD: Mg ↓; ***During recovery:*** ≥ LD: ALT ↑ (F), Alb ↓; ≥ MD: ALT ↑ (M), AST ↑, TRIG ↓ (M), Urea ↑, CREA ↑, Na ↓ (M), Ca ↑ (F) , P ↑; HD: Mg ↑ (F), Alb ↓ (F), G ↓ (M); ***End of recovery (week 64):*** ≥ MD: AST ↑ (M), ALT ↑ (M), TRIG ↓ (M), CREA ↑, P ↑;
Urinanalysis: ***Day 15 (2 weeks after 1 dose):*** None; ***During recovery:*** ≥ LD: Ca ↑, K ↑ (F); Epithelial cells ↑ (F); **End of recovery (week 64):** ≥ MD: CREA ↓; **Organ weights:** ≥ MD: adrenals ↑ (M), liver ↓;
Gross Pathology: ***Early deaths:*** *Jaw:* Mandible, hard swelling (MD: 1M); Lower jaw, mass/nodule (MD: 3M, 1F), *Skin:* Subcutis, mass, mandible/head (MD: 1M), *Muscle:* Mass, shoulder (MD: 1F), *Uterus:* Polyp (MD: 1F); Left horn thickened (HD: 1F); ***Scheduled necropsy:*** *Head:* Nodule (HD: 1F), *Teeth:* Broken (MD: 1M), *Skin:* Lip, thickened area (MD: 1M), *Uterus:* Left horn thickened (MD: 1F);
Histopathology: ***Early deaths: Non-neoplastic findings:*** *Teeth:* Bone socket, fibrio-osseous lesion (MD: 1F, HD: 1F), *Liver:* Karyomegaly (MD: 1M/5F, HD: 1M/6F); Bile duct hyperplasia (MD: 3F, HD: 1M/2F), *Kidneys:* Karyomegaly (MD: 5M/3F, HD: 6M/6F), *Spleen:* Increased extramedullary hematopoiesis (LD: 1M, MD: 5M/3F, HD: 6M/6F), *Uterus:* Polyp, endometrial stroma (MD: 5F, HD: 2F), *Bone, femur:* Bone marrow, decreased cellularity (Control: 1M, LD: 1M, MD: 4M/5F, HD: 5M/2F); Depletion osteocytes/osteoblasts (MD: 5M/5F, HD: 6M/6F); Hyperostosis (MD: 5M/5F, HD: 6M/6F); Physis, abnormal/disorganized (MD: 5M/5F, HD: 6M/6F)
Sternum: Bone marrow, decreased cellularity (Control: 1M, LD: 1M, MD: 3M/5F, HD: 5M/6F); Depletion osteocytes/osteoblasts (MD:5M/5F, HD: 6M/6F); Fibro-osseous lesion (MD: 1M, HD: 3M/4F); ***Neoplastic findings:*** *Teeth:* Bone socket, osteosarcoma (MD: 4M/1F); Sarcoma, NOS (MD: 1F), *Stomach, glandular:* Adenoma, exophytic (MD: 1F), *Lung:* Osteosarcoma (MD: 1M); Sarcoma, NOS (MD: 1F); Adenoma, bronchiolo-alveolar (MD: 1M, HD: 1M), *Pituitary gland:* Adenoma (Control: 1M, MD: 1F); Pituicytoma (HD: 1F)
Thyroid gland: Adenoma, C-cell (MD: 1M); Adenoma, follicular cell (MD: 1M), *Mammary gland:* Fibroadenoma (MD: 1F), *Muscle, skeletal:* Osteosarcoma (MD: 1F), *Bones:* Osteosarcoma, mandible (MD: 4M/1F); Osteosarcoma, front-leg (MD: 1M); *Head:* Rhabdomyosarcoma (HD: 1F);
Scheduled termination: Non-neoplastic findings: *Teeth:* Bone socket, fibrio-osseous lesion (MD: 1F, HD: 2M); Broken (MD: 1M), *Liver:* Karyomegaly (Control: 5F, LD: 5F, MD: 2M/3F, HD: 2F); Bile duct hyperplasia (Control: 1M/5F, LD: 2F, MD: 1M/2F, HD: 1M/1F), *Kidneys:* Karyomegaly (MD: 2M/1F, HD: 2M/2F), *Spleen:* Increased extramedullary haematopoiesis (Control: 5M/4F, LD: 6M/5F, MD: 3M/3F, HD: 2M/2F), *Uterus:* Polyp, endometrial stroma (MD: 1F, HD: 2F), *Bone, femur:* Bone marrow, decreased cellularity (Control: 5M/2F, LD: 7M/2F, MD: 3M/1F, HD: 2M/2F); Depletion osteocytes/osteoblasts (MD:3M/3F, HD: 2M/2F); Hyperostosis (MD: 3M/3F, HD: 2M/2F); Physis, abnormal/disorganized LD: 1M/2F, MD: 3M/3F, HD: 2M/2F), *Sternum:* Bone marrow, decreased cellularity (Control: 3M/3F, LD: 6M/3F, MD: 3M/1F, HD: 1M/2F); Depletion osteocytes/osteoblasts (MD:3M/3F, HD: 2M/2F); Fibro-osseous lesion (HD: 1M/2F); ***Neoplastic findings:***
Teeth: Bone socket, osteosarcoma (HD: 1F), *Lung:* Adenoma, bronchiolo-alveolar (HD: 1M), *Kidneys:* Renal liposarcoma (HD: 1M); Renal lipoma (MD: 1M), *Pituitary gland:* Adenoma (LD: 1F), *Thyroid gland:* Adenoma, C-cell (HD: 1M); Adenoma, follicular cell (Control: 1M/1F, LD: 1M, MD: 1M, HD: 2M), *Mesenteric lymph node:* Haemangiosarcoma (Control: 1M), *Testes:* Adenoma, Leydig cell (Control: 1M), *Bones:* Osteosarcoma, head (MD: 1M)

Study ID/ GLP	**Species/ Sex/ Number/Group**	**Dose [kBq/kg]/Route**	**Duration**	**NOAEL [kBq/kg]**
R-8663 GLP: yes	Rat/Wistar 12/sex/group	Control: 0, LD: 25, MD: 50, HD: 100 IV, Vehicle: Sodium citrate buffer	12 months (once every 4 weeks x 12) + 1 month postdose	< 25 kBq/kg

Major findings
Died/sacrificed moribund: LD: 4M/1F, MD: 7M/3F, HD: 3M/7F; **Body weight:** ≥ LD: ↓; **Food consumption:** ≥ LD: ↓; **Clinical observations:** ≥ MD: loss of upper incisor teeth;
Haematology: ***During treatment:*** ≥ LD: RBC ↓, RETIC ↑,MCV ↑, MCH ↑, WBC ↓, NEUTRO ↓, LYMPHO ↓, EOS ↓; ≥ MD: Hb ↓, HCT ↓; HD: MONO ↓, Plt ↓; ***Recovery (25 days after last dose):*** ≥ LD: RBC ↓, RETIC ↑, MCV ↑, MCH ↑, WBC ↓, NEUTRO ↓, LYMPHO ↓, EOS ↓; ≥ MD: Hb ↓ (F), BASO ↓ (F); ≥ HD: MONO ↓, Plt ↓;
Coagulation: ***During treatment:*** ≥ LD: Pt ↓; ≥ MD: Fib ↑;
Clinical chemistry: ***During treatment:*** ≥ LD: ALP ↓, P ↑, Alb ↓ (M), Cl ↓; HD: ALT ↑, Alb/G ratio ↓ (M), Na ↓; ***Recovery (25 days after last dose):*** ≥ LD: ALP ↓ (M), P ↑, Alb ↓ (M), Cl ↓; HD: ALT ↑;
Organ weights: ≥ LD: Spleen ↑
Gross Pathology: ***Early deaths:*** *Head:* Nodule (LD:1F), *Skin/subcutis:* Nodule, mandibular region (MD: 1M); Nodule, foreleg (MD: 1F), *Muscle, skeletal:* Nodule, upper leg: (LD. 1M, MD: 1M, HD: 1F)); Nodule, lower leg (HD: 3F), *Lung:* Spots, white (LD: 1M); Focus, red: (HD: 1M); Nodules (HD: 1M), *Spinal cord:* Nodules (HD: 2M), *Bone, vertebrae:* Nodule (MD: 1M), *Joints:* Nodules (HD: 1M)
Histopathology: ***Early death: Non-neoplastic findings:*** *Liver:* Karyomegaly, hepatocytes (HD: 1F), *Spleen:* Extramedullary hematopoiesis (LD: 2M, MD: 6M/2F, HD: 3M/6F), *Bone, femur:* Depletion osteocytes/osteoblats (LD:

1M, MD: 2M, HD: 6F); Bone depletion/fibrosis with disorganized growth line (LD: 4M/1F, MD: 7M/3F, HD: 3M/7F), *Sternum:* Bone marrow, decreased cellularity (MD: 3M, HD: 3M/1F); Bone mass decreased with occasional focal fibrosis (HD: 3M/7F); ***Neoplastic findings:*** *Brain:* Oligendroglioma (HD: 1F), *Lung:* Osteosarcoma, mestastatic (LD: 2M, MD: 3M, HD: 2M/3F); Adenoma, bronchio-alveolar (MD: 1M),
Pituitary Gland: Large glandular lymphoma (MD: 1M), *Thyroid gland:* Adenoma, follicular cell (LD: 1M, HD: 1M), *Adrenal Glands:* Osteosarcoma, metastasis (HD: 1F), *Mammary gland:* Carcinoma (LD: 1F), *Skin/subcutis:* Osteosarcoma, metastasis (MD: 1M/1F), *Muscle, skeletal:* Osteosarcoma, metastasis (LD: 1M/1F, MD: 2M, HD: 1M/4F), *Vertebrae:* Osteosarcoma (MD: 1M/1F, HD: 1M), *Bones:* Osteosarcoma, front leg (MD: 1F), *Bone, femur:* Osteosarcoma (MD: 1M/1F, HD: 1M/1F), *Systemic tumours:* Large Granular Lymphocyte Lymphoma (MD: 1M)
Scheduled termination (Control + HD): Non-neoplastic findings: *Liver:* Karyomegaly, hepatocytes (HD: 1F), *Spleen:* Extramedullary hematopoiesis (Control: all males, minimal or slight, all females, slight or moderate, HD: all animals moderate or marked), *Bone, femur:* Depletion osteocytes/osteoblast (HD: 1M/4F); Bone depletion/fibrosis with disorganized growth line (HD: all animals), Hyperostosis focal (HD 1M/2F), *Sternum:* Bone marrow, decreased cellularity (HD: 7M, 1F); Bone mass decreased with occasional focal fibrosis (HD: all animals); ***Neoplastic findings:*** *Lung:* Osteosarcoma, mestastatic (HD: 1F); Adenoma, bronchio-alveolar (HD: 1M), *Pituitary Gland:* Adenoma, pars distalis (Control: 1F), *Mammary gland:* Carcinoma (Control: 1F), *Skin/subcutis:* Haemangioma (MD: 1M)

Study ID / GLP	**Species / Sex / Number / Group**	**Dose [kBq / kg] / Route**	**Duration**	**NOAEL [kBq / kg]**
R-8670 R-8670A GLP: yes	Dog/Beagle Control: 2/sex/group Treatment group: 4/sex/group	0 (control), 50	6 months (once every 30-35 days x 6) + 35 days postdose	Not established

Major findings
Clinical observations: Pelvic fractures (6th injection); **Haematology:** WBC ↓, Plt ↓, LYMPHO, sl. ↓, MONO sl. ↓, GRANU ↓; **Clinical chemistry:** B-ALP ↓, NTX ↓ (4th injection 25 day post dose); **Histopathology:** ***Bone marrow:*** M/E ratio ↓, haematopoietic cellularity ↓, myelofibrosis, osteolysis, infiltration of vacuolated/ granulated histocytes; ***Spleen:*** extramedullary haematopoiesis ↑, pigmented macrophages ↑; ***Liver:*** extramedullary haematopoiesis ↑

Genotoxicity

No studies of the genotoxic effects or radium-223 chloride *in vitro* and/or *in vivo* were conducted (see discussion on non-clinical aspects).

Carcinogenicity

No lifetime studies of the tumorigenic potential of radium-223 chloride were conducted (see discussion on non-clinical aspects).

Reproduction Toxicity

No specific reproductive or developmental toxicity studies have been conducted or are planned with radium-223 chloride. Histological evaluation of male and female reproductive organs was performed in the single and repeat dose toxicity studies.

With regard to potential adverse effects on fertility, no adverse treatment related effects were observed in the repeat dose toxicity studies in rodents and non-rodents. In the single-dose i.v. toxicity study in rats, minimal numbers of abnormal spermatocytes were seen in the testes of male rats administered ≥ 2054 kBq/kg radium-223 chloride. In the single and repeat dose (4q5w) rat toxicity study, uterine polyps (endometrial stroma) were observed in female rats after single or repeated administration of ≥ 325 kBq/kg radium-223 chloride.

No embryonic and foetal toxicity studies, prenatal and postnatal developmental toxicity studies or studies with juvenile animals were submitted.

Toxicokinetic data

No toxicokinetic studies were conducted, either separately or as part of the toxicity studies. Biodistribution determinations including blood pharmacokinetics were performed as part of the single dose and repeat dose dog biodistribution and toxicity studies.

Local Tolerance

Radium-223 chloride was well tolerated locally after bolus intravenous administration in the GLP single and repeat dose toxicity studies described above based on the conduct of clinical observations and the histopathological evaluation of the injection site.

Transient erythema, but no oedema, haemorrhage or histological change of the injection site was observed after a single perivenous injection of 750 kBq/animal in a GLP study in rabbits (R-8667).

Other toxicity studies

Toxicity of radium-223 chloride in combination with docetaxel was evaluated in three toxicity studies conducted in rats. In these combination studies of radium-223 chloride (50 kBq/kg) with docetaxel (4mg/kg) after single and repeated dose, changes in haematology parameters were observed after treatment with both, radium-223 chloride and docetaxel and with the combination. After repeated dosing, a more pronounced effect on haematological parameters was observed with the combination.

2.3.5. Ecotoxicity / environmental risk assessment

An Environmental Risk Assessment was not submitted (see discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

Radium-223 chloride showed a cell killing effect *in vitro* by inducing DNA double strand breaks in NHIK 3025 cervical cancer cells and A549 NSCLC cells and 2 multidrug resistant cell lines derived from NHIK 3025 and A549 cells as well as in non-cycling NHIK 3025 cells. Beside this direct cytotoxic effect, an inhibition of osteoclast differentiation and osteoblast activity which was seen *in vitro* may also account to the *in vivo* efficacy. However, the inhibition of osteoblast activity was only seen at high concentrations of radium-223 chloride (800 and 1600 Bq/ml). At low concentrations of radium-223 chloride (100 and 200 Bq/ml), osteoblast activity was moderately induced. Since bone metastases in prostate cancer patients are frequently osteoblastic showing a profound local stimulation of osteoblasts adjacent to the metastatic tumour cells, the inverse effect on osteoblast activity may have an impact on the clinical efficacy dependent on the dose administered. Even though the model used is still considered not appropriate, taking into account the lack of suitable commercially available osteoblastic prostate cancer bone growth or metastasis models and of the available non clinical and clinical data, it is endorsed that based on the reduction of several serum bone formation markers seen in clinical studies and based on the *in vivo* preclinical data, a moderate inhibition of osteoblast activity would occur in patients at the clinical dose of 50 kBq/kg of radium-223 dichloride.

A significant radium-223 chloride anti-tumour effect has been demonstrated in an osteolytic experimental skeletal metastases model in nude rats intraventricularly inoculated with human breast cancer cells. Rats treated with approximately 110 kBq/kg showed a significantly increased symptom free survival compared to control animals. Additionally, radium-223 chloride was tested *in vivo* in a second osteolytic breast cancer bone metastasis model in nude mice. Radium-223 chloride significantly reduced the incidence of

cachexia, inhibited osteolytic destruction of the bone, reduced the total tumour burden and ultimately led to an increase of the median survival time in this setting. With regards to the underlying mode of action, necrotic areas within the bone metastases were found in radium-223 chloride treated animals. The nonclinical pharmacology studies indicated that radium-223 chloride delivers potent radiation targeted to bone at sites of increased bone turnover, such as skeletal metastases. In general, it would be more appropriate to perform *in vivo* pharmacodynamics studies of radium-223 chloride in an osteoblastic prostate cancer bone metastasis model. However, due to the data available from clinical studies with radium-223 chloride in patients with CRPC with bone metastasis, the efficacy on bone metastases of prostate cancer has been evaluated and no further *in vivo* non-clinical studies are required.

No secondary pharmacology studies were submitted. Due to the small mass of radium, 0.53 ng/ml corresponding to 1,000 kBq radium-223 per ml in the drug product at the date of calibration, no physiological effects are expected due to radium and its decay products itself.

No effects on CNS function, respiratory function and cardiovascular function have been observed in safety pharmacology studies conducted in rats (CNS and respiratory) and dogs (cardiovascular) that could be attributed to radium-223 chloride treatment. The doses used in the safety pharmacology studies were up to 1,000 kBq/kg in rats and up to 450 kBq/kg in dogs, which are multiples of the intended clinical dose.

No negative effects on different efficacy parameters were observed for the combination of radium-223 chloride with bisphosphonates in skeletal metastasis models in rats and mice.

The pharmacodynamic drug interaction studies with doxorubicin are of limited value for the proposed indication of radium 223 chloride, since doxorubicin is not indicated for treatment of castration-resistant prostate cancer patients with bone metastases.

Pharmacokinetic studies in mice and dogs showed that radium-223 was rapidly eliminated from the blood circulation. Elimination from blood appeared to be biphasic in mice and triphasic in dogs. In mice, initial half-life was about 0.1 h while terminal half-life was about 13 hours. In dogs, following single dose injection of radium-223 chloride the initial and intermediate half-lives were short, approximately 0.2 hours and just above 2 hours; and comparable following single and repeated injection of radium-223 chloride. The last measured half-life was about 50 hours following single dose injection. In dogs, where three different doses were investigated, distribution and elimination from blood appeared to be independent of dose.

No plasma protein binding studies have been performed for radium-223 chloride. For other earth alkaline ions plasma protein binding has been reported, e.g. ~40% for Ca2+ and ~50% for Ba2+. Therefore, it is likely that radium-223 also binds to plasma proteins. In this case, a fraction of administered radium-223-dose will probably be retained within the blood circulation. However, saturation of the bone binding sites that could theoretically lead to increased blood concentrations of radium-223 has been reasonably excluded, so that studies on plasma protein binding are not considered necessary for radium-223 chloride.

The biodistribution studies in mice, rats and dogs showed that radium-223 is primarily distributed to bone tissue with much higher affinity relative to soft tissues. However, the studies in rats and dogs had some limitations, since radioactivity levels in organs and tissues were only measured 30 days after administration of radium-223 chloride. Literature data showed that little redistribution of radium-223 daughter nuclides away from bone was found in mice after i.v. administration of radium-223 chloride (2% at 6 hours and less than 1% at 3 days). In mice where the biodistribution after a single dose of radium-223 was followed up to 56 days (approximately 5 half-lives of radium-223), radium-223 remained within the bone at least up to approximately 5 half-lives and probably for the entire decay period. Little radioactivity was detected in soft tissue with the exception of the spleen in mice, where a significant amount of radioactivity was found with a maximum level at 1 hour after administration and

then declines to levels below 1% of the administered does after 14 days. This accumulation in spleen is unclear but this could be a species-specific finding. Uptake in spleen was not seen in rats and only a very limited uptake in spleen was seen in dogs. However, in rats and dogs, investigations of biodistribution have only been performed 30 days after administration of radium-223 chloride. Therefore, it is likely that an initial accumulation occurs in the spleen shortly after administration of radium-223 chloride, which declines to low levels 30 days after dosing.

Dosimetry calculations for radium-223 in comparison to the beta-emitter strontium-89 distributed on the bone surface of marrow cavities indicated that the radium-223 alpha-emitter might have a marrow-sparing advantage compared with beta-emitters because the short-range alpha-particles irradiate a significantly lower fraction of the marrow volume than beta-particles emitted from e.g. strontium-89 (Henriksen et al, 2003).

Initially, a high level of radioactivity was found in the kidney in mice, most likely because of excretion in the urine but the level was rapidly reduced. High concentrations of radioactivity from radium-223 were found in the large intestine of mice, a finding that is confirmed by literature references citing excretion of radium isotopes (dog, rat, rabbits and cow) directly into the intestinal tract and contained in the faecal. This result was confirmed in the excretion studies in mice and dogs where it was observed that radium-223 was excreted in both faeces and urine.

No biodistribution studies directly comparing biodistribution after single and repeated dosing in the same study have been submitted by the applicant. It is agreed that an accumulation of radium-223 within the bone and a relevant saturation of the binding sites within the bone are not expected.

No known metabolic pathways exist for radium-223. Therefore, studies of the metabolism of radium-223 are neither considered appropriate nor relevant to the safety evaluation of radium-223 chloride. The decay of radium-223 to stable lead-207 (via radon-219, polonium-215, lead-211, bismuth-211 and thallium-207) is known.

In both mice and dogs, excretion of radium-223 occurred by both gastrointestinal and renal route. Maximum urinary and faecal excretion in mice was seen until 6 hours and 12 hours, respectively. In dogs, maximum urinary and faecal excretion was seen at 2 and 12 hours, the first sampling times for these parameters, respectively. In two mice studies, five days after administration on average 16% (14-18%) of the administered dose was recovered. Little or no radium-223 chloride was detected in urine and faeces 4 days after radium-223 - administration. Small detectable amounts of radium-223 were excreted in the urine and faeces in mice throughout a period of 56 days after a single dose radium-223 chloride administration. The low recovery rate of 16% can be explained by the retention of radium-223 into the bone tissue.

A mass balance calculation in mice reveals that on average about 70% of the administered single dose was bound to bone tissue. This binding occurs rapidly after the first investigated time point after administration (0.5 hours) and remains on a constant level until the end of entire study (14 days). It can be concluded that once bound to bone, radium-223 remains within the bone for the entire decay period. In all other investigated tissues, the residues of radioactivity were observed below 1% of the administered dose already 12 hours after administration, with the exception of the spleen. The cumulative urine to faeces ratios in these studies in mice were found to be 1:1 or 1:3, respectively. In the dog studies, total urine and faeces output was not measured. Therefore, a full mass balance was not calculated. Levels of radioactivity concentration in urine and faeces reveal a time dependent decrease. In addition, the radium-223 excretion was observed in a dose dependent manner. A published distribution study in dogs after intravenous administration of the radium isotope radium-224 reported a total retention of about 50% of the injected radioactivity. Another published study after subcutaneous injection of the radium isotope radium-226 to dogs showed that the faecal to urinary excretion ratio was about

10:1. Excretion into bile of radium-223 has been investigated in dogs showing that biliar excretion accounted for a small percentage of total excretion. This suggests first pass liver metabolism and probably enterohepatic circulation of radium-223. The secretion/excretion of radium from blood into the small intestine through the small intestine wall is most likely through the transport mechanisms involved for other divalent cations (e.g. Ca, Mg, Sr and Ba).

The pharmacokinetics or biodistribution of radium-223 was not affected by administration of a bisphosphonate (zoledronic acid) in mice. The transport pathways most likely used by radium are not the same as used by small molecules so no drug-drug interaction is anticipated at the small intestinal wall. As a calcium-analogue, radium-223 is incorporated into bone and other newly calcified tissues instead of calcium. Furthermore, the transport mechanisms from blood into the small intestine are most likely the same as used for other divalent cations (e.g. Ca, Mg, Sr and Ba).

In single and repeated dose toxicity studies 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 dose of 20 kBq per kg body weight (0.4 times the clinically recommended dose).

In dogs, haematological changes were observed beginning at the lowest dose of 50 kBq/kg. Dose limiting myelotoxicity was observed after a single dose of 450 kBq/kg, while single doses of 50 kBq/kg and 150 kBq/kg were considered safe and repeated administration of the clinically recommended dose of radium-223 chloride (50 kBq/kg) at intervals of 4 weeks for 6 months was well tolerated without dose-limiting toxicities. Some of the haematological changes were partially reversible after the end of treatment. In the single dose dog study, a rebound in haematology parameters to the low reference range was observed by the end of the study period in dogs given 50 kBq/kg but not 150 kBq/kg or 450 kBq/kg radium-223 chloride. In the repeat dose study with dogs given 50 kBq/kg, gradual recovery of the decreases in total white blood cell, granulocyte and platelet counts began after the third of 6 injections and continued over the remainder of the study period. However, the repeat-dose toxicity study in dogs has some limitations, since only one radium-223 treated dose group, using the clinically recommended dose of 50 kBq/kg, was used. Therefore, dose-responses of the toxicological findings and safety margins to humans could not be established.

After repeated administration of the clinically recommended dose of 50 kBq per kg body weight once every 4 weeks for 6 months, two dogs developed non-displaced pelvic fractures. Due to the presence of osteolysis of trabecular bone in other bone locations of treated animals in varying degree, a spontaneous fracture in the context of osteolysis cannot be excluded. The clinical relevance of these findings is unknown.

Retinal detachment with hypertrophy of the retinal unpigmented and/or pigmented epithelium was seen in dogs after a single injection of radium-223 chloride at dose levels of 150 and 450 kBq/kg (3 to 9 times the clinically recommended dose), but not after repeated administration of the clinically recommended dose of 50 kBq/kg. The exact mechanism for the induction of retinal detachment in dogs is unknown but might be a consequence of the enhanced delivery of alpha radiation to the ocular tissues secondary to the avidity of the canine pigmented epithelium for radium and radium daughters as described in the literature. A potential mechanism for this avidity may be the high number of calcium binding sites in pigment epithelium, especially the *tapetum lucidum*, probably reflecting a critical role for calcium in photoreceptor signaling and light adaptation. Since humans do not have a *tapetum lucidum,* the retinopathy observed in dogs may reflect a species-specific accumulation of radium in the pigmented

structures of the canine eye. Until now, no retinopathy was observed in patients treated with radium-223 chloride.

No histological changes were observed in organs involved in the excretion of the radium-223.

Osteosarcomas, a known effect of bone-seeking radionuclides, occurred in rats at extended times (7 to 12 months) in the single or repeat dose (4 q4w) study and the 12-month repeat-dose (12 q4w) study. More than 6 months after single and repeated administration of radium-223 chloride, rats were found dead or sacrificed for humane reasons mainly due to osteosarcomas. The indication for Xofigo is treatment of castration-resistant prostate cancer patients with bone metastases, an advanced cancer disease. Therefore for this patient population, the long-term risk for development of osteosarcomas is acceptable.

Studies on the mutagenic and carcinogenic potential of Xofigo have not been performed. In general, radionuclides are considered to be genotoxic and carcinogenic.

Studies on reproductive and developmental toxicity have not been submitted. In general, radionuclides induce reproductive and developmental effects.

A minimal number of abnormal spermatocytes were seen in a few seminiferous tubules in the testes of male rats after a single administration of ≥2054 kBq/kg body weight radium-223 dichloride (≥41 times the clinically recommended dose). The testes seemed to otherwise be functioning normally and the epididymides revealed a normal content of spermatocytes. Uterine polyps (endometrial stroma) were observed in female rats after single or repeated administration of ≥325 kBq/kg body weight radium-223 dichloride (≥6.5 times the clinically recommended dose).

According to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) an environmental risk assessment for radium-223 chloride is not required, because inorganic salts representing electrolytes are considered not to pose a risk to the environment. Moreover, as radium-223 chloride is a radiopharmaceutical, the Product Information contains adequate relevant warnings and precautions regarding handling and disposal.

2.3.7. Conclusion on the non-clinical aspects

Non-clinical aspects have been investigated and addressed adequately and there are no remaining non-clinical concerns preventing the marketing authorisation of radium-223 chloride.

2.4. Clinical aspects

2.4.1. Introduction

The application underwent accelerated assessment as it was considered of major interest from the point of view of public health and in particular from the view point of therapeutic innovation. The CHMP accepted the Applicant's request for accelerated assessment on the grounds of the high unmet medical need, the novel mechanism of action of the medicinal product which has the potential to offer an alternative therapeutic option and, finally, the adequacy/ completeness of the proposed data package which could allow the application to be assessed under an accelerated timetable.

In a Scientific Advice procedure the CHMP concluded that regarding the primary endpoint proposal of having SRE and OS as co-primary endpoints, two options were acceptable to the CHMP:

1. time to first SRE as a primary endpoint;

2. OS as a unique primary endpoint, and PFS (including extra osseous events) and time to first SRE as secondary endpoints.

As the primary endpoint was changed to implement option 2 proposed by the CHMP the statistical design of the study was agreed with CHMP in a follow-up advice procedure.

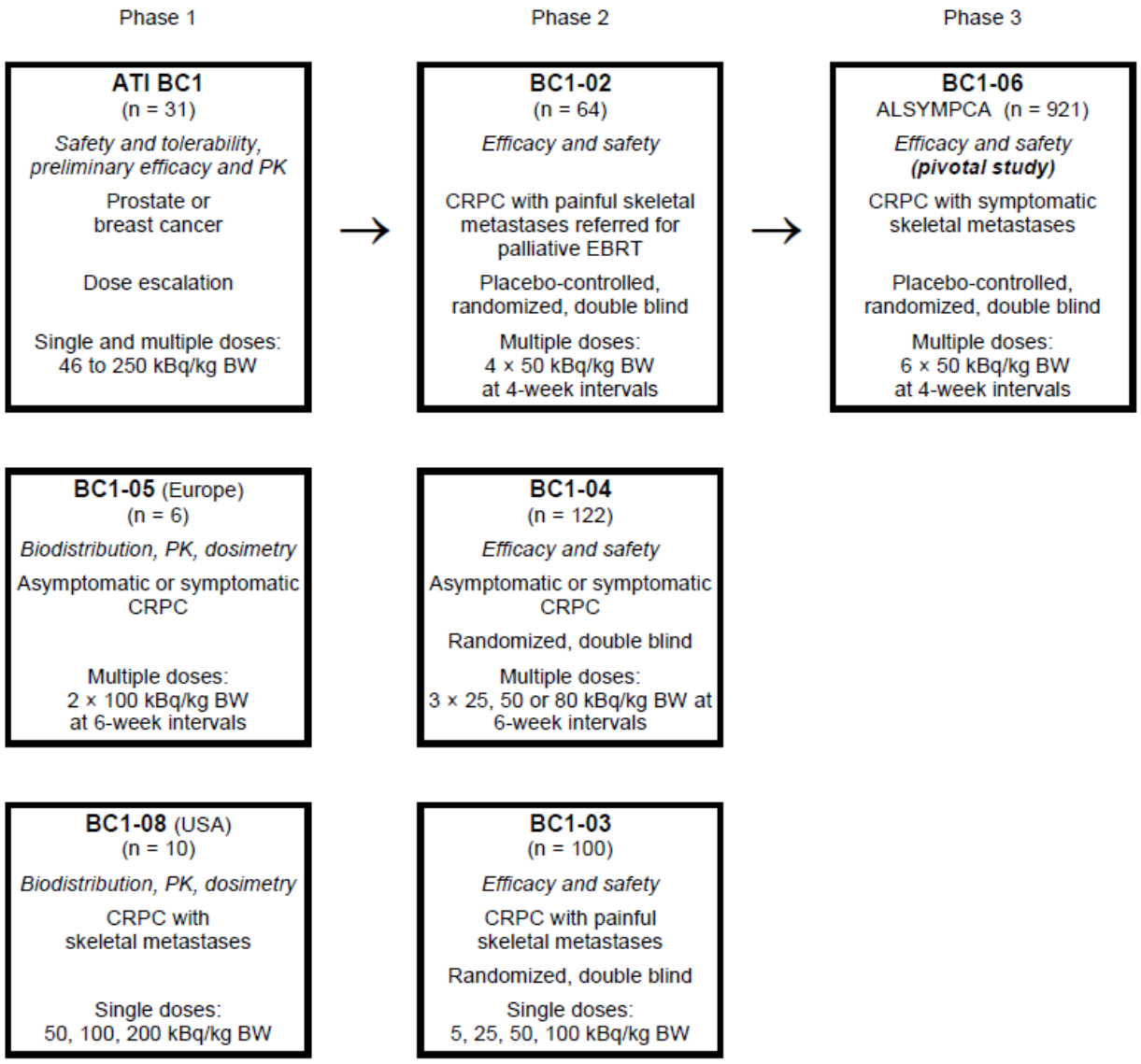
GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Figure 2. Overview of clinical studies



2.4.2. Pharmacokinetics

The pharmacokinetics, biodistribution and dosimetry data has been obtained from three Phase 1 studies (ATI BC-1, BC1-05 and BC1-08) including a total of 47 patients.

An overview of phase I studies is presented in Table 5 below.

Table 5. Overview of phase I studies

Study	Objectives	Population	Subjects	Pharmacology parameters
ATI BC-1	An open-label, multicentre, dose escalation study to evaluate safety and tolerability of escalating doses of 46, 93, 163, 213 and 250 kBq/kg BW (actual doses administered) and identification of possible dose-limiting toxicity	Patients with advanced skeletal metastases	Enrolled and analysed: 31 male patients	PK parameters: AUC, AUC/Dose, C_{max}, C_{max}/Dose, $T_{½}$, CL, V_{ss}
BC1-05	An open-label, single site study to assess pharmacokinetics, biodistribution, radiation dosimetry, and safety	Patients with castration resistant prostate cancer and bone metastases	Enrolled and analysed: 6 male patients	Whole body retention of radioactivity, blood and plasma concentrations, blood clearance, biodistribution, excretion in faeces and urine
BC1-08	A study to assess safety, pharmacokinetics, biodistribution, and radiation dosimetry at 3 dose levels (50, 100 and 200 kBq/kg)	Patients with castration resistant prostate cancer and bone metastases	Enrolled and analysed: 10 male patients	Blood and plasma concentrations, PK parameters: C_{max}, $T_{½fast}$, $T_{½slow}$, V_0, AUC, CL

In the phase I studies, no drug concentration measurements were made. However, blood samples for analyses of radioactivity were collected. The radium-223 chloride activity in blood, plasma, urine and faeces was measured using a gamma counter. The number of counts was corrected for background and dead-time and converted into activity via a measured calibration factor. The activity was corrected for decay until the time of injection. The absorbed radiation dose calculation was performed based on clinical biodistribution data.

Absorption

No studies were submitted (see discussion on clinical pharmacology).

Distribution

After intravenous injection, the fraction of the injected activity retained in the blood at 15 minutes following injection was 20 ±8% (range 9-33%). At 4 hours, only 4 ±1% (range 2-6%) of the activity remained in the blood, which had decreased to 0.4 ±0.2% (range 0.2-0.7%) at 72 hours.

The volume of distribution was higher than the blood volume indicating distribution to peripheral compartments. The initial half-life was not estimated due to the limited number of sampling points within the initial distribution phase. The second, third and fourth half-life was estimated to approximately 10 minutes, 2 hours and 30 hours, respectively.

Approximately 49% of the activity passed into the gut at 4 hours (range 19% - 69%). This increased to about 59% (range 22% - 93%) at 24 hours and decreased to about 52% (8% – 79%) at 48 hours and about 33% (3% – 70%) at 72 hours. Within 4 hours 40% (range 19% - 69%) of the injected activity passed into the small intestine. Activity then passed into the upper large intestine with a mean uptake of 45% (range 17% – 57%) at 24 hours, decreasing to 4% (range 0% – 18%) at 1 week. Maximum uptake in the lower large intestine occurred at 24 – 72 hours with an uptake of 17% (range 0% – 33%) at 48 hours.

Activity in bone was calculated as the mean of the activity per unit mass in the skull and both legs. Activity was rapidly taken up in bone. With one exception the maximum activity appeared at the time of the first scan at 4 hours. The initial level of uptake was 61% (range 44% - 77%). No specific uptake was visible in the gamma scintigraphy images of other tissues/organs such as kidneys, urinary bladder, liver, gallbladder, stomach, heart and spleen.

For an administered activity of 3.65 MBq (50 kBq/kg BW to a 70-kg adult) the calculated absorbed doses to the bone (osteogenic cells) was 4.2050 Gy and to the red marrow 0.5066 Gy. The calculated absorbed doses to the main excretory organs were 0.0265 Gy (2.65 rad) for the small intestine wall, 0.1180 Gy for the upper large intestine wall and 0.1696 Gy for the lower large intestine wall. The calculated absorbed doses to other organs were low, e.g. heart wall (0.0063 Gy), lung (0.0003 Gy), liver (0.0109 Gy), kidneys (0.0117 Gy), urinary bladder wall (0.0147 Gy), testes (0.0003 Gy), and spleen (0.0003 Gy) (Study BC1-05). The calculated absorbed organ doses (Gy/MBq) per activity radium-223 chloride are summarised in Table 6 below.

Table 6. Calculated absorbed organ doses (Gy/MBq) per activity radium-223 chloride

	Individual emission contributions (Gy/MBq)			Total	SD	Organ Dose in a 73-kg Adult given 50 kBq/kg
Target organ	**Alpha**	**Beta**	**Photon**	**(Gy/MBq)**	**(%)**	**Gy**
Adrenals	0.00E+00	2.35E-05	9.41E-05	0.00012	56	0.0004
Brain	0.00E+0	2.35E-05	7.52E-05	0.00010	80	0.0004
Breasts	0.00E+00	2.35E-05	2.53E-05	0.00005	120	0.0002
Gallbladder wall	0.00E+00	2.35E-05	2.05E-04	0.00023	14	0.0008
LLI Wall	0.00E+00	4.56E-02	8.49E-04	0.04645	83	0.1696
Small intestine wall	3.19E-03	3.60E-03	4.71E-04	0.00726	45	0.0265
Stomach wall	0.00E+00	2.35E-05	1.15E-04	0.00014	22	0.0005
ULI wall	0.00E+00	3.15E-02	8.24E-04	0.03232	50	0.1180
Heart wall	1.61E-03	7.07E-05	4.67E-05	0.00173	42	0.0063
Kidneys	2.99E-03	1.08E-04	1.06E-04	0.00320	36	0.0117
Liver	2.79E-03	1.02E-04	8.22E-05	0.00298	36	0.0109
Lungs	0.00E+00	2.35E-05	4.85E-05	0.00007	90	0.0003
Muscle	0.00E+00	2.35E-05	9.54E-05	0.00012	41	0.0004
Ovaries	0.00E+00	2.35E-05	4.62E-04	0.00049	40	0.0018
Pancreas	0.00E+00	2.35E-05	8.82E-05	0.00011	43	0.0004
Red marrow	1.32E-01	6.42E-03	2.02E-04	0.13879	41	0.5066
Osteogenic cells	1.14E+00	1.49E-02	2.98E-04	1.15206	41	4.2050
Skin	0.00E+00	2.35E-05	4.86E-05	0.00007	79	0.0003
Spleen	0.00E+00	2.35E-05	6.65E-05	0.00009	54	0.0003
Testes	0.00E+00	2.35E-05	5.96E-05	0.00008	59	0.0003
Thymus	0.00E+00	2.35E-05	3.35E-05	0.00006	109	0.0002
Thyroid	0.00E+00	2.35E-05	4.80E-05	0.00007	96	0.0003
Urinary bladder	3.71E-03	1.61E-04	1.56E-04	0.00403	63	0.0147

	Individual emission contributions (Gy/MBq)			Total	SD	Organ Dose in a 73-kg Adult given 50 kBq/kg
Target organ	**Alpha**	**Beta**	**Photon**	**(Gy/MBq)**	**(%)**	**Gy**
wall						
Uterus	0.00E+00	2.35E-05	2.32E-04	0.00026	28	0.0009
Whole body	2.22E-02	8.08E-04	1.19E-04	0.02311	16	0.0843

Elimination

Faecal excretion was the major route of elimination from the body. In the intestine, activity was already observed 10 minutes post injection, (Study BC1-08). In Study BC1-05, faecal excretion was determined by direct measurement of radioactivity in the faecal samples collected over 48 hours. There was variability in gut transit rates across the population with once daily up to once weekly bowel evacuation.

The rate of elimination of radium-223 chloride from the gastrointestinal tract is however influenced by the high variability in intestinal transit rates across the population, with the normal range from once daily to once weekly bowel evacuation.

Imaging data from Study BC1-05 and Study BC1-08 allowed for an estimate of the amount of radioactivity in the different regions of the gastrointestinal tract. After radium-223 is excreted in the gastrointestinal tract (GIT), at least about 50 to 60% of injected radium-223 is excreted via the faecal route. In particular, data from Study BC1-08 suggests that the radium was secreted into the small intestine from the blood through the small intestine wall.

Mean faecal excretion at 24 hours was 2% (range <1% - 13%) of the injected activity. At the time of discharge at 48 hours, the mean cumulative faecal excretion (at ~48 hours) was 13% (range <1% - 34%). The faecal excretion was continuing to increase at the last time point of collection.

Mean urine excretion at 24 hours was 2% (range <1% - 4%). At the time of discharge at 48 hours, the cumulative mean urine excretion was 2% (range <1% - 5%) and the rate of excretion was decreasing. There was a tendency for the rate of excretion to decrease during the patient's stay (48 hours).

The whole body measurements at 7 days after injection indicated that a median of 76% of administered activity was excreted from the body.

Dose proportionality and time dependencies

In Study AT1-BC1 (see dose response study), the pharmacokinetics of total radioactivity following administration of radium-223 chloride was evaluated in the dose range of 46 to 250 kBq/kg BW. The AUC and C_{max} values increased with increasing dose and the pharmacokinetic analyses showed very similar pharmacokinetic characteristics for all five dose-groups, indicating a close to linear dose relationship. The pharmacokinetics was linear between the dose range of 46 to 250 kBq/kg. The mean $t_{1/2}$ was 10.51 hour, CL was 0.25 IU/(h*IU/g) and V_{ss} was 2.66 IU/(IU/g).

Special populations

No relevant studies were submitted (see discussion on clinical pharmacology).

Pharmacokinetic interaction studies

No relevant studies were submitted (see discussion on clinical pharmacology).

Pharmacokinetics using human biomaterials

No relevant studies were submitted (see discussion on clinical pharmacology).

2.4.3. Pharmacodynamics

Mechanism of action

No clinical studies addressing the mechanism of action were submitted.

Primary and Secondary pharmacology

PSA, an indicator of the disease status in metastatic prostate cancer was measured in all four studies contributing efficacy information (Studies BC1 02, BC1 03, BC1 04, and BC1 06) described under the clinical efficacy section. Phase 2 studies were performed to show the pharmacodynamic effects of radium-223 chloride on skeletal-related events (placebo-controlled study BC1-02), on bone pain (study BC1-03) and on the change in bone-ALP levels (study BC1-02) as well as PSA response (study BC1-04).

Regarding secondary pharmacology, a sub-study was performed to evaluate the potential for QTc interval prolongation of radium-223 chloride in a sub-group of the patient population of the pivotal phase III BC1-06 study (the methodology of the study is described under clinical efficacy). In the radium-223 chloride group, the highest mean increase in QTcF was 5.2±6.5 msecs and the mean change from baseline in QTcF at one hour post-injection was 7.6 msecs. These findings were similar to those obtained in the placebo group. The mean maximal change from baseline in the radium 223 chloride group was 11.4±6.7 msecs while the upper limit of the 90% Confidence Interval (CI) of the mean maximal change from baseline in QTcF was 13.9 msecs. Similar results were obtained in the placebo group where the mean maximal change from baseline was 11.5±7.8 msecs while the upper limit of the 90% Confidence Interval (CI) of the mean maximal change from baseline in QTcF was 16.7 msecs. No significant differences were noted between radium-223 chloride and placebo. Similarly, no clinically-relevant changes in heart rate (HR) were found in the radium-223 chloride groups. A significant mean increase in PR interval in the radium-223 chloride group of 14.8±48.1 msecs at the three hour post-dose time point was related to a significant increase in one patient with a previous history of ischaemic heart disease, arrhythmia and bradycardia. This patient exhibited more than 200 msecs increase at the two, three and four to six hours post-dose time points. There were no clinically-relevant changes found in the QRS interval. The QTcB duration showed the same trends as the QTcF duration.

2.4.4. Discussion on clinical pharmacology

No studies of bioavailability, comparative bioavailability, bioequivalence or effect of food were conducted. This is acceptable since radium-223 chloride is a radiopharmaceutical administered by intravenous injection and consequently is completely bioavailable.

After intravenous injection, the maximal therapeutic radium plasma concentration in patients is < 1 pmol/L which is much lower (i.e. >10000) than the anticipated concentrations that might have adverse effects (≥ 0.1 µmol/L).

Radium-223 is rapidly cleared from the blood with distribution primarily to the bone with 44% to 77% of the administered activity at 4 hours post injection and into the small intestine. No significant uptake was seen in other organs such as heart, liver, kidneys, urinary bladder and spleen at 4 hours post injection. The main route of excretion from the body was via the faeces which amounted at 24 hours pi 2% (range

< 1% to 13%) and at ~48 hours 13% (range < 1% to 34%). Radium-223 is secreted into the small intestine from the blood through the small intestine wall. The transport pathways most likely used by radium are not the same as used by small molecules so no drug-drug interaction is anticipated at the small intestinal wall.

Radium-223 is an isotope which decays and is not metabolised. Faecal excretion is the major route of elimination from the body. The excretion in the urine was low (approximately 5%). At 7 days after injection, 76% of the administered activity was excreted from the body.

The absence of pharmacokinetic interaction studies and of studies using human biomaterials is considered acceptable due to the lack of *in vivo* metabolism and the small likelihood that transport pathways most likely used by radium are shared by small molecules. Moreover, no interactions were observed with several medications used by patients with prostate cancer in clinical studies and, despite the theoretical potential for calcium supplements to compete with radium-223 chloride bone uptake as well as elimination, no difference in the mean or median serum calcium concentration between patients taking and not taking calcium supplements was seen (wide distribution over the complete normal range vs. even wider range of serum calcium concentrations in subjects not taking calcium supplements). However, as interactions with calcium and phosphate cannot be excluded, pausing supplementation with these substances and/or Vitamin D should be considered some days before starting with Xofigo treatment.

Moreover, concomitant chemotherapy with Xofigo may have additive effects on bone marrow suppression (see also discussion on clinical safety). Safety and efficacy of concomitant chemotherapy with Xofigo have not been established.

The pharmacokinetics of radium-223 chloride were linear in the dose range investigated (46 to 250 kBq/kg).

No pharmacokinetic studies in special populations were submitted. The applicant discussed the effects of intrinsic factors (age, race, weight, renal and hepatic function etc.) on the efficacy and safety of radium-223 chloride and no differences were noted related to these factors, so that the impact of the lack of pharmacokinetic information in special populations could be considered acceptable.

Finally, there was no evidence to suggest that the intravenous injection of radium 223 chloride may significantly prolong the QTc interval thereby having pro-arrhythmic potential.

2.4.5. Conclusions on clinical pharmacology

In general, the Applicant has sufficiently described the pharmacokinetics of radium-223 chloride. The pharmacodynamic effects of radium-223 are discussed under the clinical efficacy section.

2.5. Clinical efficacy

Seven studies were submitted in support of the use of radium chloride in the claimed indication (see Figure 2).

2.5.1. Dose response study

The dose-response relationship of Xofigo was evaluated in a dose finding Phase 2 Study (BC1-04). In addition, Phase 1 study ATI-BC1/15522 also contributed information towards a dose-dependent response based mainly on bone biomarkers.

Study BC1-04 was a double-blind, randomised, repeat dose, multicentre study of Xofigo for the treatment of patients with hormone-refractory prostate cancer and skeletal metastases. The primary objective was to compare the proportion of patients with hormone-refractory prostate cancer and skeletal metastases showing a prostate specific antigen (PSA) response (PSA decrease ≥ 50% from baseline, confirmed three weeks later) on three different repeat dose regimens of Xofigo (25, 50, or 80 kBq/kg b.w. of radium-223 chloride at 6 week intervals for a total of 3 injections). The study enrolled 122 patients. The primary efficacy variable was the proportion of patients with a confirmed PSA response. In the Per-Protocol Set, this occurred in 0 (0 %), 2 (5.6 %) and 5 (12.8 %) of subjects in the 25 kBq/kg, 50 kBq/kg and 80 kBq/kg dose groups, respectively (p=0.0297, Jonckheere-Terpstra test for dose response; pairwise comparison between 25 kBq/kg and 80 kBq/kg dose groups was borderline significant, p=0.0548). Results in the Intention-to Treat Set were similar (p=0.0290). There was no gradient of risk across the doses up to 80 kBq/kg BW in the study.

Study ATI-BC1 was a phase I open-label, multicentre, dose-escalating study of radium-223 in patients with advanced skeletal metastases. The primary objective of the study was to evaluate the safety and tolerability of escalating doses and identify possible dose-limiting toxicity (DLT) of radium-223 administered to patients with advanced skeletal metastases. The study was conducted in 31 patients in total (25 in part 1a and 6 in part 1b) with skeletal metastases from breast or prostate cancer. The dose-escalation part of the study (designated as "study part 1a") was with single injections of radium-223 chloride to be administered to cohorts of 5 patients for each of the 5 pre-defined dose levels (46, 93, 163, 213 and 250 kBq/kg BW). During study part 1b, patients receiving multiple doses of radium-223 chloride were either allocated to receive 5 injections of 50 kBq/kg BW at 3 weeks intervals or 2 injections of 125 kBq/kg BW at 6 weeks intervals. Radium-223 was well tolerated by patients with skeletal metastases. Mild to moderate and transient haematological toxicity was observed at potentially therapeutic doses. Platelets were less affected than neutrophils and white blood cells; toxicity grade I was seen in 5 of the 31 patients. Pain relief was seen in more than 50% of the patients.

2.5.2. Main study

Study 15245/BC1-06 (ALSYMPCA)

Methods

Study 15425/BC1-06 (ALSYMPCA) was a multicentre, randomised, double-blind, placebo-controlled, pivotal phase III trial study comparing radium-223 chloride plus best standard of care (BSoC) versus placebo plus BSoC in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases.

Study Participants

The target population was patients with progressive symptomatic HRPC, treated with BSoC with at least 2 skeletal metastases on bone scan and no known visceral metastases.

Main inclusion criteria:

- Histologically or cytologically confirmed adenocarcinoma of the prostate
- Known hormone refractory disease defined as: castrate serum testosterone level: ≤ 50 ng/dL (1.7 nmol/L); bilateral orchiectomy or maintenance on androgen ablation therapy with luteinizing

hormone releasing hormone (LHRH) agonist or polyestradiol phosphate throughout the study; serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value, each measurement at least 1 week apart

- Serum PSA value ≥ 5 ng/mL (µg/L)
- Multiple skeletal metastases (≥ 2 hot spots) on bone scintigraphy within previous 12 weeks
- No intention to use cytotoxic chemotherapy within the next 6 months
- Either regular (not occasional) analgesic medication use for cancer related bone pain or treatment with EBRT for bone pain within previous 12 weeks [symptomatic disease]
- Age ≥ 18 years
- Eastern Cooperative Oncology Group Performance status (ECOG PS): 0-2
- Life expectancy ≥ 6 months

Main exclusion criteria:

- Treatment with an investigational drug within previous 4 weeks, or planned during the treatment period
- Eligible for first course of docetaxel, i.e., subjects who were fit enough, willing and where docetaxel is available
- Treatment with cytotoxic chemotherapy within previous 4 weeks, or planned during the treatment period, or failure to recover from AEs due to cytotoxic chemotherapy administered > 4 weeks earlier; however, ongoing neuropathy was permitted
- Prior hemibody external radiotherapy
- Systemic radiotherapy with strontium-89, samarium-153, rhenium-186 or rhenium-188 for the treatment of bony metastases within previous 24 weeks
- Prior treatment with radium-223
- Blood transfusion or erythropoietin stimulating agents within previous 4 weeks
- Other malignancy treated within the last 5 years (except non-melanoma skin cancer or low-grade superficial bladder cancer)
- History of visceral metastasis, or visceral metastases as assessed by abdominal/pelvic computed tomography (CT) (alternatively MRI) or chest X-ray (alternatively CT) within previous 8 weeks
- Malignant lymphadenopathy exceeding 3 cm in short-axis diameter
- Imminent or established spinal cord compression based on clinical findings and/or magnetic resonance imaging (MRI)
- Any other serious illness or medical condition such as, but not limited to (Any uncontrolled infection; Cardiac failure New York Heart Association III or IV; Crohn's disease or ulcerative colitis; Bone marrow dysplasia)

Treatments

Patients were randomised (2:1) to receive either radium-223 chloride, 50 kBq/kg b.w. or isotonic (normal) saline solution, administered as slow bolus IV injection 6 times at intervals of 4 weeks between each administration.

All patients were to receive "best standard of care" (BSoC). Best standard of care was regarded as the routine standard of care at each centre, for example local external beam radiotherapy, corticosteroids, antiandrogens, oestrogens (e.g. stilboestrol), estramustine (not regarded as cytotoxic as per exclusion criterion 3 or ketoconazole. Patients were not included in the study if the standard of care included chemotherapy, hemibody radiation or use of radionuclides.

Study drug dose level adjustment was not permitted. Treatment was discontinued when patients experienced unacceptable toxicity or initiation of cytotoxic chemotherapy, other systemic radioisotopes, hemibody external radiotherapy or other investigational drugs. In case of a treatment delay of more than 4 weeks, treatment was to be discontinued.

Subsequently, during the follow-up period, the patients were evaluated every 2 months until 1 year from first administration, and thereafter, every 4 months until 3 years from first administration. If a patient was withdrawn from the study during the treatment period, the patient was encouraged to attend a safety follow-up visit 4 weeks after last treatment visit.

Objectives

The primary objective of the study was to compare, in subjects with symptomatic hormone refractory prostate cancer (HRPC) and skeletal metastases, the efficacy of BSC plus Xofigo versus BSC plus placebo.

Secondary objectives included the comparison of the acute and long-term safety profile and quality of life (QoL) between the treatment groups.

Outcomes/endpoints

The primary endpoint was Overall Survival defined as the time from date of randomisation to the date of death, whatever the cause. Survival times for patients who were still alive at the time of the analysis or who were lost to follow-up were censored at the last available date on which the patient was known to be alive.

The key secondary endpoints included the following five ordered hierarchically (see statistical methods):

Time to total-ALP progression defined a) in patients with no total-ALP decline from baseline as ≥ 25% increase from the baseline value, at least 12 weeks from baseline; b) in patients with an initial total-ALP decline from baseline as ≥ 25% increase above the nadir value, which is confirmed by a second value obtained three or more weeks later.

(Confirmed) Total ALP response defined as ≥30% reduction of the blood level, compared to the baseline value, confirmed by a second total ALP value approximately 4 or more weeks later.

Time to occurrence of first SRE: Disease events were defined as: Use of External Beam Radiation Therapy (EBRT) to relieve skeletal symptoms (1); Use of radio-isotopes to relieve skeletal symptom (2); New symptomatic pathological bone fractures (vertebral and non-vertebral) (3); Tumour-related orthopaedic surgical intervention (4); Spinal cord compression (5); Start of any other anti-cancer treatment such as chemotherapy and hormonal treatment (6); Deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG PS) by at least 2 points from baseline (includes death) (7).

For the first 6 events above, the start date of the event/medication/therapy was used as the time of the event. For the last event, the visit at which a 2-point or more deterioration in PS was observed compared to baseline was used as the time of the event. The ECOG was assessed at every study visit. Disease events were collected for all subjects until the last subject had been followed for 3 years. If a particular event or a marked deterioration in PS had not occurred at the time of the analysis or the subject was lost to follow-up, the time-to-event variables were censored at the last disease or PS assessment date.

Disease events 1, 3, 4 and 5 were combined into a composite endpoint of Skeletal Related Events (SREs) for the analysis.

Total ALP normalisation defined as return of total ALP value to within normal range at 12 weeks in 2 consecutive measurements (at least 2 weeks apart) after start of treatment in patients who had their total ALP above ULN at baseline.

Time to PSA progression defined a) in patients with no PSA decline from baseline as ≥ 25% increase from the baseline value and an increase in absolute value of ≥ 2 ng/mL, at least 12 weeks from baseline; b) in patients with an initial PSA decline from baseline as ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir value, which is confirmed by a second value obtained three or more weeks later.

Other secondary endpoints included: time to occurrence of first use of EBRT to relieve skeletal symptoms, use of radio-isotopes to relieve skeletal symptoms, new symptomatic pathological bone fractures (vertebral and non-vertebral), tumour related orthopaedic surgical intervention, first spinal cord compression, start of any other anti-cancer treatment, deterioration of ECOG PS by at least 2 points from baseline [includes death (score of 5) by definition], changes in PSA, changes in total ALP, performance status (PS) response and progression and Quality of life (QoL) assessed using Functional Assessment of Cancer Therapy - Prostate (FACT-P) questionnaire and EuroQoL (EQ-5D).

The Functional Assessment of Cancer Therapy for patients with Prostate cancer (FACT-P) is a disease specific QoL questionnaire (i.e. Functional Assessment of Cancer Therapy-General [FACT-G] plus a prostate cancer specific module comprised of 5 subscales (Physical Well-being [PWB] Social/Family Well-being [SWB], Emotional Well-being [EWB], Functional Well-being [FWB], and Prostate Cancer [PCS]). All FACT-P items are scored on a scale of 0 to 4 representing the extent to which the item reflects the experience of the individual completing the instrument (0 = not at all; 4 = very much). Higher scores indicate better QoL. The EQ-5D is a standardised instrument for use as a measure of health outcome and has been validated for the general population. EQ-5D utility scores were calculated using 5 domains (mobility, self-care, pain/discomfort, usual activities and psychological status i.e. anxiety/depression) with 3 possible answers for each item (1 = no problems; 2 = some problems and 3 = extreme problems). Utility scores potentially range from - 0.59 to 1.0 (a score of 1 represents full health and a score of 0 represents dead, negative values indicate worse than dead).

Sample size

The sample size was calculated based on two-sided Type I error: 5%; power: 90%; 50% of patients have had prior docetaxel treatment (median survival time in the placebo – no prior docetaxel: 18 months; radium-223 – no prior docetaxel: 22 months; placebo– prior docetaxel: 12 months; radium-223 - prior docetaxel: 15 months).

Based on the above assumptions and further to the protocol amendments, a total of 900 subjects were required, with the final analysis to be conducted after 640 events had been observed.

Randomisation

Subjects were randomised 2:1 to receive either radium-223 chloride or placebo study treatment. Three binary variables were used for stratification: total ALP < 220 U/L versus total ALP ≥ 220 U/L; current use of bisphosphonates: yes versus no; any prior use of docetaxel: yes versus no.

Blinding (masking)

This was a double-blind study: both patients and treating physicians were to be blinded. In view of the necessity of dose calculation, personnel at the nuclear department were unblinded.

Statistical methods

For the purpose of analysis, the following populations were defined:

The ITT population was defined as all patients randomised to their respective treatment. The ITT population was the primary population for the analysis of the primary efficacy endpoint and for the analysis of all secondary efficacy and clinical benefit endpoints.

The Per Protocol population was only used for the interim analysis and it is not described further.

The safety population was defined as all randomised patients who have received study medication. The safety population was used in the analysis of all safety endpoints.

The primary endpoint was analysed using the stratified log-rank test stratified for the randomisation factors. A formal interim analysis (IA) was performed when a total of 314 deaths had been observed (cut-off date 14 October 2010) following IDMC recommendation to stop the study as the primary efficacy analysis of overall survival had crossed the pre-specified boundary for efficacy.

The final analysis (data cut-off date 15 July 2011) was applied on the cumulative database of all data collected. However, the database did not include the last injection of 2 subjects. The data included within this cumulative database were not fully blinded since the study was unblinded on 1 July 2011 but no cross-over of placebo subjects had occurred by the data cut-off date.

O'Brien-Fleming-type boundaries were used to preserve an overall two sided type I error rate of 0.05 for the interim and final analysis. The actual interim analysis boundary would be calculated based on the actual number of events for the interim analysis and this was 0.00275.

In the time-to-event analyses, patients without the event were supposed to be censored. It was planned that patients who withdrew early from the study would be followed for survival. For withdrawals with no survival status data or who were lost to follow up, time to death was censored at the time of withdrawal (i.e. the last date on which these patients were known to be alive).

The Independent Data Monitoring Committee (IDMC) was to recommend the Sponsor whether to continue, modify, or stop the clinical trial on the basis of efficacy and safety considerations. The pre-planned interim efficacy analysis assessed the effect of radium-223 on overall survival, with the intent to stop the study early if there was overwhelming evidence of treatment benefit.

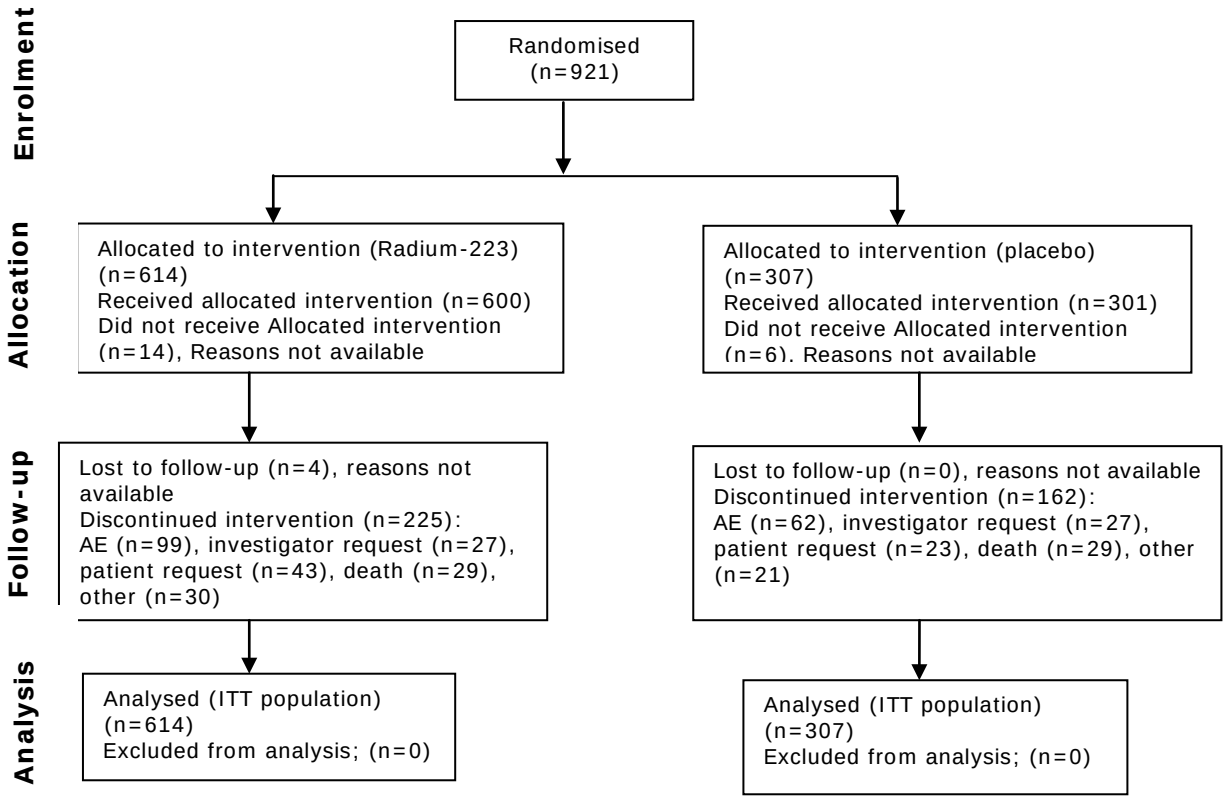
Subgroup analyses were performed on the primary efficacy variable for the ITT population. These analyses were defined by the three binary randomisation stratification and the following additional baseline covariates: ECOG performance status at baseline (0 and 1, vs. 2 or greater); Extent of Disease (Number of hot spots); Presence/absence of pain at baseline; Opiate use vs. non-use at baseline; Ethnicity (collected as Caucasian, Hispanic, Black, Asian and Other).

ALP progression was defined as >=25% increase from baseline at least 12 weeks from baseline ("12 week rule"). Post hoc analyses were conducted with ALP progression from day 1.

Finally, the key secondary endpoints were ordered hierarchically for interim analysis in the course of a gatekeeping procedure in order to control for overall type I error rate at 0.05.

Results

Participant flow



Recruitment

Patients were enrolled from June 2008 until February 2011 from 136 study centres worldwide (Australia; Belgium; Brazil; Canada; Czech Republic; France; Germany; Hong Kong; Israel; Italy; Norway; Poland; Singapore; Slovakia; Spain; Sweden; The Netherlands; UK; USA).

Conduct of the study

The original study protocol, dated 14 December 2007, was subsequently amended 6 times:

- Amendment 1 (dated 23 May 2008): changes regarding the stratification factors (removed stratification factors for ECOG and any prior cytotoxic therapy and added stratification factors for current use of bisphosphonates (yes or no) and prior use of docetaxel (yes or no).

- Amendment 2 (dated 9 July 2008): changed the sample size from 450 to 750 subjects randomized; planned for an unblinded interim analysis of overall survival, changed PSA outcome and reporting to adhere to the Prostate Cancer Clinical Trials Working Group 2 (March 2008).
- Amendment 3 (dated 10 July 2009): screening haematology values were measured at a maximum of 1 week prior to randomization and it was required to be at least 10 g/dL (it should not have been lower than 8 g/dL within 24 hours before any injection); after documented PSA progression, the PSA could decline prior to randomization provided that the screening value was at least 5 ng/mL; changed the interval between injection of bisphosphonates and injection of study drug (at least 2 hours before or after study drug administration); changed the analysis of the primary efficacy endpoint from Cox proportional hazards regression to a stratified log-rank test; changed the definition of the Safety population from all randomized subjects to all randomized subjects who had received at least 1 study drug administration; added sub-group analyses for safety and secondary efficacy variables in order to examine relationships between exposure and response.
- Amendment 4 (dated 23 June 2010): increase of the statistical power from 80% to 90%; the sample size from 750 to 900 with an increase in the accrual period from 24 to 30 months, changed time of interim analysis to be after approximately 320 events.
- Amendment 5 (dated 20 January 2011): to control for overall false positive rate (type I error rate), five secondary endpoints have been identified (including creating a composite endpoint for the time to occurrence of first SRE based on disease events already being collected and adding total ALP normalisation) and ordered hierarchically according to their clinical importance.
- Amendment 6 (dated 24 June 2011): due to IDMC approval to unblind the study, changes to study design and reference therapy (placebo), allowing access to Xofigo for subjects who previously received placebo.

The most common violations recorded were for subjects not having the required castrate serum testosterone levels ≤ 50 ng/dL (14/54 (12.6%) in the radium-223 group; 7/268 (2.6%) in the placebo group) and not showing the required serum PSA progression at the time of randomization (17/541 (3.1%) in the radium-223 group; 7/268 (2.6%) in the placebo group).

Protocol violations resulted in the exclusion from the PP population in the interim analysis.

Baseline data

Baseline demographics, baseline disease characteristics and previous treatment information are summarised in the following tables.

Table 7. Baseline demographic and disease characteristics (ITT population)

Characteristic	Alpharadin N=614[a]	Placebo N=307	Overall N=921
Age (years), n(%)[b]	614 (100)	307 (100)	921 (100)
Mean (SD)	70.2 (8.10)	70.8 (7.87)	70.4 (8.03)
Median	71.0	71.0	71.0
Min – Max	49 – 90	44 – 94	44 - 94
Age Category (years), n(%)			
< 65	158 (25.7)	73 (23.8)	231 (25.1)
65 – 75	285 (46.4)	144 (46.9)	429 (46.6)
> 75	171 (27.9)	90 (29.3)	261 (28.3)
Race, n (%)			
Caucasian	575 (93.6)	290 (94.5)	865 (93.9)
Hispanic	1 (0.2)	1 (0.3)	2 (0.2)
Black	10 (1.6)	3 (1.0)	13 (1.4)
Asian	21 (3.4)	12 (3.9)	33 (3.6)
Other	7 (1.1)	1 (0.3)	8 (0.9)
Height (cm)			
n	587	294	881
Mean (SD)	173.9 (7.29)	173.5 (8.43)	173.7 (7.69)
Median	174.0	174.0	174.0
Min – Max	151 – 195	124 – 196	124 – 196
Weight (kg) at screening			
n	610	305	915
Mean (SD)	83.0 (14.62)	82.7 (14.87)	82.9 (14.70)
Median	82.0	82.0	82.0
Min – Max	40 – 139	47 – 130	40 – 139
Total ALP, n (%)			
< 220 U/L	348 (56.7)	169 (55.0)	517 (56.1)
≥ 220 U/L	266 (43.3)	138 (45.0)	404 (43.9)
Concurrent use of bisphosphonates, n (%)			
Yes	250 (40.7)	124 (40.4)	374 (40.6)
No	364 (59.3)	183 (59.6)	547 (59.4)
Any prior use of docetaxel, n (%)			
Yes	352 (57.3)	174 (56.7)	526 (57.1)
No	262 (42.7)	133 (43.3)	395 (42.9)
ECOG PS grade[c], n (%)			
0	165 (26.9)	78 (25.5)	243 (26.4)
1	371 (60.5)	187 (61.1)	558 (60.7)
2	76 (12.4)	40 (13.1)	116 (12.6)
3	1 (0.2)	1 (0.3)	2 (0.2)
Missing, n	1	1	2
WHO Ladder for cancer pain, n (%)			
0	12 (2.0)	2 (0.7)	14 (1.5)
1	257 (41.9)	137 (44.6)	394 (42.8)
2	151 (24.6)	78 (25.4)	229 (24.9)
3	194 (31.6)	90 (29.3)	284 (30.8)
EBRT within 12 weeks of Screening, n (%)			
Yes	99 (16.1)	48 (15.6)	147 (16.0)
No	515 (83.9)	259 (84.4)	774 (84.0)
Albumin (g/L)[c]			
N	612	307	919
Mean (SD)	39.5 (4.67)	39.4 (4.63)	39.5 (4.66)
Median	40.0	40.0	40.0
Min – Max	24 – 53	23 – 50	23 – 53

Hemoglobin (g/dL)[c]			
n	614	307	921
Mean (SD)	12.11 (1.463)	12.06 (1.474)	12.09 (1.466)
Median	12.20	12.10	12.20
Min – Max	8.5 – 15.7	8.5 – 16.4	8.5 – 16.4
LDH (U/L)[d]			
n	608	306	914
Mean (SD)	393.0 (277.10)	445.6 (420.79)	410.6 (332.89)
Median	315.0	335.5	323.5
Min – Max	76 – 2171	132 – 3856	76 – 3856
PSA (µg/L)[d]			
n	576	297	873
Mean (SD)	430.24 (826.724)	497.48 (1141.257)	453.12 (945.422)
Median	146.27	172.88	156.00
Min – Max	3.8 – 6026.0	1.5 – 14500.0	1.5 – 14500.0
Total ALP (U/L)[c]			
n	614	307	921
Mean (SD)	378.9 (526.78)	385.8 (505.22)	381.2 (519.43)
Median	211.0	223.0	214.0
Min – Max	32 – 6431	29 – 4805	29 – 6431

Table 8. Diagnosis and previous treatments of prostate cancer and bone metastases

Subject status	**Alpharadin N=614**	**Placebo N=307**	**Overall N=921**
Time since diagnosis of PC (months), n	543	271	814
Mean (SD)	69.36 (46.431)	63.84 (48.793)	67.52 (47.272)
Median	58.83	52.00	56.82
Min – Max	7.6 – 312.5	1.2 – 347.2	1.2 – 347.2
Time since diagnosis of BM (months), n	526	258	784
Mean (SD)	30.51 (27.234)	30.05 (27.052)	30.36 (27.158)
Median	24.80	22.03	23.93
Min – Max	0.0 – 254.2	0.2 – 183.2	0.0 – 254.2
Time between diagnosis of PC and BM (years)[c], n, n (%)	484	234	718
< 0	38 (7.9)	31 (13.2)	69 (9.6)
0 – 1	167 (34.5)	95 (40.6)	262 (36.5)
1 – 5	152 (31.4)	57 (24.4)	209 (29.1)
> 5	127 (26.2)	51 (21.8)	178 (24.8)
Missing, n	130	73	203
Extent of Disease (EOD) Grading, n, n (%)			
EOD 1 (<6 metastases)	100 (16.4)	38 (12.4)	138 (15.0)
EOD 2 (6-20 metastases)	262 (42.9)	147 (48.0)	409 (44.6)
EOD 3 (>20 lesions but not a Superscan)	195 (31.9)	91 (29.7)	286 (31.2)
EOD 4 (Superscan)	54 (8.8)	30 (9.8)	84 (9.2)
Missing, n	3	1	4
Received any previous treatment for PC, n (%)	605 (98.5)	303 (98.7)	908 (98.6)
Radical prostatectomy	119 (19.4)	31 (10.1)	150 (16.3)
External radiotherapy to the prostate	215 (35.0)	89 (29.0)	304 (33.0)
Brachytherapy	15 (2.4)	9 (2.9)	24 (2.6)
Orchiectomy bilateral	94 (15.3)	49 (16.0)	143 (15.5)
LHRH agonists	213 (34.7)	97 (31.6)	310 (33.7)
Antiandrogens	532 (86.6)	264 (86.0)	796 (86.4)
Cytotoxic chemotherapy	357 (58.1)	175 (57.0)	532 (57.8)
Bisphosphonates	121 (19.7)	56 (18.2)	177 (19.2)
Systemic radiotherapy	24 (3.9)	8 (2.6)	32 (3.5)
External radiotherapy to bone	306 (49.8)	149 (48.5)	455 (49.4)
Other	162 (26.4)	84 (27.4)	246 (26.7)

Numbers analysed

The ITT population comprised 921 subjects, 614 in the Xofigo treatment group and 307 in the placebo group. The Safety population comprised 901 subjects, 600 in the Xofigo treatment group and 301 in the placebo group.

The ITT population (921 subjects receiving BSoC: 614 Alpharadin and 307 placebo) was used for the updated analysis of the primary efficacy endpoint and for the analysis of all secondary efficacy and clinical benefit endpoints. The efficacy results presented for the updated analysis relate to the study up until the cut-off date of 15 July 2011; no cross-over of placebo subjects had occurred by the data cut-off date.

Outcomes and estimation

The efficacy results in terms of the primary endpoint of Overall Survival and for both the primary (cut-of date 14 October 2010) and the updated (cut-of date 15 July 2011) analysis are summarised in the following table and figures.

Table 9. Overall survival (ITT, interim and updated analysis)

	Interim analysis		**Updated analysis**	
	Xofigo	**Placebo**	**Xofigo**	**Placebo**
	N = 541	N = 268	N = 614	N = 307
Number (%) of deaths	191 (35.3%)	123 (45.9%)	333 (54.2%)	195 (63.5%)
Median (months) (95% CI)	14.0 (12.1 – 15.8)	11.2 (9.0 – 13.2)	14.9 (13.9 – 16.1)	11.3 (10.4 – 12.8)
Hazard ratio (95% CI)	0.695 (0.552 – 0.875)		0.695 (0.581 – 0.832)	
p-value (2-sided)	0.00185		0.00007	

Figure 3. Kaplan Meier plot of OS (ITT, interim analysis)

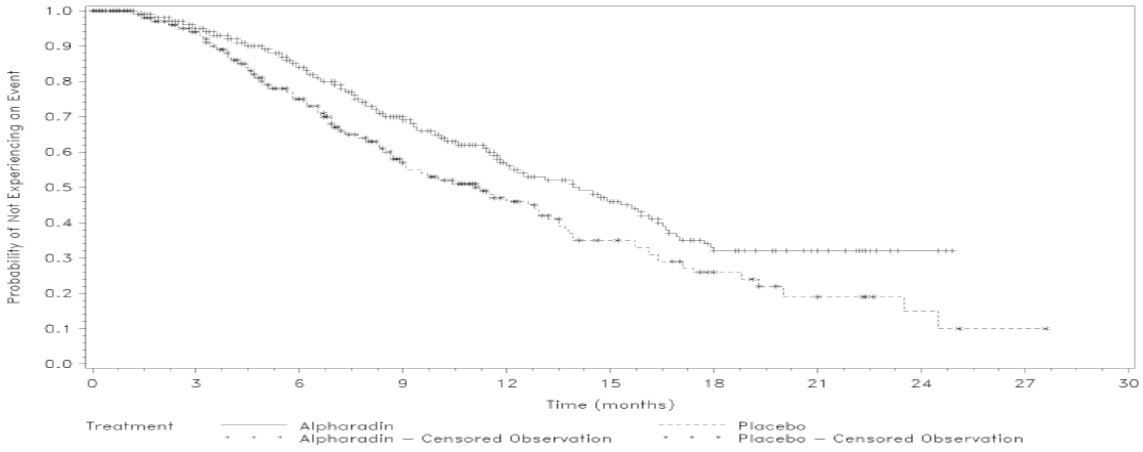
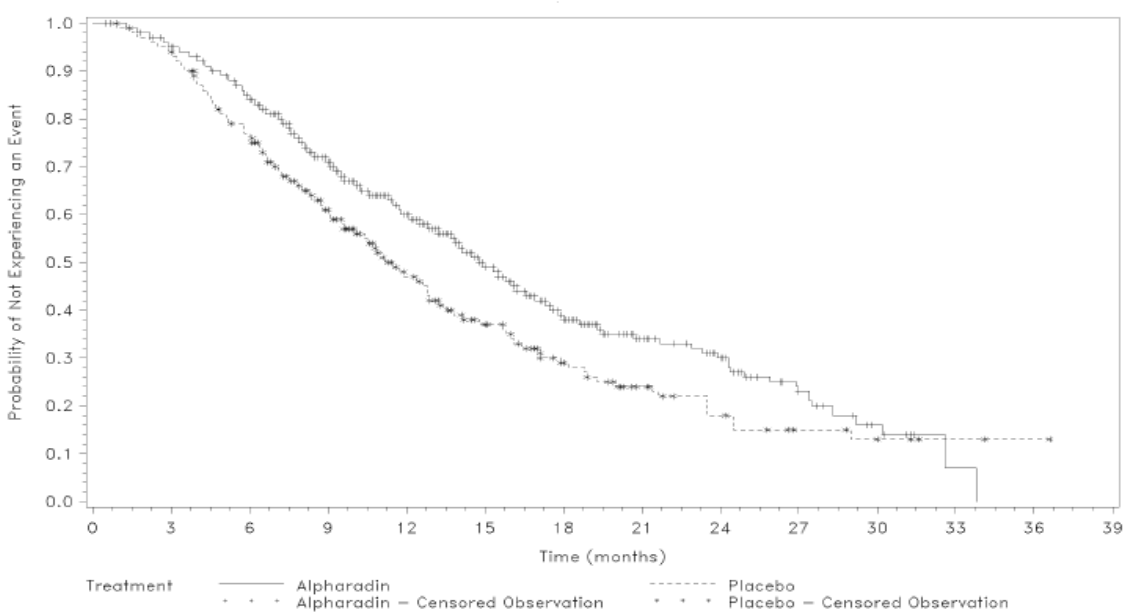


Figure 4. Kaplan Meier plot of OS (ITT, updated analysis)



Results of the key secondary endpoints are summarised in the following tables and figures.

Table 10. ALP progression, confirmed total ALP response and ALP normalisation (ITT)

	Interim analysis		**Updated analysis**	
	Radium-223 chloride N = 614	**Placebo** N = 307	**Radium-223 chloride** N = 614	**Placebo** N = 307
Total-ALP progression [no. (%) of patients]				
Experienced	79 (14.6%)	116 (43.3%)	106 (17.3%)	151 (49.2%)
Censored	462 (85.4%)	153 (57.1%)	508 (82.7%)	156 (50.8%)
Time to total-ALP progression (months)				
Median (95% CI)	NE	3.7 (3.5 –4.1)	7.4 (7.1-NE)	3.8 (3.6-4.2)
Hazard ratio (95% CI)	0.162 (0.120–0.220)		0.167 (0.129-0.217)	
P value	<0.00001		<0.00001	
Confirmed total ALP response [no. (%)* of patients]				
≥30% reduction	176/381 (46.2%)	4/160 (2.5%)	233/497 (46.9%)	7/211 (3.3%)
P value	<0.001		<0.001	
Total ALP normalisation [no. (%)** of patients]				
ALP normalisation	83/252 (32.9%)	1/107 (0.9%)	109/321 (34.0%)	2/140 (1.4%)
P value	<0.001		<0.001	

* Only patients with total ALP measurements at both baseline and Week 12 were included.
** Only patients who had their total ALP above ULN at baseline were included.

Figure 5. Kaplan Meier plot of total ALP progression with the 12 week rule (ITT, interim analysis)

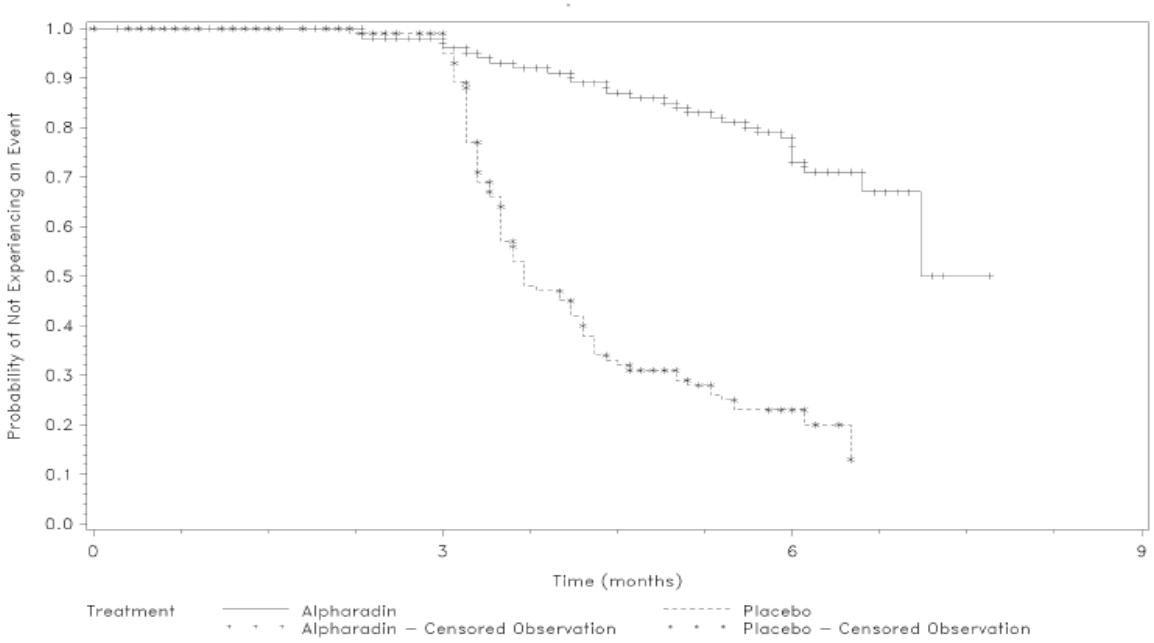


Figure 6. Kaplan Meier plot of total ALP progression without the 12 week rule (ITT, interim analysis)

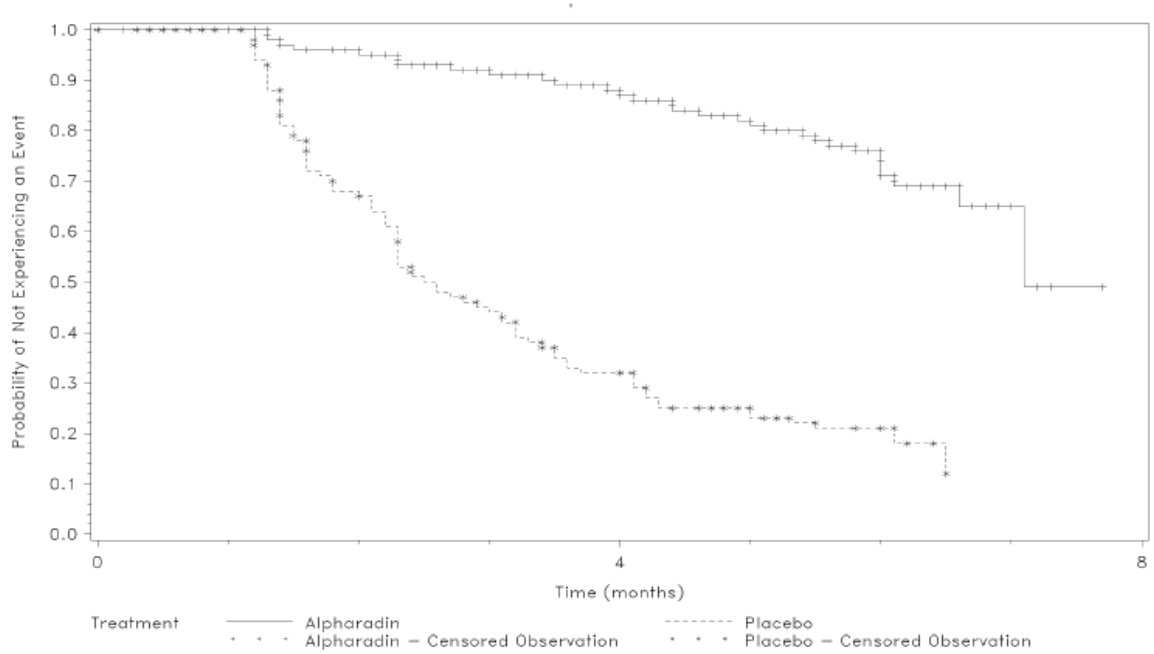


Table 11. Skeletal-related events (ITT, interim and updated analysis)

	Interim analysis		Updated analysis	
	Radium-223 chloride N = 541	**Placebo** N = 268	**Radium-223 chloride** N = 614	**Placebo** N = 307
SRE [no. (%) of patients]				
Experienced	132 (24.4)	82 (30.6)	202 (32.9)	116 (37.8)
Censored	409 (75.6)	186 (69.4)	412 (67.1)	191 (62.2)
Time to first SRE (months)				
Median (95% CI)	13.5 (12.2 –19.6)	8.4 (7.2 –NE)	15.6 (13.5-18.0)	9.8 (7.3-23.7)
Hazard ratio (95% CI)	0.610 (0.461–0.807)		0.658 (0.522-0.830)	
***P* value**	0.00046		0.00037	

Table 12. Summary of first use of EBRT, other cancer treatment, and deterioration of ECOG PS (months), ITT population; updated analysis

Variable	Alpharadin N=614	Placebo N=307	p-value[a]	Hazard Ratio[b] (95% CI)
Number (%) of subjects experienced an event that required EBRT	186 (30.3)	105 (34.2)	0.00117	0.670 (0.525 – 0.854)
Censored	428 (69.7)	202 (65.8)		
Time to need for EBRT (months)				
N	614	307		
25th percentile (95% CI)	7.4 (6.7 – 8.3)	4.6 (3.7 – 5.8)		
Median (95% CI)	17.1 (14.1 – 19.8)	17.5 (7.9 – 29.0)		
75th percentile (95% CI)	NE	29.0 (23.7 – 29.0)		
Number (%) of subjects experienced an event that required other cancer treatment	159 (25.9)	82 (26.7)	0.02670	0.737 (0.562 – 0.966)
Censored	455 (74.1)	225 (73.3)		
Time to need for other cancer treatment (months)				
N	614	307		
25th percentile (95% CI)	8.7 (7.9 – 9.4)	6.7 (6.0 – 9.4)		
Median (95% CI)	16.2 (13.2 – NE)	13.5 (11.0 – 17.0)		
75th percentile (95% CI)	NE	23.8 (17.0 – NE)		
Number (%) of subjects experienced a marked deterioration of ECOG PS	168 (27.4)	101 (32.9)	0.00168	0.670 (0.520 – 0.861)
Censored	446 (72.6)	206 (67.1)		
Time to marked deterioration of ECOG PS (months)				
N	614	307		
25th percentile (95% CI)	8.7 (8.0 – 10.8)	6.2 (5.5 – 7.4)		
Median (95% CI)	20.3 (17.0 – NE)	16.8 (12.7 – 20.5)		
75th percentile (95% CI)	NE	26.0 (20.5 – NE)		

a. Taken from the log rank test stratified by total ALP, current use of bisphosphonates, and prior use of docetaxel.
b. The HR (Alpharadin:placebo) is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior use of docetaxel.
Note: Subjects who did not experience an event are censored at the last disease assessment date.
ALP = alkaline phosphatase; CI = confidence interval; EBRT = external beam radiotherapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; NE = not estimable.
Source: Tables 14.1/11.M, 14.1/16.M, and 14.1/17.M.

Figure 7. Kaplan-Meier curves for skeletal-related events (ITT, interim analysis)

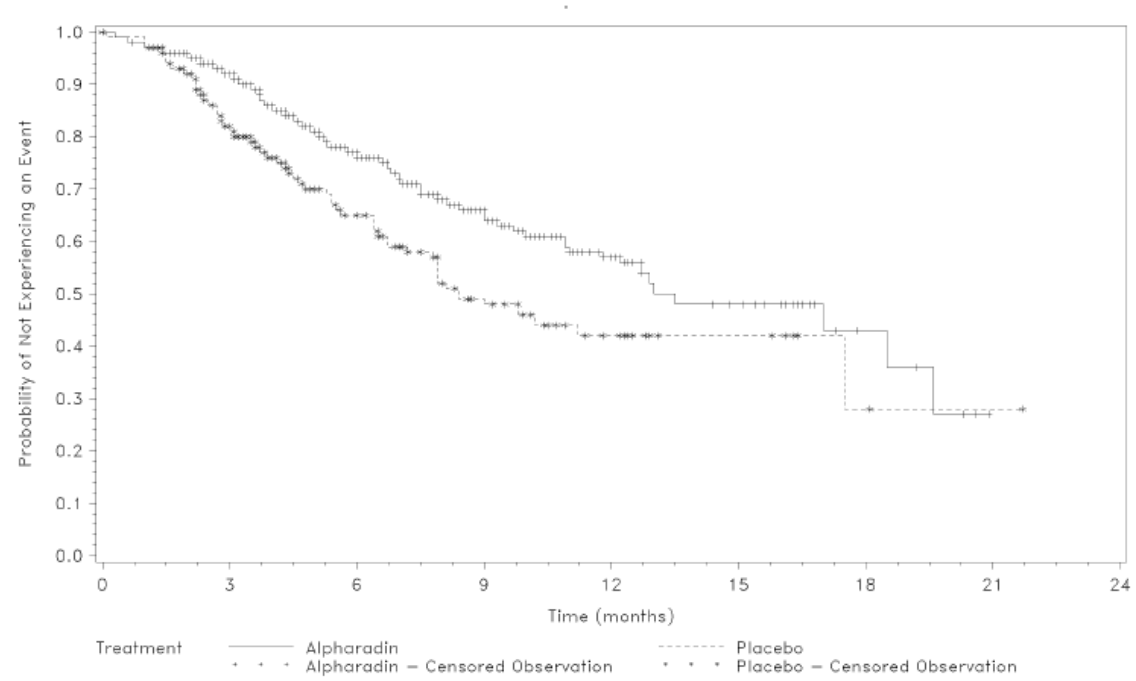


Figure 8. Kaplan-Meier curves for skeletal-related events (ITT, updated analysis)

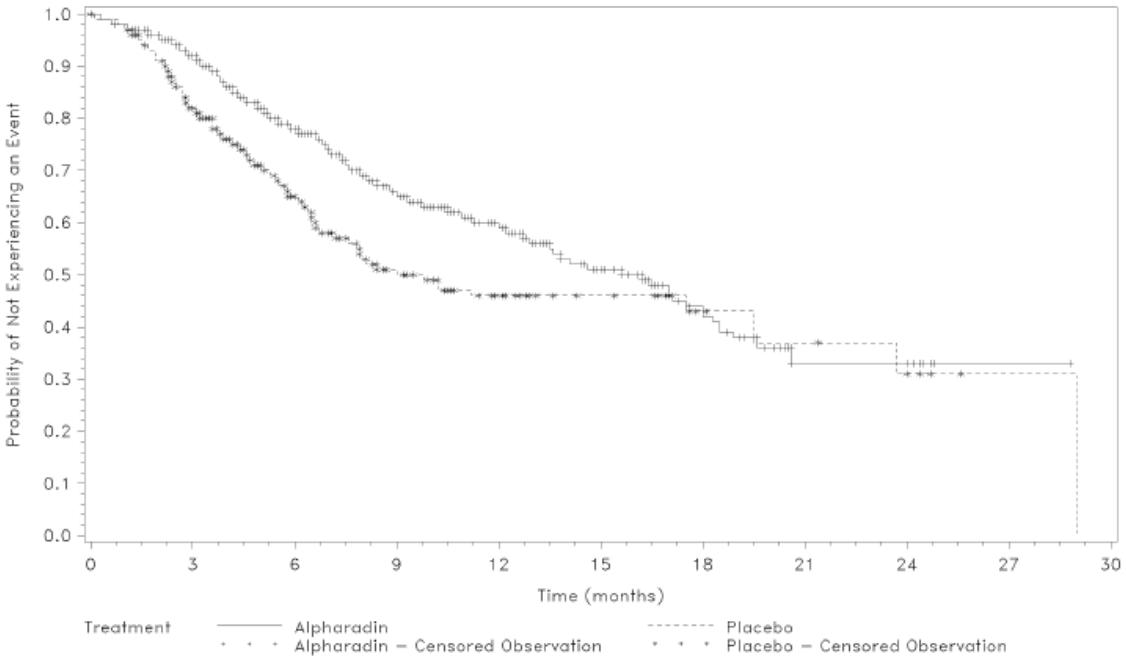
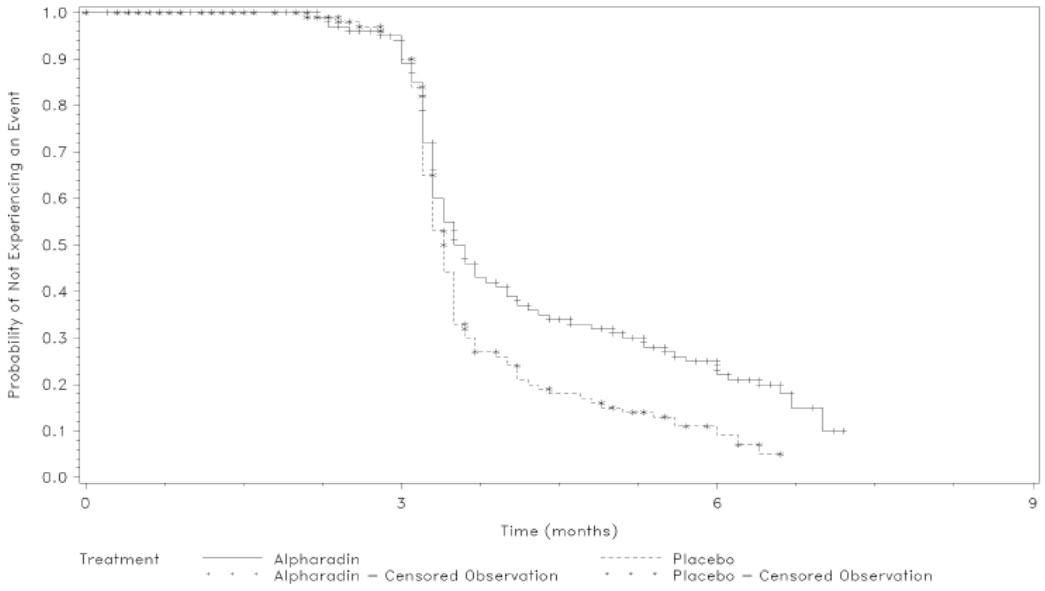
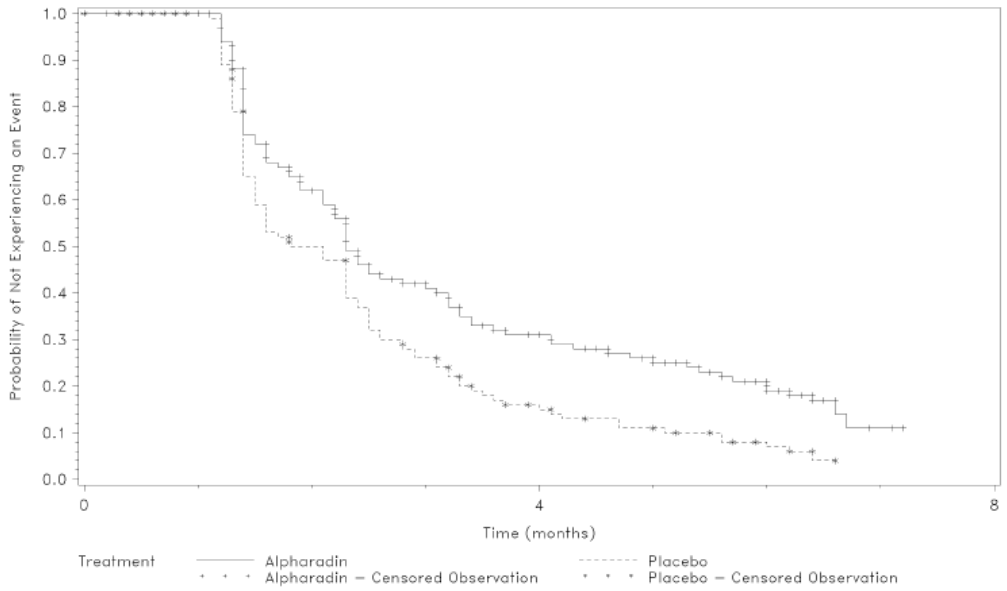


Table 13. PSA progression (ITT, updated analysis)

	Interim analysis		Updated analysis	
	Radium-223 chloride N = 541	**Placebo** N = 268	**Radium-223 chloride** N = 614	**Placebo** N = 307
PSA progression [no. (%) of patients]				
Experienced	288 (53.2)	141 (52.6)	388 (63.2)	193 (62.9)
Censored	253 (46.8)	127 (47.4)	226 (36.8)	114 (37.1)
Time to PSA progression (months)				
Median (95%CI)	3.6 (3.5 –3.7)	3.4 (3.3 –3.5)	3.6 (3.5-3.8)	3.4 (3.3-3.5)
Hazard ratio (95% CI)	0.671 (0.546–0.826)		0.643 (0.539-0.768)	
***P* value**	0.00015		<0.00001	

Figure 9. Kaplan-Meier curves for PSA progression with 12 week rule (upper) and without 12 week rule (lower) (ITT, interim analysis)





As mentioned earlier, other secondary endpoints included: time to occurrence of first use of EBRT to relieve skeletal symptoms, use of radio-isotopes to relieve skeletal symptoms, new symptomatic pathological bone fractures (vertebral and non-vertebral), tumour related orthopaedic surgical intervention, first spinal cord compression, start of any other anti-cancer treatment, deterioration of ECOG PS by at least 2 points from baseline [includes death (score of 5) by definition], changes in PSA, changes in total ALP, performance status (PS) response and progression and Quality of life (QoL) assessed using Functional Assessment of Cancer Therapy - Prostate (FACT-P) questionnaire and EuroQoL (EQ-5D).

Table 14. Disease-related events associated with skeletal-related events (ITT, updated analysis)

Event		**Radium-223 chloride** N = 614	**Placebo** N = 307	**Hazard ratio** (95% CI) ***P* value**
External beam radiotherapy	Exp. event [n(%)]	186 (30.3)	105 (34.2)	0.670 (0.525 – 0.854) 0.001
	Censored [n(%)]	428 (69.7)	202 (65.8)	
	Time to event (mo) [med (95% CI)]	17.1 (14.1-19.8)	17.5 (7.9 – 29.0)	
Radio-isotopes	Exp. event [n(%)]	9 (1.5%)	14 (4.6%)	0.292 (0.125 – 0.678) 0.00239
	Censored [n(%)]	605 (98.5%)	293 (95.4%)	
	Time to event (mo) [med (95% CI)]	NE (NE - NE)	NE (NE - NE)	
Pathological bone fracture	Exp. event [n(%)]	32 (5.2)	20 (6.5)	0.620 (0.351 – 1.093) 0.095
	Censored [n(%)]	582 (94.8)	287 (93.5)	
	Time to event (mo) [med (95% CI)]	NE	NE	
Surgical Intervention	Exp. event [n(%)]	12 (2.0)	7 (2.3)	0.715 (0.280 – 1.821) 0.479
	Censored [n(%)]	602 (98.0)	300 (97.7)	
	Time to event (mo) [med (95% CI)]	NE	NE	
Spinal cord compression	Exp. event [n(%)]	25 (4.1)	21 (6.8)	0.516 (0.286 – 0.931) 0.025
	Censored [n(%)]	589 (95.9)	286 (93.2)	
	Time to event (mo) [med (95% CI)]	NE	NE	
Start of any cancer treatment	Exp. event [n(%)]	159 (25.9)	82 (26.7)	0.737 (0.562 – 0.966) 0.02670
	Censored [n(%)]	455 (74.1)	225 (73.3)	
	Time to event (mo) [med (95% CI)]	16.2 (13.2 – NE)	13.5 (11.0 – 17.0)	
Deterioration of ECOG PS	Exp. event [n(%)]	168 (27.4)	101 (32.9)	0.670 (0.520 – 0861) 0.00168
	Censored [n(%)]	446 (72.7)	206 (67.1)	
	Time to event (mo) [med (95% CI)]	20.3 (17.0 – NE)	16.8 (12.7 – 20.5)	

Changes in PSA or total ALP (defined as responses compared to baseline at different levels -30% or 50%) invariably favoured the Xofigo arm (data not shown).

Regarding the QoL endpoints, a smaller decrease median FACT-P score was noted in the radium-223 chloride arm when compared to the placebo group at both weeks 16 and 24 (i.e. radium-223 chloride -2.0 and placebo -5.57. For the EQ-5D endpoint, changes from baseline were observed at week 16 and 24; the changes were in favour of radium-223 chloride.

Overall, both treatment groups experienced loss of quality of life captured by both instruments. The loss of quality of life was more pronounced in the placebo group. Compliance with filling out the questionnaires became very low during follow up.

Ancillary analyses

Pre-specified subgroup analyses for OS are shown in the following figure.

Figure 10. Forest plot overall survival by subgroup (ITT)

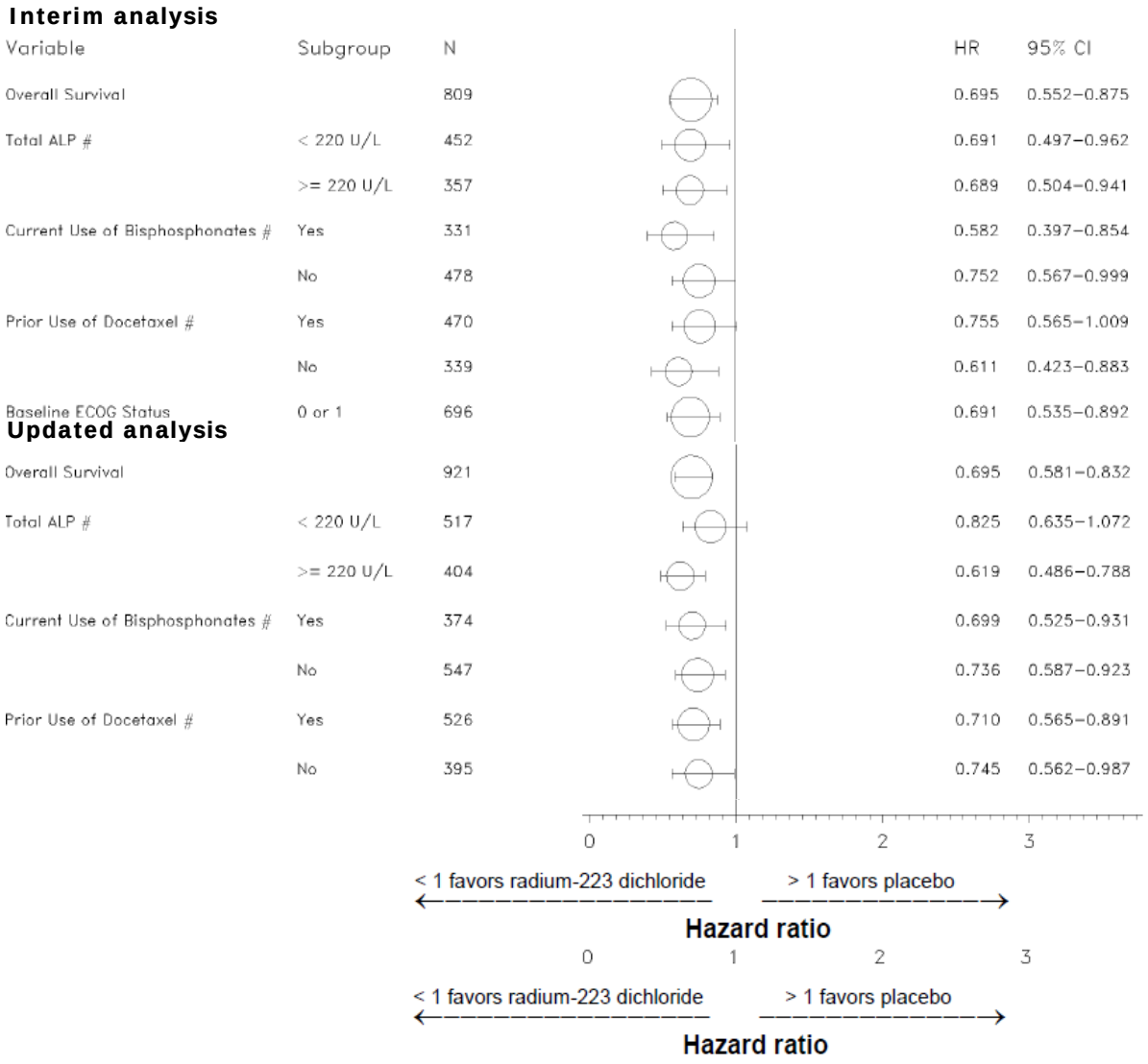


Table 15. Study BC1 06: Overall survival including baseline covariates

	Interim analysis[a]			**Updated analysis[b]**		
Population: Intent-to-treat	**Parameter estimate**	**Hazard ratio[c]**	***P* value**	**Parameter estimate**	**Hazard ratio[c]**	***P* value**
Randomized treatment group	-0.297	0.743	0.0136	-0.245	0.783	0.0086
Baseline albumin value	-0.038	0.963	0.0048	-0.028	0.973	0.0047
Log baseline LDH value[d.]	>0.999	5.994	<0.0001	>0.999	3.476	<0.0001
Baseline ECOG PS	0.530	1.699	0.0005	0.478	1.612	0.0001
Log baseline PSA value[d.]	0.270	1.310	0.0037	0.337	1.401	<0.0001
Log baseline total ALP value[d.]	0.596	1.816	0.0003	0.716	2.046	<0.0001
Age	0.017	1.017	0.0274	0.014	1.014	0.0179

a. Interim analysis includes data up to cut-off date of 14 October 2010.
b. Updated analysis includes data up to cut-off date of 15 July 2011.
c. The HR is from an adjusted Cox proportional hazards model.
d. Total ALP, PSA and LDH had heavily skewed distributions; therefore, these variables were modelled using log transformation.

Note: Patients who did not experience an event are censored at the last date known to be alive.
Note: Covariates are baseline albumin, LDH, ECOG PS, PSA, total ALP, and age.
Note: p-values for updated analyses are for descriptive purposes only.
ALP = alkaline phosphatase; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; LDH = lactate dehydrogenase; PSA = prostate specific antigen.

Table 16. Study BC1 06: Overall survival sensitivity analysis – Adjusting for potential imbalance in Gleason score

Interim database (October 2010)

Bayer 888223-15245 BC1-06 — Page 1 of 1
Alpharadin in Patients with Symptomatic HRPC with Skeletal Metastases — Data as of 14OCT2010

Table FDA60.4.1.5
Overall Survival Sensitivity Analysis - Adjusting for Imbalance in Gleason Score
ITT Population

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	P-Value	Hazard Ratio*(95% CI)
Randomized Treatment Group	1	-0.374	0.1184	9.995	0.0016	0.688 (0.545 - 0.867)
Gleason Score						
>7 vs <=7	1	-0.010	0.1257	0.007	0.9357	0.99 (0.774 - 1.267)
Missing vs <=7	1	-0.108	0.1809	0.358	0.5498	0.897 (0.63 - 1.279)

Updated database (July 2011)

Bayer 888223-15245 BC1-06 — Page 1 of 1
Alpharadin in Patients with Symptomatic HRPC with Skeletal Metastases — Data as of 15JUL2011

Table FDA61.4.1.5
Overall Survival Sensitivity Analysis - Adjusting for Imbalance in Gleason Score
ITT Population

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	P-Value	Hazard Ratio*(95% CI)
Randomized Treatment Group	1	-0.372	0.0921	16.301	<0.0001	0.689 (0.575 - 0.826)
Gleason Score						
>7 Vs <=7	1	0.066	0.0963	0.463	0.4961	1.068 (0.884 - 1.29)
Missing Vs <=7	1	-0.007	0.1401	0.003	0.9595	0.993 (0.754 - 1.307)

Note: Patients who did not experience an event are censored at the last date known to be alive
* The hazard ratio is from an adjusted Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.
Gleason score is categorized as Missing, <=7 or >7.
Global Biostatistics: /by-sasp/patdb/projects/888223/15245/stat/prod_query_c2_fdar03/t-fda61-4-1-5.sas erbjd 20FEB2013 23:40

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. Summary of Efficacy for trial ALSYMPCA

Title: A phase III, double-blind, randomized, multiple dose, placebo-controlled multicenter study of radium-223 chloride in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases.			
Study identifier	2007-006195-1, BC1-06		
Design	multicentre, randomised, double-blind, placebo-controlled (2:1)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks (6 IV administrations separated by 4 weeks intervals) not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Radium-223 chloride		50 kBq/kg b.w Radium-223 chloride + BSoC (541)
	Placebo		Placebo + BSoC (268)
Endpoints and definitions	Primary endpoint	Overall Survival	Time from date of randomization to the date of death

	Secondary endpoint	Time to total ALP progression	Defined: i) in subjects with no total ALP decline from baseline as:≥25% increase from the baseline value, at least 12 weeks from baseline ii) in subjects with an initial total ALP decline from baseline as:≥25% increase above the nadir value, which was confirmed by a second value obtained ≥ 3 weeks later
	Secondary endpoint	Time to occurrence of first SRE	An SRE was the use of EBRT to relieve skeletal symptoms or the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral) or the occurrence of spinal cord compression or a tumour-related orthopaedic surgical intervention
	Secondary endpoint	Time to PSA progression	Defined i) in subjects with no PSA decline from baseline as: ≥ 25% increase from the baseline value and an increase in absolute value of ≥ 2 ng/mL, at least 12 weeks from baseline ii) in subjects with an initial PSA decline from baseline as: ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir value, which is confirmed by a second value obtained 3 or more weeks later
Database lock	30 June 2011		

Results and analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat population (all randomized patients- the ITT population was the primary population for the analysis of the primary efficacy endpoint and for the analysis of all secondary efficacy endpoints), 30/06/2011 (310 events had occurred).		
Descriptive statistics and estimate variability	Treatment group	Radium 223 chloride	Placebo
	Number of subject	541	268
	Overall Survival (median, in months)	14.0	11.2
	95% CI	(12.1, 15.8)	(9.0, 13.2)
	Time to total ALP progression (median, in months)	NE	3.7
	95% CI		(3.5, 4.1)
	Time to occurrence of first SRE (median, in months)	13.5	8.4
	95% CI	(12.2, 19.6)	(7.2, NE)
	Time to PSA progression	3.6	3.4
	95% CI	(3.5, 3.7)	(3.3, 3.5)
Effect estimate per comparison	Overall Survival	Comparison groups	Radium-223 chloride vs. Placebo
		HR	0.695

		95% CI	(0.552, 0.875)
		Stratified log-rank p-value	0.00185
	Time to total ALP progression	Comparison groups	Radium-223 chloride vs. Placebo
		HR	0.163
		95% CI	(0.121, 0.221)
		Stratified log-rank p-value	<0.00001
	Time to occurrence of first SRE (median, in months)	Comparison groups	Radium-223 chloride vs. Placebo
		HR	0.610
		95% CI	(0.461, 0.807)
		Stratified log-rank p-value	0.00046
	Time to PSA progression	Comparison groups	Radium-223 chloride vs. Placebo
		HR	0.671
		95% CI	0.546 – 0.826
		Stratified log-rank p-value	0.00015
Notes	Stratification factors for the primary analysis (logrank): total ALP, current use of biphosphonates, and prior use of docetaxel.		
Analysis description	**Updated analysis**		
Analysis population and time point description	Intent to treat population 15 July 2011 (524 events had occurred)		
Descriptive statistics and estimate variability	Treatment group	Radium 223 chloride	Placebo
	Number of subject	614	307
	Overall Survival (median, in months)	14.9	11.3
	95% CI	(13.9, 16.1)	(10.4, 12.8)
	Time to total ALP progression (median, in months)	7.4	3.8
	95% CI	(7.1-NE)	(3.6-4.2)
	Time to occurrence of first SRE (median, in months)	15.6	9.8
	95% CI	(13.5-18.0)	(7.3-23.7)
	Time to PSA progression	3.6	3.4
	95% CI	(3.5, 3.8)	(3.3, 3.5)
Effect estimate per comparison	Overall Survival	Comparison groups	Radium-223 chloride vs. Placebo
		HR	0.695
		95% CI	(0.581, 0.832)
		Stratified log-rank p-value	
	Time to total ALP progression	Comparison groups	Radium-223 chloride vs. Placebo

		HR	0.167
		95% CI	(0.129-0.217)
		Stratified log-rank p-value	<0.00001
	Time to occurrence of first SRE (median, in months)	Comparison groups	Radium-223 chloride vs. Placebo
		HR	0.658
		95% CI	(0.522-0.830)
		Stratified log-rank p-value	0.00037
	Time to PSA progression	Comparison groups	Radium-223 chloride vs. Placebo
		HR	0.643
		95% CI	0.539 – 0.768
		Stratified log-rank p-value	<0.00001

Analysis performed across trials (pooled analyses and meta-analysis)

No efficacy analyses across trials were submitted.

Clinical studies in special populations

No studies in special populations were submitted (see discussion on clinical efficacy).

Supportive studies

Two supportive phase II Studies (BC1-02 and BC1-03) were submitted. Additionally, the dose-response study BC1-04, described earlier, is considered as supportive.

Study BC1-02

Study BC1-02 was a phase 2, randomised, placebo-controlled, multicentre study designed to evaluate the efficacy of repeated radium-223 chloride injections in prostate cancer patients with painful bone metastases.

Eligible patients had confirmed adenocarcinoma of the prostate with multiple bone metastases or 1 painful lesion with 2 consecutive rising amounts of PSA levels at least 2 weeks apart. The treatment period was three months (12 weeks), during which four injections of radium-223 chloride were given at 4-week intervals, follow-up until 24 months. All subjects received a single treatment of EBR (external beam radiotherapy) followed within 7 days by the first injection of study medication.

The primary objective was to study the biological effectiveness of radium-223 therapy measured as time to occurrence of skeletal-related events (SRE) and change in bone-specific alkaline phosphatase (bone-ALP) levels.

Results

The study population had a mean age of 72.3 years (range, 57 to 88), body mass index of 26.9 kg/m^2 (range, 18 to 38) and mean BW of 82.6 kg at inclusion (range, 54 to 109). Prostate cancer had been

diagnosed a mean of 5.12 years (range, 0.2 to 23.1) and bony metastases a mean of 1.58 years (range, 0.1 to 17.8) before entry to the study. The median extent of disease on entry to the study was category 2 (6 to 20 lesions on bone scan) and the mean pain severity index was 3.83 (of a maximum 10).

A total of 64 patients were enrolled, randomised, and treated (33 patients in the radium-223 chloride group and 31 patients in the placebo group). The 12-month visit was completed by 19 (58%) and by 12 (39%) and the 24-month visit was completed by 10 (30%) and by 3 (10%) subjects in the Xofigo and placebo group respectively.

The results of the primary and co-primary endpoint are presented in Tables 18 and 19 below.

Table 18. Time to First SRE (Primary Statistical Analysis)

Parameter	Data set		Alpharadin™	Placebo	p-value*
		Number	33	31	
Time to first SRE, all (weeks)	PPS	N obs Mean (SD) Median N Censored (%)	25 15.1 (14.0) 16.0 6 (19 %)	25 14.0 (12.5) 11.0 2 (7 %)	0.2144
	FAS	N obs Mean (SD) Median N Censored (%)	26 15.0 (13.7) 14.0 7 (21 %)	26 13.6 (12.4) 11.0 5 (16 %)	0.2570
Time to first SRE excluding pain and analgesia	PPS	N obs Mean (SD) Median N Censored (%)	20 24.3 (11.3) 28.0 11 (36 %)	21 18.8 (11.6) 26.0 6 (22 %)	0.1129
	FAS	N obs Mean (SD) Median N Censored (%)	21 23.8 (11.2) 28.0 12 (36 %)	21 18.8 (11.6) 26.0 10 (32 %)	0.1643

Table 19. Bone-ALP responses, responses/changes 4 weeks after last injection[a]

		Radium-223 chloride N = 33	Placebo N = 31	*P* value
FAS	Number of observations	33	28	
	Confirmed bone-ALP response (50%) (n,%)[c]	24 (73)	4 (14)	0.0000[f]
	≥50% reduction in blood level, (n,%)[c]	27 (82)	7 (25)	0.0000[f]
	No. observations	33	29[e]	
	Relative change from baseline (median)	-66	9	<0.001[b]
PPS	Number of observations	31	27	
	Confirmed bone-ALP response (50%) (n,%)[c]	23 (74)	4 (15)	0.0000[f]
	≥50% reduction in blood level, (n,%)[d]	26 (84)	7 (26)	0.0000[f]
	Relative change (%) from baseline (median)	-66	9	<0.001[b]

e. If a value is not available at 4 weeks after the last injection, the closest previous value was used.
f. Wilcoxon rank sum test stratified by center/country.
g. Confirmed response means there was still a response compared to baseline at the next visit.
h. Decrease of at least 50% compared to baseline.
i. Two (2) patients had only baseline data.
j. *P* value-stratified Cochran-Mantel Haenszel 2-sided.

Study BC1-03

Study BC1-03 was a double-blind, dose-response phase II, multicentre study of radium-223 designed to investigate whether there is a dose-response relationship for radium-223 in patients with painful bone metastases secondary to prostate carcinoma regarding the palliation of bone pain. Following protocol amendment 02, the study design was changed from an open-label study assessing a dose of 100 kBq/kg body weight (b.w.) radium-223 in 35 breast and prostate cancer patients, to a double-blind, randomised, dose-ranging study assessing four dose levels (5, 25, 50 and 100 kBq/kg b.w. radium-223) in 100 hormone-refractory prostate cancer patients.

The primary endpoint was the pain index defined by a combination of the change in diary pain rating, (recorded by patients on a visual analogue scale [VAS]), and the change in analgesic consumption (from baseline to Weeks 2, 4, 8, 12 and 16). Randomized patients received a single dose i.v. injection of radium-223 chloride (at 5, 25, 50 or 100 kBq/kg BW) followed by a 16-week Post-Treatment Period. At the end of this period the study was unblinded. Follow-up visits were planned 6, 9, 12, 18, and 24 months. A second injection of radium-223 chloride (fixed dose of 50 kBq/kg BW) could be offered to patients during the Follow-up Period at the Investigator's discretion.

Results

Among demographic characteristics, more than half of the enrolled population had ECOG of 1 and the extent of disease was of grade 3 (>20 mets) in 41.9% of patients.

A statistically significant (Jonckheere-Terpstra test) trend for dose-response relationship at Week 2 (*P* = 0.035) was reported on PP population since the mean pain score was higher in the 2 lowest dose groups (4.8 and 4.1 in the 5 and 25 kBq/kg BW groups, respectively) compared to the 2 highest dose groups (3.9 in both the 50 and 100 kBq/kg BW groups). The analysis on ITT population, although showed a trend in pain score reduction in the higher (5 and 25 kBq/kg BW) groups, did not showed any statistical results. Daily diary data on average bone pain (VAS recorded by patients) showed a decrease over time in all dose groups but the change in mean VAS score was higher in the lower dose group (5 and 25 kBq/kg B*W) than in the higher (50 and 100 kBq/kg BW) dose group. The highest change from baseline was seen in the 25 kBq/kg BW group (data not shown).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The indication applied for reflects the patient population included in the pivotal trial and it is independent of line of chemotherapy, i.e. encompasses chemo-naive patients as well as patients having failed first line docetaxel chemotherapy. In contrast to a population previously treated with docetaxel, which would be expected to be rather homogeneous, chemotherapy-naïve patients are rather heterogeneous as they are either not eligible for docetaxel or do not receive docetaxel due to unwillingness or non-availability of docetaxel, factors of unknown distribution between study arms in this case. Therefore, this group may unite patients with very different prognosis. Several surveys have concluded that a large proportion of patients do not receive first-line docetaxel after disease progression during castrate levels of testosterone in clinical practice, probably in view of its toxicity and the modest survival benefit around 2-3 months. However, sensitivity analyses showed that the OS results were robust, including for all baseline parameters tested, so that the uncertainty from the heterogeneity of the patient population and the imbalances in baseline characteristics does not affect the efficacy conclusions.

The pivotal trial was performed as a placebo-controlled add-on to best standard of care. Best standard of care was an oncologist's choice among overall acceptable palliative treatment regimens. No common back-bone treatment was used. Of note, there is potential impact of co-medication on endpoints such as PSA response or skeletal-related events. Imbalances in co-medication over the study period, especially after the treatment phase, may contribute to the magnitude or the maintenance of the beneficial effect with respect to SREs; this is difficult to differentiate from a treatment effect in view of selection processes in the trial. However, a survival benefit of the magnitude observed in the pivotal study of radium-223 is unlikely to be due to co-medication alone.

The dosing regimen selected by the Applicant for clinical development was a fixed-dose regimen (50 KBq /kg per body weight) administered 6 times at intervals of 4 weeks between each administration which is based on the results of the supportive BC1-02 and BC1-04 studies and seems to represent the optimal biological dose. The use of a treatment dose calculated on the basis of patient's weight and not directly measured by radioisotopic procedure is acceptable, despite the fact that it disregards pharmacokinetic variability between patients and the extent of potential Xofigo accumulation depending on factors such as the administered dose, metastatic burden and location as well as tumour permeability. This is because radium-223 rapidly goes into the bone and bone lesions and it is also rapidly excreted via the intestinal route which reduces a patient-specific variability of the activity at the target site substantially. Moreover, only about 1% of the energy is emitted as gamma radiation (which could be used for imaging and thus for dosimetric evaluation of exposure) and the total activity administered to a patient is only 50 kBq/kg body weight which is much lower than doses usually applied for other radiopharmaceuticals.

The selected interval between doses (4 weeks) was justified by the fact that haematological side effects were expected to recover in most patients after three weeks and in every patient after 4 weeks. However, study BC1-04 (dose-seeking study) evaluated efficacy and safety at a 6-week interval.

Optimisation of the dose could further explore the effect or treatment withdrawal, longer treatment duration, dose adjustments (e.g., increase in non-responders and decrease in patients experiencing excessive toxicity), use of a lower number of doses (even a single-dose as other radiopharmaceuticals) or higher interval between doses (especially because the absorbed radiation dose is likely to change during the treatment period if radium-223 works on bone metastases). Until further dose optimisation data become available, the total number of doses suggested (6 doses over a period of 5 months) is acceptable.

At the time of the design and conduct of the pivotal study, the choice of placebo plus BSC as comparator was adequate; however, this is currently questioned in relation to the therapeutic armamentarium nowadays available for the treatment of CRPC patients, primarily the use of abiraterone in asymptomatic or only mildly symptomatic patients, as well as abiraterone and cabazitaxel in patients having failed docetaxel. In addition, other radionuclides (beta radiators such as Samarium-153 or Strontium-89) are used for pain palliation associated with bone metastasis. None of the second-line treatments is curative, and patients either fail to respond, or progress after an initial response. Cabazitaxel is also associated with significant toxicity. Other bone-targeted agents have either not been studied (e.g. Samarium-153, Strontium-89), or were not studied for their impact on survival. However, it is neither known how radium-223 compares to other recently authorised products for systemic treatment of prostate cancer or how it compares to the palliative effect on bone disease of other radionuclides.

Treatment allocation was concealed and the study was double-blind. However, in view of the radioactive nature of the product, the nuclear department of the centre was unblinded. The toxicity profile was not expected to de-mask the nature of study treatment. On the other hand, administration by an unblinded member of the nuclear lab required no special flanking procedures which would facilitate the maintenance of the blind. Maintenance of the blind would be critical for quality of life analyses used as supportive endpoints.

The conduct of the pivotal study and amendments to the protocol did not give rise to concerns. There was one pre-planned increase in sample size and few losses to follow-up with respect to the primary endpoint.

In the course of the interim analysis of the pivotal trial, inconsistencies in the database were noted with respect to the secondary endpoint skeletal related-events. Individual components of this composite endpoint were captured in different parts of the CRF and it was necessary to verify, if all events which had been described in e.g. the concomitant treatment (e.g. EBRT) or adverse event (e.g. spinal cord compression) part were indeed accounted for also for the evaluation of efficacy. Sensitivity analyses were conducted which indicated the robustness of the results.

The study was terminated early as recommended by an independent data monitoring committee during a pre-specified interim analysis in view of the statistically significant prolongation of overall survival with respect to the primary endpoint and its support from further secondary endpoints. Results were updated after 6 months at the latest time-point before patients were allowed to cross-over from placebo to Xofigo. While the pre-specified interim analysis represents the confirmatory analysis, the updated analysis (a cumulative report including the data of the interim analysis) is regarded as the clinically more relevant analysis in view of data maturity of the primary endpoint, overall survival, and further time-to-event endpoints such as time-to-first-skeletal-event. The updated analysis contained some unblinded data, but in view of the little overlap (database lock 15 days after unblinding, the overall maturity of data (almost all subjects had completed injections) and the objective primary endpoint, this is acceptable. P-values of the updated analysis cannot formally be accepted from a statistical perspective, of course.

Demographic and baseline characteristics were representative of the target population. In both groups more than half of the population had basal total ALP values <220 U/L. This cut-off value identifies a population with high basal elevated levels of total ALP (the serum ALP cut-off is 120 U/L is generally used) reflecting the target population characterised by highly prevalent bone disease. Baseline categories differed mostly below 4%. However, the biggest difference between study arms to the advantage of the radium-223 group in both interim and updated analysis referred to extent of disease and PSA at baseline. More patients in the radium-223 group had less than 6 metastases in bone. Extent of disease was a strong predictor of survival (longest overall survival of all subgroups in patients with most limited extent of disease). The observed safety profile in the pivotal trial was also highly suggestive of an overall superior health status of the radium-233 group. Since an imbalance in non-prostate-cancer-related deaths contributed to the magnitude of the observed prolongation of survival in the radium-223 group, a superior health status in the active treatment group could not be excluded. This is especially relevant, as the OS was not supported by PFS or TTP data and a direct anti-tumour effect remained elusive also in view of the marginal effect on PSA. The definition of subgroups analysis of OS according to stratification factors (baseline ALP level, bisphosphonate use during study treatment, prior docetaxel therapy, see Figure 8) and of exploratory analyses of OS according to clinically relevant covariates (graded EOD at baseline, baseline pain, opiate use, ethnicity, albumin, total ALP, Hb, PSA, LDH, ECOG PS, and age, data not shown) is helpful in exploring the consistency of the result in the overall population and in depicting the effect of baseline covariates and treatment. The exploratory analyses of survival adjusted for important prognostic factors showed a consistent treatment effect. Thus important bias do to imbalance in prognostic factors is considered unlikely. The additional analyses provide sufficient reassurance about a robust beneficial effect on overall survival with some remaining uncertainty regarding the exact quantification.

The primary objective was to compare overall survival. Overall survival is an undisputed primary endpoint for late-stage cancer. However, particularly in prostate cancer, death due to non-cancer causes represents a competing risk.

The choice and hierarchy of secondary endpoints (ALP and skeletal-related effects) follows the proposed pharmacodynamic action (main effect on bone disease), but it did not allow complete tumour assessment

including extra-osseous disease by imaging data. Thus, OS is not supported by PFS or TTP in the single pivotal study.

The clinical relevance of the endpoints focussing on bone marker turnover is questionable. Although total ALP and not bone specific ALP is considered, a better radium-223 effect was demonstrated in patients having total ALP ≥220 U/L and thus in those patients having a high osteoblastic activity and probably higher extent of disease.

A direct effect on tumour is limited to a locally determined PSA concentration, with overall very few responses and high heterogeneity of response rates across trials. All aspects of the composite endpoint SRE are referring to clinically relevant issues and there is a consistent effect in three of four aspects of the composite endpoint. The clinical impact of the different event types is somewhat different: while EBRT indicates need for palliation of skeletal symptoms, it does not reflect the acute medical emergency as e.g. spinal cord compression. Symptomatic pathological fracture indicated advanced bone disease and surgical intervention aims at preventing further complications. Due to the absence of systematic follow-up by imaging, non-symptomatic fractures were not recorded. EBRT (which may be more subjective compared to the infrequent components) dominates the effect on the composite endpoint SRE (incidence in about 30% of patients compared to well below 10% for the other components).

The proportion of patients having to undergo surgical intervention it is too low (around 2%) to allow firm conclusions. The (low) number of patients experiencing spinal cord compression is half in the radium-223 group, which represents a clinically meaningful reduction.

All skeletal-related events appear as rather late occurring events (median occurrence of earliest skeletal event, in particular time to need for EBRT, in updated analyses was 17 months compared to median overall survival of 11 months). Location of metastases at baseline and whether there were imbalances with respect to developing complications due to the site of metastases between groups were not recorded. Similarly, it was not recorded whether the more infrequent SREs were occurring early or late. It is unlikely, however, that the entire magnitude of delay of skeletal-related events is due to baseline imbalances.

Current use of bisphosphonates subgroup analysis showed similar HRs (0.69 yes and 0.73 no) between the two groups. Although skeletal metastases from prostate cancer primarily have increased osteoblastic activity (a bone-forming phenotype as a result of stimulation of osteoblasts, inhibition of osteoclasts or both by cancer cells), evidence also suggests increased osteoclast activation and bone resorption. Results of the BC1-02 study, although obtained on a limited number of subjects, confirm Xofigo preferential effect in areas of new bone formation (osteoblastic metastasis) but also suggest an action on bone resorption areas (osteoclastic metastasis). The reduction (especially in view of spinal cord compression) or delay of clinically meaningful skeletal-related events is supportive of a beneficial effect of radium-223 on bone metastases. It is a relevant objective for the treatment of bone metastases in patients with symptomatic castration-resistant metastatic prostate cancer. Additional, although weak, support for a palliative effect is given by recorded changes in performance status and quality of life. The ad-hoc analysis of time-to-initial-opioid use in the pivotal study also supports the palliative effect of radium-223.

Efficacy data and additional analyses

For the primary endpoint a difference of 2.8 months in median OS was observed in the radium-223 group in the interim analysis. In the updated analysis, the difference increased to a total of 3.6 months (14.9 months in the radium-223 compared to 11.3 months in the placebo group). This is statistically significant and a difference of this magnitude is regarded as clinically meaningful in advanced cancer stages. An overall survival benefit for the Xogifo group had also been seen in a small placebo-controlled phase 2 study. Interpretation of the survival difference is impaired by baseline imbalances in both studies with

respect to extent of disease and baseline PSA. These imbalances are suggestive of a superior health status of the Xofigo group. Additional sensitivity analyses addressed this issue for the pivotal study; in the adjusted analyses the effect on overall survival appears to be slightly smaller but robust in this respect. An imbalance (of 8% absolute) with respect to non-prostate-cancer related deaths in the placebo group in the pivotal trial clearly in favour of the Xofigo treatment group appears to drive the increasing difference in overall survival in the updated analysis. The size of the impact on the observed effects on OS is currently not clear. Overall survival after a subsequent treatment was favourable in the Xofigo treatment group; however, median overall survival appears not to be relevantly influenced by the response to subsequent treatment in this subgroup. Differences in the distribution of causes of death between treatment groups should be interpreted with caution since they may be confounded by the effect of treatment. Although a confounding of non-prostate-cancer related deaths cannot be ruled out, in view of the small imbalance and the results of analyses of survival adjusted by important prognostic factors, important bias seems unlikely.

The results of the available secondary endpoints support a beneficial effect on bone disease of radium-223 compared to placebo: skeletal-related events, changes in performance status and further treatment for pain or prostate cancer and changes in ALP all favoured the Xofigo arm. Fewer patients in the radium-223 group experienced skeletal-related events or ALP progression compared to the placebo group and at a later time point. All aspects of the composite endpoint SRE referred to clinically relevant issues and there was a consistent effect in three of four aspects of the composite endpoint.

Changes in ALP as such, however, cannot be related to a patient-relevant endpoint. In addition, the effect on ALP appears to be transient and most prominent during the treatment phase. Kaplan Meier analyses were limited to the first 9 months and the other endpoints were referenced to the 12th week (mid-treatment). While an immediate controlling effect on active bone remodelling appears plausible in view of the bone-seeking nature of the alpha-radiation-emitting radium-223, the cytotoxic nature of radium-223 could also result in decreased secretion of ALP from osteoblasts.

The beneficial effect of radium-223 on pain is supported by fewer patients in the radium-223 receiving either opioids or other radioisotopes also at a later time point, as well as a delayed marked deterioration of the performance status in the radium-223 group. A mainly delaying effect is evident for the receipt of other anti-cancer treatments (with similar final proportions of patients receiving it).

In spite of a statistically significant result in the primary endpoint of overall survival and other key secondary endpoints, the effect on PSA progression did not indicate a relevant decrease in cancer cell mass with a similar final proportion of patients experiencing PSA progression at a very similar median time point and reductions in PSA in only a small subset of patients in all clinical trials. The rather limited effect on PSA is in line with the presumed mode of action. Determination of PSA in the local laboratories could also have resulted in substantial variation across centres.

Quality of life data are also suggestive of a slight delaying effect on the deterioration of quality of life during treatment, but results of the pivotal study were not consistent with the phase 2 results and they did not reach minimally important differences.

Since radium-223 chloride is neither metabolised by the liver nor eliminated via the bile, hepatic impairment was considered by the Applicant not to affect the pharmacokinetics of Xofigo. No dose adjustment is considered necessary in patients with hepatic impairment. Similarly, since excretion in urine is minimal and the major route of elimination is via the feces, renal impairment is not expected to affect the PK of radium-223 chloride and no dose adjustment is considered necessary in patients with renal impairment.

As expected, based on the epidemiology of prostate cancer, the median age of enrolled patients in the pivotal study was 70 years. No overall differences in safety or efficacy were

observed between elderly (aged ≥ 65 years) and younger patients (aged < 65 years) in the phase III study. However, the percentage of patients aged ≥85 years was very low (roughly 10 subjects in each group). Overall, no dose adjustment is considered necessary in elderly patients (see SmPC section 4.2).

2.5.4. Conclusions on the clinical efficacy

Overall efficacy results from the pivotal trial showed a statistically significant benefit in OS, the primary study endpoint, in patients with HRPC with bone metastasis treated with Xofigo plus BSC compared to placebo plus BSC. Results from secondary endpoints support the positive effect of Xofigo treatment on clinical bone metastasis sequelae (SREs) and on bone markers (ALP) confirming the target efficacy of Xofigo on bone metastases. The activity of Xofigo in CRPC patients with bone metastasis is biologically supported and it is consistent with preclinical evidence.

2.6. Clinical safety

Patient exposure

The safety database of radium 223-chloride has been presented in 3 different populations:

- Pool 2: Safety data from the randomised, double-blind, placebo-controlled Study BC1-06 (n=600).
- Pool 4: Safety data (50 kBq/kg data only) from studies: ATI-BC-1 (n=3), BC1-02 (n=33), BC1-03 (n=25), BC1-04 (n=39), BC1-08 (n=3), BC1-06 (n=600).
- Pool 5: Safety data (50 kBq/kg data only) from studies: ATI-BC-1 (n=3), BC1-02 (n=33), BC1-03 (n=25), BC1-04 (n=39), BC1-08 (n=3).

Patients in Pool 5 have often been treated only with a single dose of the recommended dose and overall treatment regimes in the patients included in this pool were very heterogeneous. Therefore, the safety analysis below is focused on the population defined in pool 2 which represents the population of the pivotal study. In the pivotal study, 901 patients (600 treated with radium-223 chloride and 301 treated with placebo) received at least 1 injection of study drug and were included in the safety population. Twenty patients (14 in radium-223 chloride and 6 in the placebo group) were randomised but never received treatment. One subject was randomised to placebo but received radium 223 chloride at Week 0; thus the subject was summarised in the placebo group for the ITT population and in the radium 223 chloride group for the safety population. The median duration of exposure to study treatment in the safety population was 141 days in the radium-223 chloride group and 128 days in the placebo group. The mean number of injections of study treatment was 5.1 for radium-223 chloride treated patients and 4.5 for the placebo group.

The duration of exposure to radium 223 chloride for the above different populations is summarised in Table 20.

Table 20. Duration of exposure and duration of exposure by number of injections

		Pool 2 **Study BC1-06**		Pool 5 (50 kBq/kg BW) **Phase 1/2 studies**		Pool 4 (50 kBq/kg BW) **All studies**	
		Persons	**Person-time** (months)	**Persons**	**Person-time** (months)	**Persons**	**Person-time** (months)
Duration of exposure							
	≤4 weeks	23	5.20	N/A	N/A	N/A	N/A
	≤6 weeks	N/A	N/A	29	4.2	82	39
	>4 to 8 weeks	34	36.53	N/A	N/A	N/A	N/A
	>6 to 12 weeks	N/A	N/A	13	25.93	65	131.4
	>8 to 12 weeks	48	98.57	N/A	N/A	N/A	N/A
	>12 to 24 weeks	474	2149.44	61	178.53	535	2328.0
	>24 weeks	21	122.43	0	0	21	122.4
	Missing	0	0	0	0	0	0
	Total	600	2412.17	103	208.67	703	2620.8
Number of injections							
	1 injection	18	0.6	26	0.87	44	1.5
	2 injections	37	37.4	12	23.9	49	61.3
	3 injections	48	96.8	34	95.13	82	191.9
	4 injections	60	180.43	29	83.1	89	263.5
	5 injections	49	195.4	2	5.67	51	201.1
	6 injections	388	1901.53	0	0	388	1901.5
	>6 injections	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	600	2412.17	103	208.67	703	2620.8

Adverse events

An overall summary of adverse events in the pivotal study is presented in Table 21.

Table 21. Overall summary of adverse events (Study BC1-06, Safety population)

	Radium-223 chloride N = 600	**Placebo** N = 301
Pre-treatment AE	191 (31.8%)	94 (31.2%)
Treatment-emergent AE	558 (93.0%)	290 (96.3%)
Treatment-related AE	380 (63.3%	171 (56.8%)
Treatment-emergent SAE	281 (46.8%)	181 (60.1%)
Treatment-related SAE	72 (12.0%)	30 (10.0%)
Treatment-emergent AE		
CTC Grade 3 or 4	339 (56.5%)	188 (62.5%)
Leading to discontinuation of study treatment	99 (16.5%)	62 (20.6%)
Leading to death	96 (16.0%)	67 (22.3%)

	Radium-223 chloride N = 600	**Placebo** N = 301
Post-treatment AE	20 (3.3%)	7 (2.3%)

The Treatment-emergent adverse events (TEAEs) most frequently observed in the radium 223 chloride group were bone pain (50.0%), nausea (35.5%) and anaemia (31.2%) (see Table 22). Specific TEAEs with a notably higher frequency in the radium 223 chloride group as compared to placebo were diarrhoea (25.2% versus 15.0%), thrombocytopenia (11.5% versus 5.6%) and neutropenia (5.0% versus 1.0%).

Table 22. Treatment-emergent adverse events by MedDRA system organ class and preferred term, occurring in ≥ 5% of subjects in either treatment group by preferred term (Study BC1-06, Safety population)

	Radium-223-chloride N=600		**Placebo N=301**	
	n (%)	**Events**	**n (%)**	**Events**
MedDRA System organ class / Preferred term				
Subjects with at least 1 TEAE	558 (93.0)	4505	290 (96.3)	2269
Blood and lymphatic system disorders	232 (38.7)	477	106 (35.2)	159
Anaemia	187 (31.2)	288	92 (30.6)	125
Neutropenia	30 (5.0)	37	3 (1.0)	5
Thrombocytopenia	69 (11.5)	80	17 (5.6)	19
GI disorders	380 (63.3)	1000	174 (57.8)	406
Constipation	108 (18.0)	117	64 (21.3)	73
Diarrhoea	151 (25.2)	238	45 (15.0)	63
Nausea	213 (35.5)	297	104 (34.6)	133
Vomiting	111 (18.5)	166	41 (13.6)	52
General disorders and administration site conditions	280 (46.7)	488	142 (47.2)	235
Asthenia	35 (5.8)	44	18 (6.0)	20
Fatigue	154 (25.7)	19077	91	
General physical health deterioration	27 (4.5)	29	21 (7.0)	22
Peripheral oedema	76 (12.7)	83	30 (10.0)	36
Pyrexia	38 (6.3)	64	19 (6.3)	31
Infections and infestations	183 (30.5)	272	98 (32.6)	141
Pneumonia	18 (3.0)	20	16 (5.3)	17
Urinary tract infection	47 (7.8)	58	28 (9.3)	29
Investigations	100 (16.7)	127	67 (22.3)	89
Weight decreased	69 (11.5)	69	44 (14.6)	45
Metabolism and nutrition disorders	182 (30.3)	245	92 (30.6)	109
Anorexia	102 (17.0)	112	55 (18.3)	59
Decreased appetite	35 (5.8)	38	13 (4.3)	13
Musculoskeletal and	349 (58.2)	712	209 (69.4)	465

connective tissue disorders				
Bone pain	300 (50.0)	522	187 (62.1)	364
Muscular weakness	9 (1.5)	9	17 (5.6)	20
Pathological fracture	22 (3.7)	25	15 (5.0)	17
Neoplasms benign, malignant and unspecified				
(including cysts and polyps)	100 (16.7)	112	58 (19.3)	68
Malignant neoplasm progression	77 (12.8)	80	44 (14.6)	47
Nervous system disorders	170 (28.3)	262	115 (38.2)	175
Dizziness	43 (7.2)	51	26 (8.6)	30
Spinal cord compression	25 (4.2)	25	23 (7.6)	24
Psychiatric disorders	87 (14.5)	109	55 (18.3)	68
Insomnia	27 (4.5)	28	21 (7.0)	21
Renal and urinary disorders	108 (18.0)	168	60 (19.9)	87
Haematuria	30 (5.0)	36	15 (5.0)	18
Urinary retention	25 (4.2)	27	18 (6.0)	21
Respiratory, thoracic and mediastinal disorders	118 (19.7)	166	58 (19.3)	96
Dyspnoea	49 (8.2)	58	26 (8.6)	27

The incidence of subjects who experienced a Grade 3 or 4 TEAE was higher in the placebo group (62.5%, 188/301), compared to the Radium-223 group (56.5%, 339/600). The Grade 3 or 4 TEAEs with the highest proportion of subjects were bone pain (20.8%, 125/600 Radium-223; 25.6%, 77/301 placebo) and anaemia (12.8%, 77/600 Radium-223; 13.0%, 39/301 placebo).

Table 23 below summarises the Adverse Drug Reactions (ADRs) for Xofigo.

Table 23. Adverse drug reactions (ADRs) reported in patients treated with radium-223 chloride, study BC1-06

MedDRA 14.1 System Organ Class	MLG / PT	**Radium-223 dichloride** N = 600	**Placebo** N = 301
Blood and lymphatic system disorders	Thrombocytopenia	11.5%	5.6%
	Neutropenia	5.0%	1.0%
	Leukopenia	4.2%	0.3%
	Pancytopenia	2.0%	0%
	Lymphopenia	0.8%	0.3%
Gastrointestinal disorders	Nausea	35.5%	34.6%
	Diarrhea	25.0%	15.0%
	Vomiting	18.5%	13.6%
General disorders and administration site conditions	Injection site reactions (incl. erythema, pain and swelling)	1.2 %	0%

MLG: MedDRA Labeling Grouping

Adverse Events of special interest (AESI) included injection site reactions, new primary malignancies, thrombocytopenia and neutropenia, osteonecrosis of the jaw and eye disorders.

Grade 1 and 2 injection site reactions, such as erythema, pain and swelling, were reported in 1.2% of patients treated with Xofigo and in 0% of patients receiving placebo, in the pivotal study.

Like any other radiation therapy, Xofigo contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Overall none of the 12 cases of primary cancers observed during the clinical development (8 of them in BC1-06) were considered likely primarily due to radium-223 chloride.

Thrombocytopenia (all grades) occurred in 11.5% of patients treated with Xofigo and 5.6% of patients receiving placebo. Grade 3 and 4 thrombocytopenia was observed in 6.3% of patients treated with Xofigo and in 2% of patients receiving placebo. Overall, the frequency of grade 3 and 4 thrombocytopenia was lower in patients that did not previously receive docetaxel (2.8% in patients treated with Xofigo versus 0.8% in patients receiving placebo) compared to patients that previously received docetaxel (8.9% in patients treated with Xofigo versus 2.9% in patients receiving placebo).

Neutropenia (all grades) was reported in 5% of patients treated with Xofigo and in 1% of patients receiving placebo. Grade 3 and 4 neutropenia was observed in 2.2% of patients treated with Xofigo and in 0.7% of patients receiving placebo. Overall, the frequency of grade 3 and 4 neutropenia was lower in patients that did not previously receive docetaxel (0.8% in patients treated with Xofigo versus 0.8% in patients receiving placebo) compared to patients that previously received docetaxel (3.2% in patients treated with Xofigo versus 0.6% in patients receiving placebo).

In the pivotal study, the incidence rate of osteonecrosis of the jaw (ONJ) was 0.67% (4/600 patients) in the radium-223 chloride group compared to 0.33% (1/301 patients) in the placebo group. No other cases of ONJ were reported from other studies. All patients with ONJ were exposed to prior or concomitant zolendronic acid and prior chemotherapy.

Due to the observation of retinal detachment in dogs, eye disorders were of special interest during the clinical development. In the pivotal study, 2 patients (1 in each treatment group) experienced an SAE categorized as an eye disorder: 1 (0.2%) case of cataract in a radium-223 chloride patient and 1 (0.3%) case of glaucoma in a placebo patient. However, no case of retinal detachment has been reported in clinical trials.

Serious adverse event/deaths/other significant events

Deaths

During the pivotal study, 518 deaths occurred in the safety population: 327 (54.5%) of the included patients died in the radium-223 chloride group and 191 (63.5%) in the placebo group. Overall, 26 (4.3%) patients in the radium-223- chloride group and 22 (7.3%) patients in the placebo group died during the treatment period of the study. The largest proportion of subjects died between 24 weeks and 1 year after their first injection of study drug (22.2% in radium-223 chloride group versus 25.6% in placebo group). During the 3-year follow-up period deaths were balanced between the treatment groups. The rate of patients with at least 1 TEAE leading to death was significantly 16 % in patients within the radium-223 chloride group versus 22.3 % in the placebo group. Most of the deaths observed were reported due to disease progression in 48.2% of patients in the radium-223 chloride group and 49.5% of patients in the placebo group. Skeletal metastases were the most frequent type of prostate cancer-related death (40.7% in radium-223 chloride and 44.9% in placebo), while cardiac disorders were the most common non prostate cancer-related causes of death (2% % in radium-223 chloride and 3% in placebo).

A summary of deaths is presented in Table 24 below.

Table 24. Summary of deaths, study BC1-06

	Radium-223 chloride N = 600	**Placebo** N = 301
Patients who died	327 (54.5%)	191 (63.5%)
During treatment period	26 (4.3%)	22 (7.3%)
During 3-year follow-up period	301 (50.2%)	169 (56.1%)
Prostate cancer-related death	289 (48.2%)	149 (49.5%)
Skeletal metastases	244 (40.7%)	135 (44.9%)
Liver metastases	24 (4.0%)	8 (2.7%)
Lung metastases	10 (1.7%)	2 (0.7%)
Lymph metastases	27 (4.5%)	5 (1.7%)
Brain metastases	15 (2.5%)	5 (1.7%)
Other metastases	35 (5.8%)	13 (4.3%)
Non-prostate cancer-related death	34 (5.7%)	41 (13.7%)
Relationship between death and study treatment		
Probable	0	1 (0.3%)
Possible	8 (1.3%)	0
Unrelated	316 (52.7%)	190 (63.1%)
Missing	3 (0.5%)	0
Time to death from first injection		
0 - ≤4 Weeks	4 (0.7%)	4 (1.3%)
4 - ≤8 Weeks	12 (2.0%)	8 (2.7%)
8 - ≤12 Weeks	12 (2.0%)	9 (3.0%)
12 - ≤16 Weeks	16 (2.7%)	19 (6.3%)
16 - ≤20 Weeks	20 (3.3%)	18 (6.0%)
20 - ≤24 Weeks	26 (4.3%)	11 (3.7%)
24 Weeks - ≤1 Year	133 (22.2%)	77 (25.6%)
1 Year - ≤2 Years	91 (15.2%)	42 (14.0%)
>2 Years	11 (1.8%)	3 (1.0%)
Missing	2 (0.3%)	0

Serious adverse events (SAEs)

In the pivotal study BC1-06 the number of patients with any SAE was 46.8% in the radium-223 group versus 60.1% in the placebo group.

The most common (≥5% in either group) treatment-emergent SAEs were: bone pain (10.0% radium-223 chloride; 16.3% placebo), malignant neoplasm progression (11.0% radium-223 chloride; 12.0% placebo), anaemia (8.2% radium-223 chloride; 8.6% placebo) and spinal cord compression (3.5% radium-223 chloride; 5.3% placebo). The main difference seen between the treatment groups where the highest occurrence was in the radium 223 chloride group was thrombocytopenia (2.3% radium-223 chloride; 1.0% placebo).

The following events were reported more frequently in the placebo group: bone pain (10.0% radium-223 chloride; 16.3% placebo), fatigue (1.0% radium-223 chloride; 3.0% placebo), pathological fracture (2.3% radium-223 chloride; 3.7% placebo), and spinal cord compression (3.5% radium-223 chloride; 5.3% placebo).

Treatment-emergent SAEs considered by the investigator to be related to study treatment were experienced by 72 subjects (12.0%) in the radium-223 chloride group and 30 subjects (10.0%) in the placebo group. The treatment-emergent SAEs considered related to study drug reported by ≥ 1% of subjects in both groups were: anaemia (6.0% radium-223 chloride; 3.7% placebo), thrombocytopenia (1.8% radium-223 chloride; 1.0% placebo) and bone pain (1.0% radium-223 chloride; 2.0% placebo).

SAEs of thrombocytopenia occurred in higher rates for patients in both treatment groups who received external beam radiation to bone. SAEs rates of nausea, vomiting, and diarrhoea were two- to three-fold higher for the radium-223 chloride group who received EBRT compared with those who did not receive EBRT.

Laboratory findings

A summary of haematology values after start of treatment to end-of-treatment (EOT) and from EOT to 1 year is presented in Table 25 below.

Table 25. Haematology – Nadir value after start of study treatment by CTCAE severity grade, Safety population

		From start of study treatment to EOT[a]		From EOT[a] to 1 year	
Parameter	CTCAE severity grade for nadir value	Alpharadin (N=600) n (%)	Placebo (N=301) n (%)	Alpharadin (N=427) n (%)	Placebo (N=196) n (%)
Hemoglobin (g/dL)	N	586	286	408	173
	Normal	33 (5.6)	24 (8.4)	11 (2.7)	11 (6.4)
	Grade 1	345 (58.9)	165 (57.7)	208 (51.0)	90 (52.0)
	Grade 2	176 (30.0)	81 (28.3)	138 (33.8)	60 (34.7)
	Grade 3	24 (4.1)	15 (5.2)	40 (9.8)	11 (6.4)
	Grade 4	8 (1.4)	1 (0.3)	11 (2.7)	1 (0.6)
	Grade 5	0	0	0	0
	Missing[b]	14	15	19	23
White Blood Cells ($\times 10^9$/L)	N	586	286	407	173
	Normal	378 (64.5)	256 (89.5)	290 (71.3)	146 (84.4)
	Grade 1	113 (19.3)	28 (9.8)	66 (16.2)	16 (9.2)
	Grade 2	77 (13.1)	2 (0.7)	40 (9.8)	8 (4.6)
	Grade 3	17 (2.9)	0	9 (2.2)	3 (1.7)
	Grade 4	1 (0.2)	0	2 (0.5)	0
	Grade 5	0	0	0	0
	Missing[b]	14	15	20	23
Neutrophils (Absolute) ($\times 10^9$/L)	N	584	285	404	167
	Normal	484 (82.9)	272 (95.4)	361 (89.4)	152 (91.0)
	Grade 1	46 (7.9)	8 (2.8)	16 (4.0)	6 (3.6)
	Grade 2	42 (7.2)	5 (1.8)	16 (4.0)	6 (3.6)
	Grade 3	9 (1.5)	0	9 (2.2)	2 (1.2)
	Grade 4	3 (0.5)	0	2 (0.5)	1 (0.6)
	Grade 5	0	0	0	0
	Missing[b]	16	16	23	29
Lymphocytes (Absolute) ($\times 10^9$/L)	N	584	284	402	168
	Normal	168 (28.8)	129 (45.4)	111 (27.6)	80 (47.6)
	Grade 1	117 (20.0)	76 (26.8)	89 (22.1)	40 (23.8)
	Grade 2	182 (31.2)	59 (20.8)	121 (30.1)	33 (19.6)
	Grade 3	115 (19.7)	19 (6.7)	78 (19.4)	13 (7.7)
	Grade 4	2 (0.3)	1 (0.4)	3 (0.7)	2 (1.2)
	Grade 5	0	0	0	0
	Missing[b]	16	17	25	28
Platelets ($\times 10^9$/L)	N	586	286	407	173
	Normal	408 (69.6)	222 (77.6)	271 (66.6)	129 (74.6)
	Grade 1	131 (22.4)	49 (17.1)	81 (19.9)	31 (17.9)
	Grade 2	32 (5.5)	10 (3.5)	24 (5.9)	5 (2.9)
	Grade 3	12 (2.0)	4 (1.4)	19 (4.7)	7 (4.0)
	Grade 4	3 (0.5)	1 (0.3)	12 (2.9)	1 (0.6)
	Grade 5	0	0	0	0
	Missing[b]	14	15	20	23

No trends in the changes in median values and no differences between the treatment groups for alanine transaminase (ALAT / ALT), aspartate transaminase (ASAT / AST), total bilirubin and creatinine. Albumin

median values showed a small decrease over time in both treatment groups but the changes observed were not clinically meaningful.

Safety in special populations

The safety of radium-223 chloride in children and adolescents below 18 years of age has not been studied.

In the pivotal study, 447 patients (74.5%) were 65 years of age and over, while 196 patients (32.7%) were 75 years of age and over. No overall differences in safety were observed between elderly (aged ≥65 years) and younger patients (aged <65 years) in the pivotal study population.

Safety of radium-223 chloride has not been studied in patients with hepatic impairment.

In the pivotal study no relevant differences in safety were observed between patients with mild renal impairment and those with normal renal function. Only limited data is available on patients with moderate renal impairment. No data are available on patients with severe renal impairment or end-stage renal disease.

Safety related to drug-drug interactions and other interactions

Please refer to the discussion on clinical pharmacology.

Discontinuation due to adverse events

Treatment-emergent adverse events that led to permanent discontinuation of study treatment were experienced by a total of 16.5% (99/600) patients in radium 223 chloride group and 20.6% (62/301) patients in the placebo group (see Participant flow in the pivotal study Study BC1-06).

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

Safety evaluation in the clinical development programme of radium-223 chloride was appropriate in all trials submitted and allows an adequate safety assessment. The study design and the sample size of the pivotal trial of the pivotal phase 3 trial BC1-06 is acceptable. With respect to safety aspects, no general doubts about the quality of the submitted data was raised; in general missing safety data was not an issue of concern in this application and all limitations resulting from missing exposure due to exclusion criteria are adequately covered in the product information.

As usual in the advanced cancer setting, nearly all patients had adverse events and almost all adverse events could be manifestations of the disease itself. Until the end-of-treatment period, TEAES, SAEs, discontinuations due to TEAEs and mortality were consistently in favour of radium-223-chloride.

A total of 93% (558/600) of patients in the radium-223 chloride group and 96.3% (290/301) of patients in the placebo group reported treatment emergent adverse events (TEAEs). The difference in favour of radium-223 chloride is even larger for the SAE event rate, were in the radium-223 chloride group only 46.8% (281/600) of the patients experienced serious TEAEs in comparison to 60.1% (181/301) in the placebo group.

The incidence of subjects who experienced a Grade 3 or 4 TEAE was higher in the placebo group (62.5%, 188/301), compared to the radium-223 group (56.5%, 339/600). The Grade 3 or 4 TEAEs with the highest frequency were bone pain (20.8%, 125/600 Radium-223; 25.6%, 77/301 placebo) and anaemia (12.8%, 77/600 Radium-223; 13.0%, 39/301 placebo).

Mortality was also lower in the radium-223 group: overall, 4.3% (26/600) of patients in the radium-223-chloride group and 7.3% (22/301) in the placebo group died during the treatment period of the study. The largest proportion of subjects died between 24 weeks and 1 year after their first injection of study drug (radium-223:22.2%, 133/600 versus placebo: 25.6%, 77/301). With respect to safety as a primary endpoint, it seems interesting that again the rate of patients with patients with at least 1 TEAE leading to death was significantly lower in patients within the radium-223 chloride group (16 %) versus 22,3 % in the placebo group.

With respect to drug-related adverse events the following specific TEAEs were identified and observed with a notably higher frequency in the active group than in the placebo group: Diarrhoea (25.2% versus 15.0%), thrombocytopenia (11.5% versus 5.6%) and neutropenia (5.0% versus 1.0%).While diarrhoea may reflect direct radiation effect on the intestine surface cells during excretion, thrombocytopenia, neutropenia and lymphocytopenia as well as anaemia may be caused by radiation effect on the bone marrow. Most of diarrhoea, nausea and vomiting adverse events were of Grade 1 or 2. Higher-grade drug related events were mainly observed with thrombocytopenia, neutropenia and anaemia. Most of those patients were pre-treated with docetaxel and/or EBRB, which may have contributed to the SAE. However, higher frequencies for thrombocytopenia and neutropenia/leukopenia did not result in an increased rate of haemorrhages or infections, which indicates that acute toxicity is manageable in clinical practice.

Therefore, haematological evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Before the first administration, the absolute neutrophil count (ANC) should be ≥ 1.5 x 109/l, the platelet count ≥ 100 x 109/l and haemoglobin ≥ 10.0 g/dl. Before subsequent administrations, the ANC should be ≥ 1.0 x 109/l and the platelet count ≥ 50 x 109/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 e.g. following prior cytotoxic chemotherapy and/or radiation treatment should be treated with caution.

Bone radiation with radium-223 may increase the general risk for osteonecrosis, in particular in combination with bisphosphonate treatment. About 1 % of the target population develops osteonecrosis of the jaw (ONJ) if treated with zoledronic acid for bone metastases. The rate of ONJ in the radium-223 chloride group was (0,67%). It was concluded that radium-223 appeared not to increase the overall rate of ONJ in the target population treated. However, data were considered inconclusive due to the overall limited low event rate and relatively small study population for an event of such frequency. A warning is included in the SmPC aiming to clarify that radium-223 chloride may increase the rate of osteonecrosis of the jaw (ONJ) in particular in combination with zoledronic acid and previous cytostatic treatment.

Active inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease, acute intestinal infections) may increase the risk for septic complications or intestinal perforation upon treatment with radium-223. This is because excretion of radium-223 is mainly via the gastrointestinal system, which leads to a high local radiation activity on intestine mucosa and might exacerbate pre-existing intestinal damage. Xofigo should only be administered after a careful benefit-risk assessment in patients with acute inflammatory bowel disease (see SmPC section 4.4).

In patients with untreated imminent or established spinal cord compression, treatment with standard of care, as clinically indicated, should be completed before starting or resuming treatment with Xofigo.

Similarly, in patients with bone fractures, orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with Xofigo (see SmPC section 4.4).

Cases of retinal detachment were observed only in dogs as a late complication during the non-clinical studies, but no cases were observed in the clinical studies (see discussion on Non-clinical aspects).

The proposed injection duration (generally up to 1 minute) takes into consideration avoidance of injection site reactions and radiation protection for the clinical personnel. Injection site reactions with erythema, pain and swelling (all Grade 1 or 2) were observed in only 1.2% of patients (see SmPC section 4.8).

Overall, drug-related adverse events reported were manageable during the study.

Acute toxicity is deemed favourable in comparison to cytostatic drugs like docetaxel, which is also used in the target population. It was clarified that supportive therapy with blood components and growth factors was balanced between the groups.

The development of secondary malignancy, in particular osteosarcoma, and diseases of the hematopoietic tissues, such as myelodysplasia, aplastic anaemia, and myeloid leukaemias are known long-term risks during treatment with alpha-particle emitter radium-224 as a pharmacological class effect. A similar alpha particle emitter product (radium-224) was licensed for treatment of juvenile ankylosing spondylitis in Germany until 2000, when it was withdrawn from the market due to the long-term safety concern. At that time a cohort study found that after a mean follow-up time of 26 years (n=1006) in the exposed group or 25 years (n=1072) in a control group, 19 cases of leukaemia were observed in the exposure group (vs. 6.8 cases expected<0.001) compared to 12 cases of leukaemia in the control group (vs. 7.5 cases expected). The leukaemia developed after a latency time between 15 to 33 years. Insofar, this safety concern has not the same relevance in the target population of patients with castration-resistant prostate cancer patients with bone metastases, since the life-expectancy of these patients is much shorter. No case of haematologic malignancy occurred in the clinical development programme and also no case of osteosarcoma was observed. In total, 16 cases of other primary cancers were reported during the clinical development programme (12 of them in the pivotal BC1-06 in the updated analysis). However, biodistribution as well as the latency period of radiation-induced malignancies (solid tumours) argue against a strong evidence of causality. Missing information on secondary malignancies is included in the RMP and a warning on secondary malignancies is included in the SmPC.

Patients with evidence of compromised bone marrow reserve e.g. following prior cytotoxic chemotherapy and/or radiation treatment (EBRT) or prostate cancer patients with advanced diffuse infiltration of the bone (EOD4; “superscan”) should be treated with caution. An increased incidence of haematological adverse reactions such as neutropenia and thrombocytopenia was observed in these patients during the phase III study (see SmPC section 4.4).

The efficacy and safety of cytotoxic chemotherapy performed after treatment with Xofigo has not been established. The limited available data indicates that patients receiving chemotherapy after Xofigo had a similar haematological profile compared to patients receiving chemotherapy after placebo (see SmPC section 4.4).

Because of potential effects on spermatogenesis associated with radiation, men should be advised to use effective contraceptive methods during and up to 6 months after treatment with Xofigo.

Xofigo is not indicated in women. Xofigo is not to be used in women who are, or may be, pregnant or breast-feeding.

There are no human data on the effect of Xofigo on fertility. Based on studies in animals, there is a potential risk that radiation from Xofigo could cause adverse effects on fertility. Male patients should seek advice on conservation of sperm prior to treatment.

Relevant restrictions of study population as well as remaining uncertainties regarding the product's safety profile are adequately reflected in the product information and included in the RMP, respectively.

For all potential risks, routine and enhanced pharmacovigilance activities as well as active surveillance are being and will be conducted.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, radium-223 has an acute toxicity profile which is deemed as relatively favourable. Only drug-related adverse events as thrombocytopenia, neutropenia and diarrhoea and decreased appetite occurred more often in the radiun-223 group.

Moreover, drug-related adverse events were obviously manageable and of lower intensity than those associated with the use of cytostatic drugs (e.g. docetaxel) also used in the target population.

Long-term risks of secondary malignancies (osteosarcoma, haematological disorders) are sufficiently characterised, but no events were reported during the clinical development. As overall frequency of secondary malignancies was very low, the study population is not large enough to clarify these issues adequately. Further exploration is included in the RMP and a warning regarding the possibility of secondary malignancies is included in the product information. In general, biodistribution of radium-223 chloride and latency times known for radium products seems to exclude a clinical relevant risk for the CRPC target population at present, since this advanced cancer population has a limited life-expectancy, which seems not to overlap with the reported latency times.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk-management plan

The CHMP received the following PRAC advice on the submitted risk-management plan.

PRAC advice

Based on the PRAC review of the Risk Management Plan version 1.3, the PRAC considers that the risk management system for radium-233 (XOFIGO) in the treatment of castration-resistant prostate cancer patients with bone metastases is approvable.

This advice is based on the following content of the Risk Management Plan.

Safety concerns

The applicant identified the following safety concerns in the RMP to which the PRAC agreed.

Table 26. Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Bone marrow toxicity leading to reduction in formed elements in blood
Important potential risks	Late bone marrow toxicity Myelodysplastic syndrome/Acute myeloid leukaemia (MDS/AML) Bone sarcoma Secondary malignancies (other than MDS/AML and bone sarcoma) Osteonecrosis of the jaw Off-label use in women and 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	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

Pharmacovigilance plans

Table 27. Ongoing and planned studies in the post-authorisation pharmacovigilance development plan

Study / Activity	**Objective**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final report**
BC1-06 A double-blind, randomised, multiple dose, Phase III,	**Primary Objective:** To compare, in patients with symptomatic hormone refractory prostate cancer	- Late bone marrow toxicity - MDS/AML	Ongoing	2015

Study / Activity	Objective	Safety concerns addressed	Status	Date for submission of interim or final report
multicentre study of Alpharadin in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases	(HRPC) and skeletal metastases, the efficacy of best standard of care plus Alpharadin versus best standard of care plus placebo, with the primary efficacy endpoint being overall survival (OS). **Secondary Objectives:** To compare, in patients with symptomatic HRPC and skeletal metastases receiving either best standard of care plus Alpharadin versus best standard of care plus placebo: • Time to occurrence of specified disease events • Changes and time to progression in serum prostate specific antigen and total alkaline phosphatase concentrations • The acute and long term safety profile • Quality of life • Health economics	- Bone sarcoma - Second primary malignancies (other than MDS/AML and bone sarcoma)		
15995 – Early Access Programme Radium-223 dichloride in Castration-Resistant (Hormone-Refractory) Prostate Cancer Patients with Bone Metastases	- To provide radium-223 dichloride to patients diagnosed with CRPC/HRPC with symptomatic bone metastasis - To assess the acute and long-term safety of radium-223 dichloride	- Late bone marrow toxicity - MDS/AML - Bone sarcoma - Second primary malignancies (other than MDS/AML and bone sarcoma)	Ongoing	End 2015
16216 - Early Access	- To assess the acute and long-term safety of	- Late bone	Ongoing	End 2015

Study / Activity	Objective	Safety concerns addressed	Status	Date for submission of interim or final report
Programme Radium-223 dichloride in Castration-Resistant (Hormone-Refractory) Prostate Cancer Patients with Bone Metastases	radium-223 dichloride - To assess the overall survival of this patient population	marrow toxicity - MDS/AML - Bone sarcoma - Second primary malignancies (other than MDS/AML and bone sarcoma)		
16913 – Observational PASS Long Term Safety of radium-223 in Castrate Resistant Prostate Cancer (CRPC) patients with bones metastasis in Routine Clinical Practice Settings	To assess the long term safety profile and risks of developing second primary malignancies and their potential relationship to radium-223 in the routine clinical practice setting	Late bone marrow toxicity MDS/AML Bone sarcoma Second primary malignancies (other than MDS/AML and bone sarcoma) Osteonecrosis of the jaw	Planned	Final draft protocol: October 2013 Submission to PRAC: End of October 2013 Study initiation: Q1/2014 1st Interim Report: End 2017 2nd Interim Report: End 2019 Final report: End 2024
Drug utilisation study of radium-223 using Swedish Registers	Determine the extent of off-label use of radium-223 in women and children Determine the extent of off-label use of repeated courses of treatment, or other administration of doses in excess of those	Off-label use in women or children Off-label administration of repeated courses of treatment, or other	In preparation	Final draft protocol: End of December 2013 Submission to PRAC:

Study / Activity	Objective	Safety concerns addressed	Status	Date for submission of interim or final report
	recommended in the product information	administration of doses in excess of those recommended in the product information		January 2014 Study initiation: June 2014 Final Report: End 2017

The PRAC, having considered the data submitted, was of the opinion that the proposed pharmacovigilance plan is sufficient to characterise the risk of the product.

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 28. Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Bone marrow toxicity leading to reduced formed elements in blood	*(Proposed) text in SmPC:* Warning and Precautions Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, has been reported in patients treated with Xofigo (see section 'Undesirable effects'). Therefore, haematological evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Before the first administration, the absolute neutrophil count (ANC) should be ≥1.5 x 10^9/L, the platelet count ≥100 x 10^9/L and haemoglobin ≥10.0 g/dL. Before subsequent administrations the ANC should be ≥ 1.0 x 10^9/L and the platelet count ≥50 x 10^9/L. In case there is no recovery to 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 e.g. following prior cytotoxic chemotherapy and/or radiation treatment (EBRT) or prostate cancer patients with advanced diffuse infiltration of the bone (EOD4; "superscan") should be treated with caution. Thrombocytopenia is listed as a very common adverse drug reaction (ADR), and neutropenia, pancytopenia and leukopenia are listed as common ADRs in Section 4.8 Undesirables effects in the SmPC. Instructions for use / handling Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings.	None

Late bone marrow toxicity	*(Proposed) text in SmPC:* Warning and Precautions Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, has been reported in patients treated with Xofigo (see section 'Undesirable effects'). Therefore, haematological evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Before the first administration the absolute neutrophil count (ANC) should be ≥1.5 x 10^9/L, the platelet count ≥100 x 10^9/L and haemoglobin ≥10.0 g/dL. Before subsequent administrations the ANC should be ≥1.0 x 10^9/L and the platelet count ≥50 x 10^9/L. In case there is no recovery to 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 e.g. following prior cytotoxic chemotherapy and/or radiation treatment (EBRT) or prostate cancer patients with advanced diffuse infiltration of the bone (EOD4; "superscan") should be treated with caution. Instructions for use / handling Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings.	None
Myelodysplastic syndrome, Acute myelogenous leukaemia	*(Proposed) text in SmPC:* Undesirable effects: Radium-223 contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Instructions for use / handling Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings.	None
Bone sarcoma	*(Proposed) text in SmPC:* Undesirable effects: Radium-223 contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Instructions for use / handling Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings.	None

Secondary malignancies (other than bone sarcoma and myelodysplastic syndrome, acute myelogenous leukaemia)	*(Proposed) text in SmPC:* Undesirable effects: Radium-223 contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Instructions for use / handling Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings.	None
Osteonecrosis of the jaw	*(Proposed) text in SmPC* Warning and Precautions: Osteonecrosis of the jaw: In patients treated with bisphosphonates and Xofigo, an increased risk of development of osteonecrosis of the jaw (ONJ) cannot be excluded. In the phase III study, cases of ONJ have been reported in 0.67% (4/600) patients in the Xofigo arm compared to 0.33% (1/301) patients in the placebo arm. However, all patients with ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid) and prior chemotherapy (e.g. docetaxel).	None
Off-label use in women and children	*(Proposed) text in SmPC:* Therapeutic indication: Xofigo is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases. Paediatric population: The safety and efficacy of Xofigo in children and adolescents below 18 years of age have not been studied. There is no relevant use of this medicinal product in the paediatric population in the indication of prostate cancer. Pregnancy and breast-feeding: Xofigo is not indicated in women. Xofigo is not to be used in women who are, or may be, pregnant or breast-feeding.	None
Off-label administration of repeated courses of treatment, or other administration of doses in excess of those recommended in the product information	*(Proposed) text in SmPC:* Posology: The dose regimen of Xofigo is 50 kBq per kg body weight, given at 4 week intervals for 6 injections. Safety and efficacy beyond 6 injections with Xofigo have not been studied.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-risk balance

Benefits

Beneficial effects

In the single pivotal study in patients with symptomatic bone metastases from castration-resistant prostate cancer without visceral metastases overall survival was longer in the radium-223 group by 2.8 months during the pre-specified interim analysis (HR 0.695, 95% CI 0.552-0.875, p=0.00185). The results were consistent at an updated OS analysis performed with later cut-off, with a total difference of 3.6 months in favour of radium-223(HR 0.695, 95% CI 0.581-0.832, p=0.00007). Treatment effect on OS was robust after adjustment for stratification factors and was consistently favourable across all subgroups.

The beneficial effect on survival was supported by the secondary endpoints. Overall, treatment of patients with radium-223 delayed and in some aspects also reduced the occurrence of unfavourable events. The composite endpoint symptomatic skeletal events favoured the radium-223 group with the first SRE occurring 5.8 months later (HR 0.658, 95% CI 0.552-0.830, p=0.00037). The most frequent component of SRE was external beam radiotherapy (EBRT), which in itself was supporting the palliative effect of radium-223. There was a clear effect in terms of time to total ALP progression (7.4 vs. 3.8 months, HR 0.167, 95% CI 0.129-0.217, p<00001), response (e.g. confirmed 50% reduction: 27.2% vs. 0% in the updated analysis) and normalisation at week 12 (34% vs. 1.4%) all in favour of the radium-223 group.

The effect on PSA as a marker of tumour progression showed only a marginal effect. Median time to PSA progression paralleled treatment (3.6 vs. 3.4 months, i.e. mid-treatment) and confirmed reductions in PSA by 50% occur in only 5% of patients in the radium-223 group compared to less than 2% in the placebo group. The rather limited effect on PSA was in line with the presumed mode of action, i.e. cytotoxic radiation on a thin peripheral part of bone metastases. Support for a palliative effect of radium-223 was derived from the following further secondary endpoints such as time-to-further anticancer treatment, and (time-to) other radionuclides or marked deterioration of performance status.

Uncertainty in the knowledge about the beneficial effects

The imbalance (8% absolute) with respect to non-prostate-cancer related deaths in the placebo group in the pivotal trial clearly in favour of the Xofigo treatment group appeared to contribute to the increasing difference in overall survival in the updated analysis. It remains currently unclear whether or to what extent this might reflect an unusual and not understood beneficial treatment effect on putatively not cancer-related death (i.e. difficulties to distinguish disease-related from not disease related death) or more likely whether the difference in non-prostate-cancer related deaths was a consequence of an imbalanced distribution of disease stages at randomisation (i.e. more patients with less advanced disease in the Xofigo group). Heterogeneity in baseline characteristics is expected due to the subjective nature of

the definition of eligibility for docetaxel treatment with unknown distribution between study arms. Best standard of care was an oncologist's choice with overall acceptable choice of palliative treatment regimen. No common back-bone treatment was used. Of note, there is potential impact of co-medication on endpoints such as PSA response or symptomatic skeletal events. Imbalances in co-medication over the study period, especially after the treatment phase, increase the uncertainty regarding the magnitude or the maintenance of the beneficial effect with respect to SREs. In view of selection processes in the trial, it is difficult to differentiate these confounders from a true treatment effect. However, the possible impact of these factors does not put the OS results into question, in view of the large treatment effect. Furthermore, the exploratory analyses of survival adjusted for important prognostic factors showed a consistent treatment effect. Thus, important bias due to imbalances in prognostic factors is considered unlikely. The additional analyses provide sufficient reassurance about a robust beneficial effect on overall survival with some remaining uncertainty regarding the exact quantification.

The pivotal study was the first study of a bone-targeted agent resulting in a prolongation of survival. Radium-223 forms complexes with the bone mineral hydroxyapatite, which is enriched in areas of bone turnover, e.g. bone metastases and releases cytotoxic radiation to adjacent cells. While the mode of action on bone metastasis is plausible and a delay in symptomatic SRE is clearly demonstrated, the exact mechanism of action of prolonging overall survival in the absence of a demonstrated effect on PFS/TTP remains elusive. A direct anti-tumour effect has not been demonstrated. In addition to the endpoints overall survival and symptomatic skeletal events, patients were only followed by serum markers, which were measured at the local laboratories, potentially introducing significant variability. Serum markers do not represent a clinical benefit experienced by patients. Radiographic assessments in order to ascertain disease progression, either in bone or in extra-osseous tissues, were not collected. In any case, despite the uncertainties about the exact mechanism of action, this does not put the OS results into question in view of the statistically significant and clinically relevant effect observed.

The endpoint time to symptomatic skeletal events was dominated by the time to first EBRT with the highest incidence in all patients. The impact on the other skeletal-related events was associated with a higher degree of uncertainty in view of the low event rate. Competing risks may have played a role especially for late-occurring events. An impact of co-medication (such as steroids or bisphosphonates) on symptomatic skeletal events could not be entirely ruled out. It is unlikely, however, that the entire magnitude of delay of skeletal-related events is due to baseline imbalances. Thus, the effect on symptomatic skeletal events is overall considered supportive of the effect on OS.

There was an excess of use of bisphosphonates reported in the experimental arm during the follow-up phase, maybe contributing to the maintenance of the beneficial effect. An increase in the time until the need for other cancer treatments was observed with Xofigo (16.2 months vs. 13.5 months). Limited survival data after chemotherapy were indicative of neither a benefit nor a disadvantage for patients having received radium-223 previously. The effect of post-progression treatments is generally difficult to ascertain. Regardless of such effect, this does not put the OS results into question in view of the statistically significant and clinically relevant effect observed.

The effect on quality of life was marginal and results were not consistent between the pivotal trial and supportive studies. Uncertainty remained also with respect to the maintenance of the palliative effect of radium-223 after end-of-treatment. Pain and performance status seemed to deteriorate quickly after end of treatment. Compliance with questionnaires on quality of life became critically low after the end of treatment. However, even without a demonstrated positive effect on this secondary endpoint, the efficacy can be considered established.

Finally, at the time when the pivotal study was started, a placebo controlled trial could be regarded as acceptable, when overall survival was the primary endpoint. During the conduct of the pivotal clinical trial of radium-223, only docetaxel was authorised as first-line treatment of metastatic CRPC based on a

prolongation of survival by 2-3 months at the cost of significant toxicity. The pivotal study for this application was an add-on to best standard of care for patients not eligible for or not willing to receive docetaxel. Almost 60% of patients had already received docetaxel. Nowadays several new drugs were authorised and it becomes difficult to put the life-prolonging effect of a bone-specific agent into perspective. Although the efficacy of radium-233 has been established, there is no head-to-head comparison that would show how radium-223 compares to products for systemic treatment of prostate cancer or to the effect of other bone-targeted radionuclides.

Risks

Unfavourable effects

Radium-223 has relatively mild acute haematological and gastrointestinal toxicity. Furthermore long-term risks are known pharmacological class effects in the form of an increase rate of secondary malignancies.

With respect to drug-related adverse events the following specific TEAEs were identified and observed with a notably higher frequency in the active group than in the placebo group: Diarrhoea (25.2% versus 15.0%), thrombocytopenia (11.5% versus 5.6%) and neutropenia (5.0% versus 1.0%).

While diarrhoea may reflect direct radiation effect on the intestine surface cells during excretion, thrombocytopenia, neutropenia and lymphocytopenia as well as anaemia may be caused by radiation effect on the bone marrow. Most of diarrhoea, nausea and vomiting adverse events were of Grade 1 or 2. Higher-grade drug related events were mainly observed with thrombocytopenia, neutropenia and anaemia. Most of those patients were pre-treated with docetaxel and/or EBRT, which may have contributed to the SAE. However, higher frequencies for thrombocytopenia and neutropenia/leukopenia did not result in an increased rate of haemorrhages or infections, which indicates that acute toxicity is manageable in clinical practice.

Patients with Crohn's disease or ulcerative colitis were excluded from the pivotal study. This is currently mentioned in a special warning. Due to the local radiation during faecal excretion the risk for complication in inflammatory bowel diseases (e.g. toxic megacolon and sepsis) seems high. Appropriate warnings have been included in the SmPC and PL and the issue has been adequately addressed in the RMP.

Bone radiation with radium-223 may increase the general risk for osteonecrosis; in particular in combination with bisphosphonate treatment the risk for osteonecrosis of jaw (ONJ) the risk may increase. In prostate cancer patients treated with zoledronic acid for bone metastases the rate for development of ONJ is about 1 %. In Study BC1-06, the incidence rate of osteonecrosis was higher in the radium-223 chloride group, (0.67%), compared to (0.33%) in the placebo group. However, data were considered inconclusive due to the overall limited low event rate and relatively small study population for an event of such frequency. A warning is included in the SmPC aiming to clarify that radium-223 chloride may increase the rate of osteonecrosis of the jaw (ONJ) in particular in combination with zoledronic acid and previous cytostatic treatment.

Injection site reactions with erythema, pain and swelling (all Grade 1 or 2) were infrequent and are not a matter of particular concern due to concomitant risk from the injection procedure itself and acceptable local tolerability results for the drug.

Uncertainty in the knowledge about the unfavourable effects

The overall safety profile of radium-223 until end-of-treatment seemed to be in favour of the active treatment compared to placebo. Rates of TEAES, SAEs, discontinuations due to TEAEs and mortality were consistently lower in the radium-223-group. This finding was deemed implausible in an add-on study and

indicative of imbalances between study arms, unless unknown indirect effects of the treatment or an inadequate differentiation between disease-related and not disease-related events would be presumed. Due to imbalances at baseline, the rate of all safety events might have been higher in the radium-223 group than currently observed. Nevertheless, it is unlikely that such imbalances would significantly change the observed toxicity profile. The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

Safety and efficacy of concomitant cytostatic chemotherapy on top on radium 223 chloride has not been established. Data on safety in patients receiving chemotherapy after treatment with radium-therapy, in patients with concomitant EBRT to bone, in patients with concomitant EBRT to prostate, and safety in repeated use are limited or not available (see SmPC section 4.4).

In total, 16 cases of other primary cancers were reported during the clinical development programme (12 of them in the pivotal BC1-06 in the updated analysis). However, biodistribution as well as the latency period of radiation-induced malignancies (solid tumours) argue against a strong evidence of causality. Missing information on secondary malignancies is included in the RMP and a warning on secondary malignancies is included in the SmPC.

Cases of retinal detachment were observed only in dogs during the non-clinical studies, but not in the investigated target population. Due to the limited number of patients the overall relevance of this result remains inconclusive, but will be monitored in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

Radium-223 is the first bone targeted therapy which demonstrated a survival benefit (3.6 months) over placebo to date. This magnitude is regarded as clinically meaningful in advanced cancer stages. Although uncertainties with regard to baseline imbalances and possible confounding effects of co-medication remain, important bias seems unlikely.

The effect on SRE is considered clinically relevant: less patients in the radium-223 group experienced a SRE and time to first SRE was clinically significantly longer with 6 months difference. All aspects of the composite endpoint SRE are referring to clinically relevant issues and there is a consistent effect in three of four aspects of the composite endpoint, with EBRT being the dominant component.

The difference in symptoms, e. g. with respect to pain as also demonstrated by the delay SRE, contributes strongly to the immediate benefits for the patient.

In prostate cancer non-prostate-cancer deaths are a relevant competing risk. Due to considerable imbalances in non-prostate-cancer related deaths which can impact the size of the benefit uncertainties remain. A contribution of baseline imbalances or imbalances in co-medication on the magnitude of the effect could not be entirely ruled out. However, based on exploratory analyses adjusted for important prognostic factors, an important bias seems unlikely.

Overall, radium-223 chloride had an acute toxicity profile which was relatively favourable in comparison with the placebo results. Drug-related adverse events (gastrointestinal and haematological ADRS) were obviously manageable and of lower intensity than those associated with the use of cytostatic alternatives (e.g. docetaxel). Long-term risks as secondary malignancies are not of major concern taking into account the life expectancy of the target population of advanced prostate cancer.

Benefit-risk balance

The observed improvement in overall survival together with the observed effect on symptomatic skeletal events is supported by secondary endpoints, e.g. the biomarker ALP reflecting the activity of bone disease. The clinical benefit in terms of survival and palliation for bone metastases has clearly been shown.

In terms of safety profile, the data shown a low acute toxicity (better than most pharmacological anti-cancer therapies) of the product and in addition, although there is a long-term risk for secondary malignancies this is not of major concern taking into account the life expectancy of the target population of advanced prostate cancer. The mild to moderate haematological and gastrointestinal toxicity was manageable.

Overall, the benefits overweigh the risks in patients with castration-resistant prostate cancer with symptomatic bone metastases.

Discussion on the benefit-risk balance

Radium-223 is a novel alpha particle emitter, meant for the treatment of bone metastases of HRPC, bearing the favourable characteristics of having a short ionisation path length that may reduce toxicity to tumour adjacent healthy tissues.

Radium-223 is the first bone target therapy which demonstrated a survival benefit (3.6 months) over placebo. This magnitude is regarded as clinically meaningful in advanced cancer stages. The safety profile of radium-223 is considered sufficiently characterised, the main TAEs being haematological toxicity and gastrointestinal disorders, both manageable and reversible.

From a clinical perspective the benefit in terms of SRE delay and the benefit in OS -even in light of the uncertainties regarding the size of the effect that is truly due to treatment with radium-223- are considered to outweigh the safety risks.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Xofigo in the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic safety update reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New active substance status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that radium-223 chloride is qualified as a new active substance.

References

Beardsley E, Chi K. Low usage of docetaxel among patients with metastatic hormone refractory prostate cancer (HRPC): A population based analysis. Genitourinary Cancers Symposium, 2008 – Abstract 205.

Henriksen G, Breistol K, Bruland OS, Fodstad O, Larsen RH. Significant antitumor effect of bone-seeking, α-particle–emitting ^{223}Ra demonstrated in an experimental skeletal metastases model. Cancer Res. 2002;62:3120-3125.

Henriksen G, Fisher DR, Roeske JC, Bruland OS, Larsen RH. Targeting of osseous sites with α-emitting ^{223}Ra: comparision with the β-emitter ^{89}Sr in mice. J Nucl Med. 2003;44:252-259.

Lloyd RD, Mays CW, Taylor GN, Atherton, DR, Bruenger FW, Jones CW. Radium-244 retention, distribution, and dosimetry in beagles. Radiation Res. 1982;92:280-295.

Morris MJ, Scher HI. Clinical approaches to osseous metastases in prostate cancer. The oncologist, 2003; 8: 161-173.

Soloway MS, Hardeman SW, Hickey D et al. Stratification of Patients With Metastatic Prostate Cancer Based on Extent of Disease on Initial Bone Scan. Cancer 1988; 61: 195-202.