Post-Authorisation Safety Study (PASS) Information

Acronym/title	DIRECT: **D**rug Utilisat**I**on Study of **R**adium 223 Under Routin**E** **C**linical Prac**T**ice in Europe
Protocol version and date	v 2.0, 15 July 2019
IMPACT study number	20702
Study type/study phase	PASS ☒ Joint PASS: ☐ YES ☒ NO
EU PAS Register number	Study not yet registered
Active substance	Various Therapeutic Radiopharmaceuticals (V10XX03), radium (^{223}Ra) dichloride
Medicinal product	Xofigo (Radium-223 (Ra-223))
Product reference	EU/1/13/873/001
Procedure number	EMEA/H/C/002653/MEA/014
Comparator/reference therapy	None
Study initiator and funder	Bayer AG
Research question and objectives	The purpose of this study will be to assess the effectiveness of the risk minimisation measures for radium-223 (Xofigo), that is, to assess compliance with the indications and contraindications introduced in the October 2018 European Union label change as a result of the referral procedure under article 20 of Regulation (EC) No. 726/2004 (Procedure number: EMEA/H/A-20/1459/C/002653/0028): • Therapeutic indications: "Xofigo monotherapy or in combination with luteinising hormone-releasing hormone (LHRH) analogue is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment"

	• Contraindications: "Xofigo is contraindicated in combination with abiraterone acetate and prednisone/prednisolone" The study will evaluate compliance with the new contraindication after label changes regarding use of radium-223 in combination with abiraterone acetate and/or other systemic therapies (except for LHRH analogues) and compliance with restriction of radium-223 to use in patients who have had at least two prior lines of systemic therapy for mCRPC (i.e., third- and fourth-line use). There will be a reference period before the label change where compliance will also be measured and compared with that after the label change. Use of radium-223 as first- or second-line therapy is restricted to patients who are not eligible to receive any other available therapies for mCRPC (other than LHRH analogues). Since eligibility cannot be evaluated in the study databases, use of radium-223 as first- or second-line therapy will be described, but an assessment of whether this use represents on or off-label use is not possible. The main research question will be: 'What proportion of users of radium-223 receive it in compliance with the new indication and contraindication introduced in October 2018?' The primary objective is to estimate, among the population of patients receiving radium-223, (1) the proportion who receive radium-223 in combination with abiraterone acetate; (2) the proportion who receive radium-223 in combination with other systemic therapies for mCRPC; and (3) the proportion who receive radium-223 without having received at least two prior lines of systemic therapy for mCRPC. The secondary objectives are (4) to estimate the difference before and after the label change in the proportions estimated in the primary objective, and (5) to characterise the population of new users of radium-223, irrespective of combination with other systemic therapies for CRPC, by describing the patients' characteristics, including the presence, and when available location, of metastasis on the date of initiation of radium-223 (index date).
Country(-ies) of study	The Netherlands, Denmark, Germany
Author	PPD (RTI Health Solutions), PPD (RTI Health Solutions), and PPD (Bayer Epidemiology), on behalf of the DIRECT team

Marketing authorisation holder

Marketing authorisation holder(s)	Bayer AG
MAH contact person	PPD

The study will be conducted in compliance with the protocol

and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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2. List of abbreviations

ADT	Androgen-Deprivation Therapy
ATC	Anatomical Therapeutic Chemical
CAPRI	Castration-Resistant Prostate Cancer Registry
CRPC	Castration-Resistant Prostate Cancer
CSPC	Castration-Sensitive Prostate Cancer
DIRECT	Drug UtilisatIon Study of Radium 223 Under RoutinE Clinical PracTice in Europe
DNPR	Danish National Patient Register
DUS	Drug Utilisation Study
EBM	Einheitlicher Bewertungsmaßstab
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERA-223	A Phase III Randomised, Double-blind, Placebo-controlled Trial of Radium-223 Dichloride in Combination With Abiraterone Acetate and Prednisone/Prednisolone in the Treatment of Asymptomatic or Mildly Symptomatic Chemotherapy-naïve Subjects With Bone Predominant Metastatic Castration-resistant Prostate Cancer (CRPC)
EU PAS Register	European Union Electronic Register of Post-Authorisation Studies
GePaRD	German Pharmacoepidemiological Research Database
HR	Hazard Ratio
ICD-10	International Classification of Diseases, 10th Revision
ICD-10-GM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification
ICT	Information Communication Technology
IKNL	The Netherlands Comprehensive Cancer Organization
IV	Intravenous
LHRH	Luteinising Hormone-Releasing Hormone
MAH	Marketing Authorisation Holder
mCRPC	Metastatic Castration-Resistant Prostate Cancer
NCR	The Netherlands Cancer Registry
OPS	Operationen und Prozedurenschlüssel
OS	Overall Survival
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PRAC	Pharmacovigilance Risk Assessment Committee

PSUR	Periodic Safety Update Report
QOL	Quality of Life
RCT	Randomised Controlled Trial
RTI-HS	RTI Health Solutions
SHI	Statutory Health Insurance
SOP	Standard Operating Procedure

3. Responsible parties

3.1 Study initiator and funder

Role:	OS Conduct Responsible
Name:	PPD
E-mail:	PPD
Role:	Qualified Person responsible for Pharmacovigilance (QPPV)
Name:	PPD
Role:	OS Safety Lead
Name:	PPD
Role:	OS Clinical Lead
Name:	PPD
Role:	OS Statistician
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Medical Expert Netherlands
Name:	PPD
Role:	OS Market Access Netherlands
Name:	PPD
Role:	OS Epidemiologist
Name:	PPD
Role:	Regulatory Affairs responsible
Name:	PPD

Contact details of the responsible parties at Bayer AG are available upon request.

3.2 Collaborator(s)/external partner(s)/committee(s)

This study will be led by Bayer Epidemiology and conducted in collaboration with data source research institutions in the Netherlands, Denmark, Germany, and a coordinating centre in Spain, who have developed or reviewed the protocol and confirmed interest in participating. The responsible external collaborators are as follows:

- PPD, RTI Health Solutions (RTI-HS) (project coordinators):
  - PPD
  - PPD
  - PPD
  - PPD
- The Castration-Resistant Prostate Cancer Registry (CAPRI) 3.0 (CAPRI 3.0 research partner):
  - PPD
  - PPD
  - PPD
- PPD from the Aarhus University, Denmark (Danish Registries and other Danish data source research partners):
  - PPD
  - PPD
- PPD, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany (German Pharmacoepidemiological Research Database [GePaRD] research partner):
  - PPD

Bayer Epidemiology and the collaborators are responsible for the design, conduct, analysis, and dissemination of the study in a manner that meets regulatory standards. The study shall be conducted as described in the approved protocol.

Administrative changes of responsible persons and/or the composition of the committees will be documented by updating the respective lists but do not require formal protocol amendments.

4. Abstract

Acronym/title	DIRECT: **D**rug Utilisat**I**on Study of **R**adium 223 Under Routin**E** **C**linical Prac**T**ice in Europe
Protocol version and date	v 2.0, 15 July 2019
IMPACT study number	20702
Study type/study phase	Post-market surveillance, Phase 4
Author	PPD (RTI-HS), PPD (RTI-HS), and PPD (Bayer Epidemiology) on behalf of the DIRECT team.
Rationale and background	Radium-223 is a first-in-class alpha particle-emitting, radioactive agent indicated as monotherapy or in combination with LHRH analogue for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases, and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues) or ineligible for any available systemic mCRPC treatment. The ALSYMPCA randomised controlled trial (ERA-223 RCT) compared radium-223 plus best standard of care vs. placebo plus best standard of care. Radium-223 prolonged median overall survival (OS) by 3.6 months (14.9 months vs. 11.3 months) when compared with placebo in patients with mCRPC, symptomatic bone metastases, and no visceral metastases. The ERA-223 RCT evaluated the efficacy and safety of radium-223 in combination with abiraterone acetate and prednisone/prednisolone vs. placebo in combination with abiraterone acetate and prednisone/prednisolone in asymptomatic or mildly symptomatic chemotherapy-naive subjects with bone predominant mCRPC. This trial was unblinded in November 2017 per an independent data monitoring committee's recommendation due to the observation of an imbalance of more fractures and deaths in the arm treated with radium-223 and abiraterone acetate and prednisone/prednisolone than in the control arm (placebo in combination with abiraterone acetate and prednisone/prednisolone). This outcome triggered a Referral Procedure under article 20 of Regulation (EC) No. 726/2004 (Procedure number: EMEA/H/A-20/1459/C/002653/0028) led by the Pharmacovigilance Risk Assessment Committee (PRAC) and resulted in a change in the EU product information in 2018, with the contraindication of the use of radium-223 "in combination with abiraterone acetate and

	prednisone/prednisolone," and the restriction of use among patients who are in progression after at least two prior lines of systematic therapy for mCRPC (other than LHRH analogues) or who are ineligible for other any available systemic mCRPC treatment." Bayer is proposing to perform a drug utilisation study (DUS) in Europe to assess the effectiveness of these risk minimisation measures by assessing compliance with the new indication and contraindication.
Research question and objectives	The main research question will be: 'What proportion of users of radium-223 receive it in compliance with the new indication and contraindication introduced in October 2018?' The primary objectives are to estimate, among the population of patients receiving radium-223, (1) the proportion who receive radium-223 in combination with abiraterone acetate; (2) the proportion who receive radium-223 in combination with other systemic therapies for mCRPC; and (3) the proportion who receive radium-223 without having received at least two prior lines of systemic therapy for mCRPC. The secondary objectives are (4) to estimate the difference before and after the label change in the proportions estimated in the primary objective, and (5) to characterise the population of new users of radium-223, irrespective of combination with other systemic therapies for CRPC, by describing the patients' characteristics, including the presence of metastasis, when radium-223 was started (index date).
Study design	This will be an observational, European prospective cohort DUS of new users of radium-223 in the Netherlands, Denmark, and Germany. The study will use existing data sources (secondary data collection) through electronic medical record and medical record abstraction in the Netherlands and Denmark and through claims data from a population-based database in Germany. There will be a reference period before the label change and a period after the label change. Compliance with the indication and contraindication introduced in the October 2018 EU label change will be measured during these two periods. A common study design and protocol will be followed in all three participating data sources. Each country-specific data source will be managed and analysed locally.
Population	The study population will include new users of radium-223 during the study periods captured in each data source. The study period will include time periods before and after the label change. The "before" period will start in November 2013, the month of radium-223 approval, and will end the in November 2017, the month when the

	first Direct Healthcare Professional Communication (DHCP) letter was sent. The "after" period will include an enrolment phase during which patients initiating radium-223 in each data source will be identified. The enrolment phase will last at least 1 year, starting in April 2019 (6 months after the label change), and will continue through a follow-up phase of at least 6 months after the last new user of radium-223 is identified. A 6-month follow-up will allow for the evaluation of radium-223 in combination with abiraterone acetate or other systemic therapies for mCRPC after the last radium-223 new user is identified, so that this patient can be followed during the approximately 6-month duration of radium-223 treatment.
Variables	New users will be defined as those patients who initiate treatment (first use) with radium-223 during the before label change study period or during the enrolment phase of the after label change study period and who have not used it ever before (naive). The day radium-223 therapy was started will be the index date. The primary study outcomes will be (1) use of radium-223 in combination with abiraterone acetate, (2) use of radium-223 in combination with other systemic therapies for mCRPC (except LHRH analogues), (3) use of radium-223 among patients who have not received at least two previous systemic therapies for mCRPC. Use of radium-223 in combination with abiraterone will be defined as having at least one dispensing/administration of abiraterone acetate on the same date or within 30 days *after* a dispensing/administration of radium-223 or as having a dispensing/administration of radium-223 within 0 and 5 days after the last dispensing/administration administration of abiraterone. Use of radium-223 in combination with other systemic therapies for mCRPC (except LHRH analogues) will be defined as having at least one dispensing/administration of other systemic therapies for mCRPC (other than abiraterone acetate) on the same date or within 30 days *after* a dispensing/administration of radium-223. The outcome "use of radium-223 without use of at least two prior lines of systemic therapies for mCRPC" will be defined as receiving radium-223 in first or second line. Users of radium-223 will be classified as receiving it in the first-line, second-line, third-line, or fourth-line based on having received at least one dispensing/administration of abiraterone, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, or pembrolizumab prior to the index date. Each drug substance will count as a prior line, irrespective of the number of dispensings/administrations of the specific drug substance. The following variables will be described at the index date: age, calendar year of index date, time since first available prostate cancer

	diagnosis, confirmed diagnosis of mCRPC, prior use of systemic therapy for castration-resistant prostate cancer (CRPC) and hormone-sensitive prostate cancer (HSPC), presence of metastasis at baseline (bone or visceral), total level of serum alkaline phosphatase, prior use of bone-health agents, prior use of systemic corticosteroids, and history of osteoporosis.
Data sources	The study will be conducted in the following existing secondary data sources: • Electronic medical record data of all new users of radium-223 from an already existing register of patients with CRPC (CAPRI registry) identified in approximately 20 hospitals in the Netherlands. CAPRI 2.0 will be used to identify users of radium-233 before the label change, and CAPRI 3.0 will be used after the label change. Users of radium-223 will be identified through drug substance or product names identified in the electronic medical records of patients in the CAPRI 2.0 and 3.0 from participating hospitals. Data extracted for the CAPRI 2.0 have already been retrieved; data from CAPRI 3.0 will have been retrieved from patient medical records by trained employees of the Institute of Medical Technology at the time of the analysis. • Data abstracted from existing medical records of all new users of radium-223 in all treating hospitals in Denmark. Initially, users of radium-223 will be identified using the treatment code for "isotope therapy with radium-223 dichloride" as recorded in the Danish National Patient Registry (DNPR), a population-based administrative database, which contains information on all hospital encounters in Denmark since 1977 and is updated continually. Once potential users of radium-223 have been identified, data from hospital medical records for these patients will be retrieved by trained employees of the Aarhus University Hospital. To supplement data from the medical record abstraction, additional data on comorbidities, cancer, and comedications will be obtained through linkage to the DNPR, the Danish Cancer Registry, and the Danish National Health Services Prescription Database. Linkage to all Danish registries is possible via the centralised Civil Registration System that allows for personal identification of each person in the entire Danish population (5.78 million).

	• Claims data from all new users of radium-223 captured in the German Pharmacoepidemiological Research Database (GePaRD), which is a population-based claims database. Users of radium-223 will be identified based on prescriptions for radium-223 recorded in the database. GePaRD covers approximately 15 to 17 million individuals per year from four statutory health insurance (SHI) providers in Germany and provides data on hospital diagnoses and procedures, ambulatory care diagnoses and procedures, and ambulatory prescriptions, including date of prescription and date of pharmacy dispensing.
Study size	The estimated study target size for before the label change is to include all users of radium-223 available in each data source during the before-label-change period. At the time of this protocol, there were approximately 70 users of radium-223 per year in CAPRI 2.0 (n = ~300, 2014-2017), 40 patients per year in the Danish health registries (n = 170, 2014-2017), and around 56 patients per year in GePaRD (n = 167, 2014-2017). The estimated study target size after the label change is 50 to 100 new users of radium-223 per year for each country. A study size with between 50 and 100 new users per year per data source will provide an informative level of precision for the different prevalence estimate scenarios when estimating the percentage of compliance with the current product label.
Data analysis	Separately, in each country-specific data source, the main analysis will estimate the proportion of patients who use (1) radium-223 in combination with abiraterone acetate, (2) radium-223 in combination with other systemic therapies for mCRPC, or (3) radium-223 without having received at least two prior systemic therapies for mCRPC. The denominator for the estimates will be the total number of users of radium-223 during, before, or after label change study periods. In each country-specific data source, the secondary analysis will (4) estimate the difference in these proportions before and after the label change and (5) describe the baseline variables in the study population (all users of radium-223, irrespective of combination therapies) during the study periods, using standard descriptive statistics (e.g., mean, median, and standard deviation for continuous variables and number and proportion for categorical variables).

Milestones	In each data source, the start of data collection (data extraction) will occur after the data up to the end of the "after label change" period are available for the data source, given the lag time from data recording and data availability, and when all approvals are obtained. End of data collection will occur when the analytical data set is completely available. Given differences in data availability, study timelines regarding data collection will differ by country: The Netherlands: • Start of data collection will be Q4 2020 • End of data collection will be Q1-Q2 2021 Denmark: • Start of data collection will be Q3-Q4 2021 • End of data collection will be Q3 2022 Germany: • Start of data collection will be Q3 2022 • End of data collection will be Q4 2022 Study results will be presented as follows: • Study progress reports aligned with regulatory reports (e.g., PSURs/PBRER), as required • An interim report with results from the Netherlands will be provided by Q3 2021 • The final study report with results from the Netherlands (derived from interim report), Germany, and Denmark will be provided by Q1-Q2 2023

5. Amendments

Protocol version 1.0 was submitted for review by the Pharmacovigilance Risk Assessment Committee (PRAC) in January 2019. The PRAC assessment report did not endorse the protocol. Protocol version 2.0 is an update of protocol version 1.0 to reflect changes based on PRAC questions and requests. These updates are presented below.

Version number	Date	Section of study protocol	Amendment or update	Reason
2.0	15 July 2019	8	Updated study objectives to include the assessment of treatment line and use of radium-223 in combination with other systemic therapies for mCRPC	As per PRAC request
2.0	15 July 2019	9.2.2	Updated study time frame to include a "before label change" period	As per PRAC request
2.0	15 July 2019	9.3.2	Updated outcome section to modify the definition of use in combination with abiraterone and to include evaluation of treatment line and use in combination with other systemic therapies for mCRPC	As per PRAC request
2.0	15 July 2019	9.3.3	Updated patient characteristics to include the evaluation of metastasis, serum alkaline phosphatase, and confirmed diagnosis of mCRPC	As per PRAC request
2.0	15 July 2019	9.7.1	Updated analysis to add a sensitivity analysis of the primary outcomes among patients with confirmed diagnosis of mCRPC, and a sensitivity analysis adding 5 additional days of lag time after the last administration of abiraterone	As per PRAC request
2.0	15 July 2019	9.9	Updated limitations section to describe limitations of the assessment of the updated outcomes and limitations in the evaluation of off-label use	As per PRAC request

6. Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project by the research partners and the European Medicines Agency.

Table 1: Milestones

Milestone	Planned date
Registration in the EU PAS Register	After protocol endorsement by EMA and before the earliest date of start of data collection
Start of data collection[a]	Q4 2020 in the CAPRI 2.0 and 3.0 registry in the Netherlands Q3-Q4 2021 in the Danish Registries and other data sources, Denmark Q3 2022 in GePaRD, Germany
End of data collection[±]	Q1-Q2 2021 in the CAPRI 2.0 and 3.0 registry in the Netherlands Q3 2022 in the Danish National Registries and other data sources, Denmark Q4 2022 in GePaRD, Germany
Study progress reports	Aligned with regulatory reports (e.g., PSURs/PBRER)
Interim report	Q3 2021 Results from Hospitals in the Netherlands
Final report of study results	Q1-Q2 2023 Results from CAPRI 3.0 registry in the Netherlands (derived from interim report), the Danish Registries and other data sources (Denmark), and GePaRD (Germany)

EMA = European Medicines Agency; EU PAS Register = European Union electronic register of post-authorisation studies; GePaRD = German Pharmacoepidemiological Research Database; PSUR = Periodic Safety Update Report; PBRER = Periodic Benefit-Risk Evaluation Report.

[a] Start of data collection: the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts [IR Art 37(1)]. Simple counts in a database to support the development of the study protocol, for example, to inform the sample size and statistical precision of the study, are not part of this definition (1).

[±] End of data collection: the date from which the analytical data set is completely available [IR Art 37(2)] (1).

7. Rationale and background

In the last few years, several new therapies for patients with metastatic castration-resistant prostate cancer (mCRPC) have been developed. Existing guidelines recommend androgen-deprivation therapy (ADT) and chemotherapy (docetaxel, cabazitaxel), novel second-generation antiandrogen agents (e.g., abiraterone acetate and enzalutamide), and alpha-emitting therapy (radium-223) (2, 3).

Radium-223 is a first-in-class alpha particle-emitting, radioactive agent used as monotherapy or in combination with luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of adult patients with mCRPC, symptomatic bone metastases, and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH

analogues) or ineligible for any available systemic mCRPC therapy. Given the radioactive nature of radium-223, it must be administered by a radiation oncologist or nuclear medicine physician in a designated clinical setting, including a licensed practice or a hospital outpatient setting, where a radiology infrastructure is available. The patient-ready dose is 1.49 microcurie (55 kBq) per kg body weight and should be administered intravenously during at least 1 minute. Each dose should be administered every 4 weeks, for up to a total of six injections, and the treatment may be completed in 5 to 6 months.

The ALSYMPCA RCT compared radium-223 plus best standard of care vs. placebo plus best standard of care. Radium-223 prolonged median OS by 3.6 months (14.9 months vs. 11.3 months; hazard ratio [HR] 0·70; 95% confidence interval [CI], 0·58-0·83, $P < 0.001$) (4), regardless of previous docetaxel exposure (5) and the median time to first symptomatic skeletal event by 5.8 months (15.6 vs. 9.8 months; HR, 0·66; 95% CI, 0·52-0·83, $P < 0.001$) (6). Radium-223 was well tolerated and associated with a low incidence of grade 3 or 4 myelosuppression (radium-223 vs. placebo: anaemia, 13% vs. 13%; neutropenia, 2% vs. 1%; and thrombocytopenia, 7% vs. 2%). A 3-year follow-up of the ALSYMPCA trial confirmed a good safety profile (7). Quality of life (QOL) data from the ALSYMPCA RCT demonstrated that radium-223 provides significant QOL benefits, including a higher percentage of patients with meaningful improvement in EQ-5D utility score (odds ratio 1.82; 95% CI, 1.21-2.74; $P = 0·004$) and an overall slower decline in QOL over time (8).

The ERA-223 RCT was designed to evaluate the efficacy and safety of radium-223 in combination with abiraterone acetate and prednisone/prednisolone vs. placebo in combination with abiraterone acetate and prednisone/prednisolone in asymptomatic, or mildly symptomatic, chemotherapy-naive subjects with bone predominant mCRPC. Subjects had ≥ 2 bone metastases, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and no known brain metastasis or visceral metastasis. The primary endpoint was symptomatic, skeletal, event-free survival (time from randomisation to the first of the following: use of external beam radiotherapy to relieve skeletal symptoms, new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgery) (9).

The ERA-223 trial was unblinded in November 2017 per an independent data monitoring committee's recommendation resulting from the observation of an imbalance of more fractures and deaths in the arm treated with radium-223 in combination with abiraterone acetate and prednisone than in the control arm treated with abiraterone acetate and prednisone only (10). These results triggered an article 20 referral procedure led by PRAC and resulted in a change in the European Union product information in 2018. The updated radium-223 label indication and contraindication are as follows (10):

- Therapeutic indications: *"Xofigo monotherapy or in combination with luteinizing hormone-releasing hormone (LHRH) analogue is indicated for the treatment of adult patients with mCRPC, symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment*"
- Contraindications: *"Xofigo is contraindicated in combination with abiraterone acetate and prednisone/prednisolone."*

As per the risk management plan (RMP) requirements agreed upon, Bayer is proposing to perform a drug utilisation study (DUS) in Europe to describe compliance with the label contraindication of using radium-223 in combination with abiraterone acetate or other systemic therapies for mCRPC

and to describe the use of radium-223 without having received two prior lines of systemic therapy for mCRPC, i.e., use of radium-223 as first- or second-line therapy, but an assessment of whether this use represents on or off-label use is not possible.

The marketing authorisation holder (MAH) performed an initial evaluation of the feasibility of performing such DUS, using existing data sources in European countries. The feasibility evaluation was based mainly on the ability to capture the use of radium-223 and its combination with abiraterone acetate or other systemic therapies for mCRPC, and on the possibility of defining ineligibility. The following 14 European registries and databases in 10 European countries were evaluated:

- The Norwegian Clinical Registry (Norway)
- The Castration-Resistant Prostate Cancer Registry (CAPRI) (the Netherlands)
- The Integraal Kankercentrum Nederland (the Netherlands)
- The Belgian Cancer Registry (Belgium)
- The Hospital Disease Database (Belgium)
- The National Institute for Cancer Epidemiology and Registration (Switzerland)
- The Germany Cancer Registry (Germany)
- The System National de Donées de Santé database (France)
- The Clinical Practice Research Datalink database (United Kingdom)
- The EpiChron database (Spain)
- The Italian Regional Claims Databases (University of Milano-Bicocca and Tuscany Agenzia Regionale di Sanità, Italy)
- The PHARMO Database Network (the Netherlands)
- The Danish Registries and other data sources (Denmark) linked through Civil Personal Registration Number
- The German Pharmacoepidemiological Research Database (GePaRD) (Germany)

Of the European registries and data sources evaluated, radium-223 use and its combination with abiraterone acetate or other systemic therapies for mCRPC was captured only in the CAPRI 2.0 and 3.0 registry, GePaRD, and the Danish data sources. These were proven to be appropriate for the current study, given the possibility of capturing the use of radium-223 and its combination with abiraterone acetate or other systemic therapies for mCRPC that would be used to identify combination use, use of prior lines of systemic therapy for mCRPC (i.e., line of therapy), and characteristics of patients treated with radium-223. To allow for the inclusion of the maximum number of data sources possible, "non-eligibility for other systemic therapies as first-line or second-line" and "availability of information on metastasis" were not used as criteria to further restrict the data sources included in the study. Information on metastasis (i.e., bone vs. visceral), and total alkaline phosphatase will be described, with the maximum level of detail available. Information on eligibility for treatment, whether bone metastases are symptomatic or asymptomatic, and the number of metastasis is not available in any of the registries or data sources included in the study.

8. Research questions and objectives

The purpose of this study will be to assess potential off-label use of radium-223 defined as its use in combination with abiraterone acetate.

The main research question will be: 'What proportion of users of radium-223 receive it in compliance with the new indication and contraindication introduced in October 2018?'

8.1 Primary objectives

The primary objectives are to estimate the following, among the population of patients receiving radium-223:

1) The proportion of patients who receive radium-223 in combination with abiraterone acetate
2) The proportion of patients who receive radium-223 in combination with other systemic therapies for mCRPC, except LHRH analogues
3) The proportion of patients who receive radium-223 without having received at least two prior lines of systemic therapy for mCRPC, except LHRH analogues

8.2 Secondary objectives

The secondary objectives are as follows:

4) To estimate the difference before and after the label change in the proportions estimated in the primary objective
5) To characterise the population of new users of radium-223, irrespective of combination with other systemic therapies for mCRPC, by describing the following variables when radium-223 was started (index date):
    - Age at radium-223 start
    - Calendar year of radium-223 start
    - Time since first available prostate cancer diagnosis
    - Confirmed diagnosis of mCRPC
    - Prior use of therapies for castration-resistant prostate cancer (CRPC) and hormone-sensitive prostate cancer (HSPC), i.e., cytotoxic drugs, immunotherapies, first- and second-generation antiandrogens, LHRH agonists/analogues, LHRH antagonists, and corticosteroids
    - Presence of metastasis at baseline: bone and/or visceral metastasis
    - Total level of serum alkaline phosphatase
    - Prior use of bone-health agents (e.g., bisphosphonates, denosumab, others)
    - Prior diagnosis of osteoporosis

9. Research methods

9.1 Study design

This will be an observational, European, prospective cohort DUS of new users of radium-223 in the Netherlands, Denmark, and Germany. The study will use existing secondary data sources through electronic medical record and medical record abstraction in the Netherlands and Denmark and through claims data from a population-based database in Germany. There will be a reference period before the label change and a period after the label change. Compliance with the indication and contraindication introduced in the October 2018 EU label change as a result of the article 20 referral procedure will be measured during these two periods.

A common study design and protocol will be followed in all three participating data sources. Each country-specific data source will be managed and analysed locally.

9.2 Setting

9.2.1 Study population

The study population will include new users of radium-223 during the before or after label change study periods (Table 2) captured in each *data source*. The study will be implemented in the three participating countries taking into consideration the time lag between data recording and data availability in each secondary data source. In the Netherlands, new users of radium-223 will be all those identified in the hospitals participating in CAPRI 2.0 and 3.0. A total of 20 hospitals participated in CAPRI 2.0, and the CAPRI investigators expect that approximately 20 hospitals will participate in CAPRI 3.0 by the end of 2020. In Denmark and Germany, all users of radium-223 identified in the Danish and GePaRD data sources will be included.

All patients from CAPRI 2.0 and 3.0 will have CRPC as per inclusion criteria to the registry. It is not expected that radium-223 will be used in cancers other than prostate cancer, specifically, in mCRPC. To avoid excluding radium-223 users due to absence of a prostate cancer diagnosis, the study population will include all new users of radium-223 irrespective of their cancer diagnosis (i.e., prostate cancer, CRPC, mCRPC, or other), although the proportion of patients that have a confirmed mCRPC diagnosis will be described. A cancer diagnosis is very unlikely to be missing in the Netherlands and Danish data sources but could be missing in GePaRD. In addition, it is very unlikely that radium-223 is prescribed for any other type of cancer (EUPAS8494, available at: http://www.encepp.eu/encepp/viewResource.htm?id=23207). Time since first prostate cancer diagnosis will be described as part of the patient's characteristics (see Section 9.3.3)

9.2.2 Study time frame

All users of radium-223 identified in each data source during the before or after periods defined for each data source will be included in the study.

The period before the label change will start the date when radium-223 was marketed in all countries (13 November 2013), and end in November 2017, the month when the first Direct Healthcare Professional Communication (DHCP) letter was sent.

The study period after the label change for all three data sources will include an enrolment phase of at least 1 year starting in April 2019 (6 months after the label change), during which all new users of radium-223 in each data source will be identified. The after-label change period will also include a

follow-up of at least 6 months after the last new user of radium-223 is identified in the respective data sources. The proposed follow-up of at least 6 months will allow for the evaluation of "use in combination" after the last new radium-223 user is identified. This means that patients identified at the end of the enrolment phase will be followed for the 6-month maximum duration of radium-223 treatment (see Figure 1 and Table 2 for details). The duration of the enrolment phase will be up to June 2020 in Denmark and GePaRD, given that data extraction occurs annually for the full calendar year in these data sources; at the time of data extraction, the study period will have 6 months of follow-up, i.e., data through December 2020 will be available.

Follow-up (patient observation time): Patients will be followed from the date of the first dose of radium-223 (index date) until disenrollment from the database (because of death or migration) or the administrative end of the study period, whichever is first.

Data extraction will occur when data for the whole study time frame are available, that is, from 2 to 24 months after the end of the after label change study period, depending on the data source time lags (see Figure 1 and Table 2 for details). Given the differences in data availability in each data source, there will be two reports of study results, an interim report in Q2, 2021 including data from the Netherlands, and a final report in Q1Q2, 2023, including results from the three countries, individually presented. Figure 1 and Section 9.2.2 detail the time frame.

Figure 1: Study overview

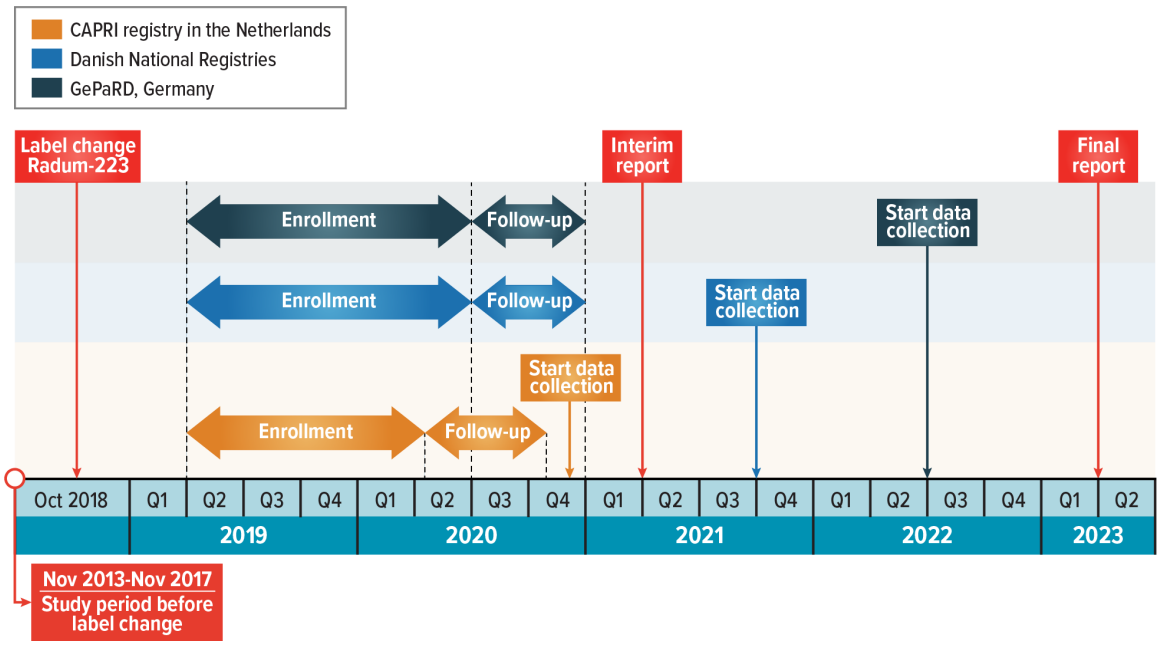


Table 2: Estimated study period in each study data source

Event	CAPRI 2.0 and 3.0 registry in the Netherlands	Danish registries and other data sources in Denmark	GePaRD, Germany
Radium-223 label change	October 2018	October 2018	October 2018
Anticipated study period before the label change[a]	November 2013-November 2017	November 2013-November 2017	November 2013-November 2017
Anticipated study period after the label change[a]	Enrolment phase: April 2019-March 2020 Follow-up phase (6 months): April 2020-September 2020	Enrolment phase: April 2019-June 2020 Follow-up phase (6 months): July 2020-December 2020	Enrolment phase: April 2019-June 2020 Follow-up phase (6 months): July 2020-December 2020
Data source time lag	~2 months	~6-12 months	~18-24 months
Start of data collection (data extraction)	Q4 2020	Q3-Q4 2021	Q3 2022
Medical record abstraction	Q4 2020	Q1-Q2 2022	NA
Interim study report[b]	Q3 2021	NA	NA
Final study report[c]	Q1-Q2 2023	Q1-Q2 2023	Q1-Q2 2023

GePaRD = German Pharmacoepidemiological Research Database; NA = not applicable; Q1, Q2, Q3, Q4 = first, second, third, fourth quarter of calendar year.

[a] Study periods of observation are estimated based on the October 2018 EU endorsement of label change, start of study period 6 months later, and the following lag times in each data source: medical record abstraction will take around 6 months in the hospitals in the Netherlands, data up to December 2020 will be available during Q2, to Q4, 2021 in Denmark, and to 2022 in GePaRD. Note that data in Denmark and GePaRD are updated annually, although it can be more frequent in Denmark, and, once updated, contain data up to December of each year. For example, in GePaRD, data up to June 2020 could be obtained in Q2 2022, at the same time when data up to December 2020 will be obtained. Contracts for the study are pending.

[b] Interim report in the study milestones (see Section 6).

[c] Final report in the study milestones (see Section 6).

9.2.3 Selection criteria

- Inclusion criteria: patients who fulfil all the following criteria will be included in the respective study periods (before or after the label change):
    1. Patients who receive a first dispensing/administration of radium-223 during the before or after study period
    2. Patients who have at least 6 months of continuous enrolment in the study databases before the first dispensing/administration of radium-223 (to allow for evaluation of recent medical history and medication use)
- Exclusion criterion: patients who used radium-223 ever before the start of the before study period

9.2.4 Representativeness

In the CAPRI 2.0 and 3.0 registry in the Netherlands, the study will include approximately 20 hospitals, with approximately 25% of the total number of patients with CRPC in the Netherlands and that are balanced geographically and by type of hospital, with the aim to provide a representative selection of all patients with CRPC in the Netherlands.

In Denmark, data for this study will be assumed representative of the whole country, as the Danish National Registries and other data sources, from which users of radium-223 will be identified, are nationwide and population based, with uniform treatment guidelines in place (11, 12).

In Germany, data from GePaRD are based on medical claims data from four German statutory health insurance (SHI) providers (AOK Bremen/Bremerhaven, Die Techniker (TK), DAK-Gesundheit, and hkk Krankenkasse). Overall, the database includes data on more than 22 million insured persons from all regions in Germany. Analyses regarding age and sex distribution, the number of hospital admissions, and drug use have shown that the database is representative of the German population and that the insurance population is generally stable over time (13-15).

In this study, all findings will relate to radium-223 use and patient demographic and clinical characteristics and will apply to the patient populations in the Netherlands, Denmark, and Germany as representative of three different health care settings in Europe.

9.3 Variables

9.3.1 Exposure definition

New users of radium-223 will be defined as those patients who initiated treatment (first use) with radium-223 during the before label change study period or during the enrolment phase of the after label change study period and who had not used it ever before.

- In the Netherlands, use of radium-223 will be identified based on drug substance or product name recorded in the electronic medical records in the participating hospitals.
- In Denmark, all cancer therapies are administered in hospitals (note: hospital-administered therapies are not available in the Danish prescription registry, which captures only outpatient dispensings). Potential users of radium-223 will be identified based on a hospital treatment code available in the Danish National Patient Registry (DNPR): BWGG5 “Isotope therapy

with radium-223 dichloride." Once potential users of radium-223 have been identified via this code, use of radium-223 will be confirmed during the abstraction of hospital medical records (16). Selected hospital-administered therapies are assigned local codes, which can be used to document treatment in the DNPR. The completeness and consistency of use of any given code are unknown.

- In Germany, use of radium-223 will be identified based on the records for prescriptions for radium-223 codes (Einheitlicher Bewertungsmaßstab [EBM] code [40582], Operationen und Prozedurenschlüssel [OPS] code 8-530.1, and ATC code V10XX03) in GePaRD.

The dose of radium-223 administered will be described, when available and as recorded in each data source.

- The Netherlands: Total dose of radium-223 per cycle as recorded in the medical records
- Denmark: Formulation strength or total dose of radium-223 per cycle as recorded in the medical records
- Germany: Formulation strength of a single tablet, defined daily dose, medical knowledge or information on dosing schemes from the summary of product characteristics

9.3.2 Outcomes definition

9.3.2.1 Use of radium-233 in combination with abiraterone

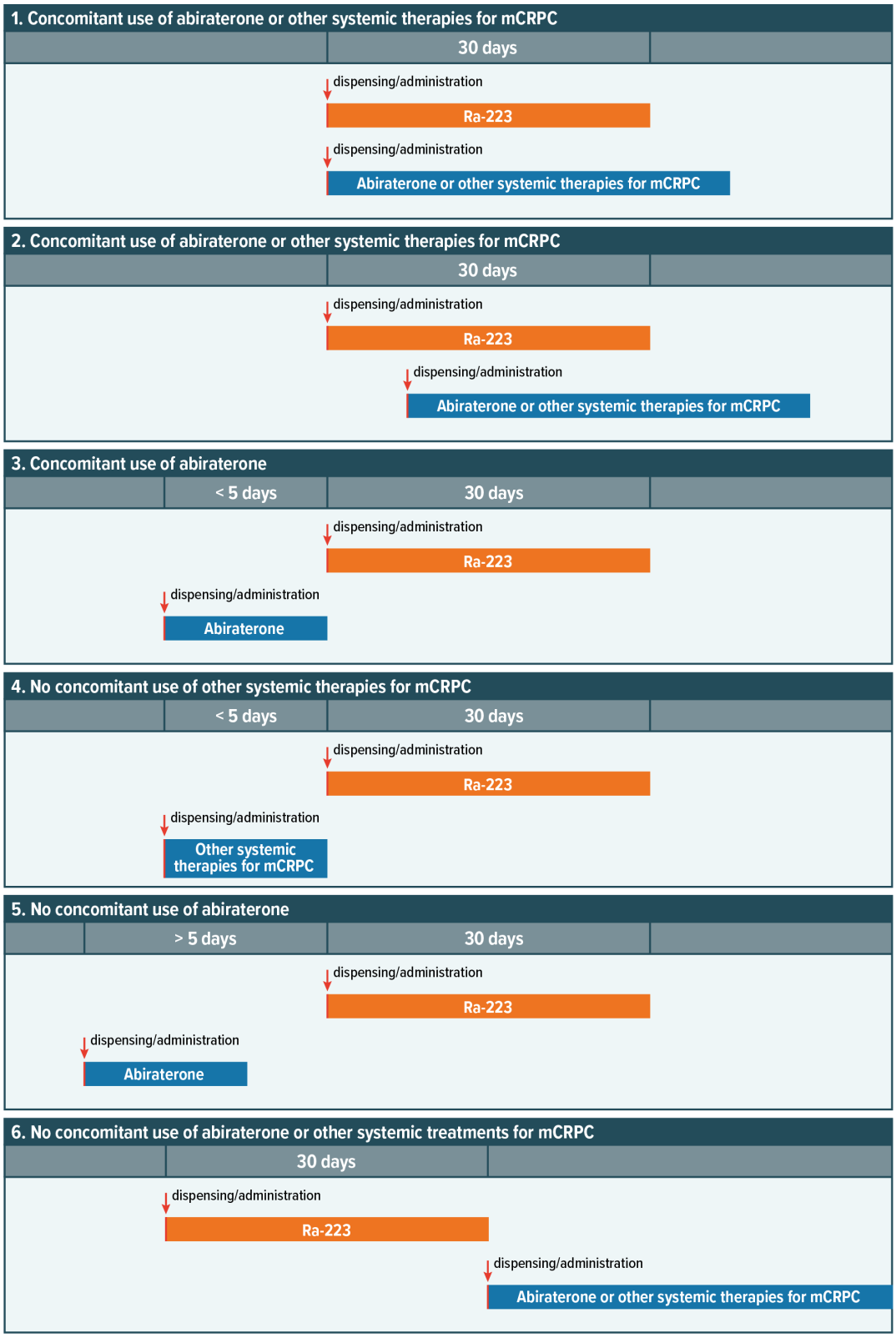
Xofigo is contraindicated in combination with abiraterone acetate and prednisone/prednisolone. In addition, based on the elimination half-life of radium-223 and abiraterone, it is recommended that subsequent treatment with radium-223 not be initiated for at least 5 days after the last dispensing/administration of abiraterone acetate in combination with prednisone/prednisolone.

The outcome "use of radium-223 in combination with abiraterone acetate" will be defined as having at least one dispensing/administration of abiraterone acetate on the same date or within 30 days *after* a dispensing/administration of radium-223 or as having a dispensing/administration of radium-223 within 0 and 5 days after the last dispensing/administration of abiraterone (Figure 2, examples 1 to 3). If abiraterone acetate is dispensed and/or administered 5 or more days *before* the index date (the first radium-223 prescription) but there are no further prescriptions of abiraterone acetate within 30 days *after* any dispensing/administration of radium-223, it will not be considered use in combination, even if the duration of use of that dispensing/administration overlaps with radium-223 use (Figure 2, example 5). Dispensings/administrations of abiraterone acetate occurring beyond the 30 days after the last dispensing/administration of radium-223 will not be considered use in combination (Figure 2, example 6).

In GePaRD, a sensivity analysis of the primary outcomes, with an additional 5 days lag time after the last dispensing/administration of abiraterone, will be performed, where the outcome "use of radium-223 in combination with abiraterone acetate" will be defined as having at least one dispensing/administration of abiraterone acetate on the same date or within 30 days *after* a prescription for radium-223 or as having a dispensing/administration of radium-223 within 0 to 10 days after the last dispensing/administration of abiraterone.

In addition, a sensitivity analysis of the primary outcomes will be performed among users of radium-223 with a confirmed diagnosis of mCRPC.

Figure 2: Examples for the application of the use in combination rule



Note: Coloured boxes represent assumed drug duration of use. The arrows represent drug dispensing/administration date.

Identification of use of abiraterone acetate will be achieved as follows:

- In the Netherlands, use of abiraterone acetate will be identified based on data on drug substance or product name recorded in the electronic medical records in the participating hospitals.
- In Denmark, use of abiraterone acetate will be identified based on data abstracted from medical records.
- In GePaRD, use of abiraterone acetate will be identified based on the records for prescriptions for abiraterone acetate codes (ATC code L02BX03).

9.3.2.2 Use of radium-223 in combination with other systemic therapies for mCRPC

Subsequent systemic cancer therapy should not be initiated for at least 30 days after the last administration of radium-223. The outcome "use of radium-223 in combination with other, systemic therapies for mCRPC, except LHRH analogues" will be defined as having at least one dispensing or administration of systemic therapy for mCRPC, other than abiraterone, on the same date or within 30 days *after* a prescription for radium-223 (Figure 2, examples 1 and 2). Having a dispensing or administration of radium-223 within 0 to 5 days after the last dispensing/administration of abiraterone will not be considered use in combination (Figure 2, example 5). Dispensings or administrations of other systemic therapies for mCRPC occurring beyond the 30 days after the last dispensing or administration of radium-223 will not be considered use in combination (Figure 2, example 6). Each drug substance will count as a prior line, irrespective of the number of dispensings or administrations of the specific drug substance.

The following systemic therapies for mCRPC will be considered:

- Enzalutamide (oral)
- Docetaxel (intravenous [IV])
- Cabazitaxel (IV)
- Sipuleucel-T (IV)
- Pembrolizumab (IV)

Identification of use of other systemic therapies for mCRPC will be achieved as follows:

- The Netherlands: Use of other systemic therapies for mCRPC will be identified from data on drug substance or product name recorded in the electronic medical records in the participating hospitals.
- Denmark: Use of other systemic therapies for mCRPC will be identified in data abstracted from medical records.
- Germany: In GePaRD, use of other systemic therapies for mCRPC will be identified based on records of codes for prescriptions for other systemic therapies for mCRPC (relevant ATC codes in the groups L01 and L02).

9.3.2.3 Use of radium-223 without having received at least two prior lines of systemic therapy for mCRPC

The outcome "without use of at least two prior systemic therapies for mCRPC" will be defined as receiving radium-223 in the first or second line. Users of radium-223 will be classified as receiving it in first-line, second-line, third-line, or fourth-line therapy based on having received at least one dispensing/administration of the following medications prior to index date:

- Abiraterone (oral)
- Enzalutamide (oral)
- Docetaxel (intravenous [IV])
- Cabazitaxel (IV)
- Sipuleucel-T (IV)
- Pembrolizumab (IV)

Each drug substance will count as a prior line, irrespective of the number of dispensings/administrations of the specific drug substance. Patients will not be required to have received a full conventional cycle of any of these therapies to qualify for a line of treatment, that is, a single dispensing/administration will qualify as a line of treatment.

9.3.3 Patient´s demographic and clinical characteristics

Demographic and comorbidities information will be assessed using all available information prior to the index date in each data source (see Section 9.4 for information on the look-back period in each data source). Use of prior medications will be assessed for the 6-month period before the index date.

The following variables will be described at index date:

- Age (in years): as recorded in each data source. Age will also be categorised for descriptive purposes
- Calendar year: calendar year of the index date, i.e., the calendar year when radium-223 was first prescribed/dispensed, as recorded in each data source
- Time since first available prostate cancer diagnosis:
  - The Netherlands: Defined as the number of months between the first diagnosis of prostate cancer and the first administration of radium-223, as recorded in the CAPRI 2.0 and 3.0 registry
  - Denmark: Defined as the number of months between the first diagnosis of primary prostate cancer as recorded in the Danish Cancer Registry or the DNPR and the first administration of radium-223 as recorded in the DNPR and confirmed through medical chart abstraction
  - Germany: Defined as the number of months between the first diagnosis of prostate cancer and the first dispensing of radium-223, as recorded in GePaRD
- Confirmed diagnosis (yes/no) of mCRPC:
  - The Netherlands: As recorded in the CAPRI 2.0 and 3.0 registry

- Denmark: As recorded in the hospitals and identified through medical record abstraction (in-hospital medications)
- Germany: Defined using an algorithm that will include diagnosis of prostate cancer and metastasis (ICD-10 codes) and categorised as mCRPC (yes/no) as recorded in GePaRD

- Prior use (yes/no) systemic therapy for CRPC:
  - Chemotherapy: docetaxel, cabazitaxel
  - Immunotherapy: sipuleucel-T, pembrolizumab
  - Second-generation antiandrogens (abiraterone acetate, enzalutamide, apalutamide):
    - The Netherlands: As recorded in the CAPRI 2.0 and 3.0 registry
    - Denmark: Identified through medical record abstraction (in-hospital medications) and/or based on ATC codes recorded in the Danish Prescription Registry
    - Germany: Based on an algorithm that will use ATC codes for in-hospital and out-of-hospital medications recorded in GePaRD
- Prior use (yes/no) systemic therapy for HSPC:
  - First-generation antiandrogens (bicalutamide, nilutamide, flutamide)
  - LHRH agonists or analogues (goserelin, histrelin, leuprolide, or triptorelin)
  - LHRH antagonists (degarelix) and prednisone/prednisolone since first diagnosis of PC:
    - The Netherlands: As recorded in the CAPRI 2.0 and 3.0 registry
    - Denmark: As recorded in the hospitals and identified through medical record abstraction (in-hospital medications) and/or based on ATC codes recorded in the Danish Prescription Registry
    - Germany: Based on ATC codes for out-of-hospital medications recorded in GePaRD
- Presence of metastasis at baseline: bone or visceral:
  - The Netherlands: As recorded in the CAPRI 2.0 and 3.0 registry
  - Denmark: As identified through medical record abstraction
  - Germany: Defined as a diagnosis of metastasis (yes/no) (ICD-10 codes: C78, and C79) where C79.5 identifies bone metastasis, as recorded in GePaRD
- Total level of serum alkaline phosphatase, when available: as U/L and categorised as above or below a threshold (e.g., < 220 U/L and ≥ 220 U/L):
  - The Netherlands: As recorded in the CAPRI 2.0 and 3.0 registry
  - Denmark: As recorded in the Laboratory Information Systems database (LAB database)
  - Germany: Not available in GePaRD

- Prior use of bone-health agents (yes/no); bisphosphonates alone or in combination (Anatomical Therapeutic Chemical [ATC] code: M05BA, M05BB), bone morphogenetic proteins (ATC code: M05BC), and other drugs affecting bone structure and mineralisation (ATC code: M05BX) (yes/no), since first diagnosis of PC:
    - The Netherlands: As recorded in the CAPRI 2.0 and 3.0 registry
    - Denmark: As recorded in the hospitals and identified through medical record abstraction (in-hospital medications) and/or based on ATC codes recorded in the Danish Prescription Registry
    - Germany: Based on an algorithm that will use ATC codes for in-hospital and out-of-hospital medications recorded in GePaRD
- Prior use of systemic corticosteroids (ATC code: H02): yes/no, since first diagnosis of PC:
    - The Netherlands: As recorded in the CAPRI 2.0 and 3.0 registry
    - Denmark: As recorded in the hospitals and identified through medical record abstraction (in-hospital medications) and/or based on ATC codes recorded in the Danish Prescription Registry
    - Germany: Based on an algorithm that will use ATC codes for in-hospital and out-of-hospital medications recorded in GePaRD
- History of osteoporosis ever before the index date:
    - The Netherlands: Defined as a diagnosis of osteoporosis (yes/no) and/or treated for osteoporosis (yes/no)
    - Denmark: Defined as a diagnosis of osteoporosis (yes/no) recorded in the DNPR (ICD-10 codes: M80, M81, and M82) and/or treated for osteoporosis recorded as ATC codes for specific medications (bisphosphonates, denosumab (Prolia), strontium ranelate, teriparatide) recorded in the prescription registry
    - Germany: Defined as a diagnosis of osteoporosis (yes/no) (ICD-10 codes: M80, M81, and M82) and/or treated for osteoporosis as recorded in GePaRD

9.4 Data sources

The study will be conducted in the following data sources:

- The Netherlands: CAPRI 2.0 and 3.0 registry electronic medical record data from participating hospitals
- Denmark: Danish Population Registries and other data sources (i.e., information from Danish hospital medical records obtained through medical record abstraction)
- Germany: Population-based claims database obtained from four SHIs in Germany (GePaRD)

Table 3 contains a summary of the three data sources; a brief description of each follows.

Table 3: Main features of proposed European databases

Description	CAPRI 2.0 and 3.0 Registry, (the Netherlands)	Danish Population Registries and other data sources (Denmark)	GePaRD (Germany)
Data source type	Electronic medical records of patients with CRPC in hospitals participating in CAPRI 2.0 and 3.0. Existing disease registry on patients with mCRPC	Hospital record & Population-based registries and databases; link between all databases as well as data collected abstracted from medical records through Civil Personal Registration Number	Claims databases, four SHI providers
Country population	17,181,084 [a]	5,781,190 [a]	82,850,000 [a]
Proportion of the country's population covered by the database	15%	100%	22.9 million since 2004. Cross-sectionally 15 to 17 million (~19%)
Representativeness of patients	Approximately 20 hospitals participated in CAPRI 2.0, and 20 hospitals are expected to participate in CAPRI 3.0 by the end of 2020, balanced geographically and by type of hospital. This represents approximately 25% of the patient population with CRPC in the Netherlands	Full Danish population	Representative of sex and age of German population. Proportion of patients with CRPC covered not available but expected in line with general population covered
Data on medications and type of prescriptions	Systemic drugs and supportive care as recorded in electronic medical records.	Hospital medical records & all prescriptions dispensed in community pharmacies	All dispensed drugs prescribed in ambulatory settings, which are reimbursed by the SHIs
Dose	According to label Total dose of RA223 per cycle, as recorded in the medical records	Formulation strength	Formulation strength of a single tablet, defined daily dose, medical knowledge or information on dosing schemes from the summary of product characteristics

Description	CAPRI 2.0 and 3.0 Registry, (the Netherlands)	Danish Population Registries and other data sources (Denmark)	GePaRD (Germany)
Duration of treatment	As recorded in electronic medical records	Not recorded; estimated based on dispensings	Not recorded, estimated based on prescriptions
Drug dictionary codes/ therapeutic classification	NA	ATC. For radium-223, internal treatment code	ATC
Outpatient diagnosis	No, only if recorded in electronic medical records	Only outpatient hospital clinics	Yes, diagnoses can be allocated quarterly each year, but no exact date is available
Hospital diagnosis	Yes	Yes, Danish National Patient Registry	Yes
Disease and procedures codes	NA	ICD-10, NCSP	ICD-10-GM, OPS and EBM
Data availability	CAPRI 2.0 includes patients diagnosed with CRPC between 01 Jan 2010 and 31 Dec 2015 CAPRI 3.0 will include patients diagnosed with CRPC from 1 Jan 2016 through 31 Dec 2019	Since 1994 (ICD-10), since 1977 (ICD-8)	Since 2004
Approximate time lag (updates per year)	Data for CAPRI 2.0 are already available. For CAPRI 3.0, availability depends on timing of radium-223 use; data collection will start in Q4 2020	6-12 months (1 per year)	18-24 months (1 per year)

Description	CAPRI 2.0 and 3.0 Registry, (the Netherlands)	Danish Population Registries and other data sources (Denmark)	GePaRD (Germany)
Approval processes for database research for the proposed study	Individual patient consent already provided for participation in CAPRI 2.0 and 3.0 registry Hospital ethical committee approval/consent needed	Individual patient consent not required (local regulation) Approval from the Danish Patient Safety Board (for access to medical records) required Approvals from treating physicians/department heads to access patients' records required Registration in the Aarhus University roster of studies notification by the Danish Data Protection Agency required, http://www.datatilsynet.dk/english/. Danish Patient Safety Board to access medical records	Individual patient consent not required (local regulation) Approvals by SHI and their authorities (e.g., German Federal (Social) Insurance Office and the Senator for Science, Health, and Consumer Protection in Bremen) required. No other ethics approval required.

ATC = Anatomical Therapeutic Chemical; CAPRI = Castration-Resistant Prostate Cancer Registry; EBM = Einheitlicher Bewertungsmaßstab; GePaRD = German Pharmacoepidemiological Research Database ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICD-10-GM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification; NA = Not available; NCSP = NOMESCO Classification of Surgical Procedures; OPS = Operationen und Prozedurenschlüssel; SHI = Statuary Health Insurance (Germany).

[a] Population data from Eurostat. 2018. Available at: http://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tps00001&plugin=1. Accessed 27 November 2018.

9.4.1 CAPRI registry, the Netherlands

The CAPRI registry is a CRPC patient registry in the Netherlands available for observational research (17). An initial phase was completed between 2010 and 2017 (CAPRI 1.0, 2.0) including patients diagnosed with CRPC between 01 January 2010 and 31 December 2015, and a new phase will start in 2019 (CAPRI 3.0). Data for the "before" period from medical records of patients with CRPC will be retrieved from the CAPRI 2.0 registry and will include patients diagnosed with CRPC between 01 January 2010, and 31 December 2015 who were new users of radium-223 at any time between 01 November 2013 and 30 November 2017. Data for the "after" period from medical records of patients with CRPC will be retrieved from the CAPRI 3.0 registry and will include patients diagnosed with CRPC between 01 January 2016 and 31 December 2019 and who were new users of radium-223 between 01 April 2019 and 30 March 2020. The patient's registry information during April 2020 through September 2020 will be included as part of the 6-month follow-up period of each patient after the first dispensing/administration of radium-223 during the after label change period.

The Dutch component of this radium-223 DUS will be performed by the CAPRI investigators, who will collect information from the medical history of patients diagnosed with CRPC who start radium-223 at least 6 months after the label change (i.e., 1 April 2019). The study will include approximately 20 hospitals, and around 25% of all patients with CRPC in the Netherlands, balanced geographically and by type of hospital, with the aim of providing a representative selection of all patients with CRPC in the Netherlands. Data will be identified and abstracted from patient records in participating hospitals by trained employees of the institute of Medical Technology Assessment. A web-based electronic data abstraction form will be used for data abstraction from electronic medical records. The radium-223 DUS will be conducted using the CAPRI registry network and study infrastructure. Data abstraction forms will be created in collaboration with the CAPRI registry investigators and will be based on current study needs and prior experience in the CAPRI 1.0 and 2.0 registries.

Based on communications with researchers at the CAPRI registry, during the years 2014 to 2016, approximately 300 patients with CRPC were receiving radium-223 according to the CAPRI 2.0 registry.

9.4.2 Danish National Health Registries and other data sources

Potential users of radium-223 will be identified using data from the DNPR that include all treating hospitals in Denmark. Once these patients have been identified and the follow-up time has elapsed, data for this study will be retrieved from the hospital medical records through medical record abstraction. The study will include all hospitals where a user of radium-223 during the "before" or "after" periods is identified using the treatment code. No minimum number of radium-223 users per hospital will be required. Data collection forms will be created in collaboration with the Aarhus University investigators and will be based on current study needs, data available, and potential harmonisation with data collection forms in the Netherlands.

The Danish health care system provides universal coverage to all Danish residents (approximately 5.8 million inhabitants). Health care coverage includes visits to general practitioners and specialists, hospital admissions, and outpatient visits. The costs of medicines are partially covered by the Danish health system. The centralised Civil Registration System in Denmark allows for personal identification of each person in the entire Danish population and for the possibility of linkage to all Danish registries, including the DNPR, Danish National Health Services Prescription Database, the Danish Cancer Registry, and the Clinical Laboratory Information System (LABKA) Research Database, among others. Data collected in these registries are available for research purposes.

Based on communications with research partners from the Aarhus University during the years 2014 to 2017, approximately 175 patients had prostate cancer and a record of radium-233 therapy per the DNPR.

9.4.3 German pharmacoepidemiological research database (GePaRD)

GePaRD is a population-based claims database obtained from four SHIs in Germany and currently includes information on about 25 million persons who have been insured with one of the participating providers since 2004 or later (18). In addition to demographic data, GePaRD contains information on outpatient drug dispensations as well as on outpatient and inpatient services and diagnoses. Per data year, there is information on approximately 17% of the general population and all geographical regions of Germany are represented. Membership is stable over time.

The German modification of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-GM) is used for coding diagnoses, and OPS (Operationen und Prozedurenschlüssel) codes are used for surgical and diagnostic procedures. Types of therapies and diagnostic procedures with exact date are registered according to EBM (Einheitlicher

Bewertungsmaßstab) codes, developed for payment of physicians for the outpatient treatment of German SHI patients.

Based on communications with research partners from the Leibniz Institute for Prevention Research and Epidemiology, during the years 2014 to 2016, there were around 1,000 dispensations of radium-223 in the database.

9.5 Study size

The size of the study will be driven by the uptake of radium-223 in the study population and will include all new users of radium-223 captured in each data source. Table 4 presents a summary of the available number of users of radium-223 from 2014 to the latest data available, in the data sources of interest.

Table 4: Number of radium-223 users by data source and year

Calendar year	**CAPRI registry, the Netherlands**[a] Number of patients	**The DNPR in Denmark** Number of patients [±]	**GePaRD, Germany** Number of dispensations (and estimated number of patients) [±¥]
2014	NA	30	50 dispensations (~8 patients)
2015	NA	70	~700 dispensations (~117 patients)
2016	NA	40	~250 dispensations (~42 patients) (lacking data from one of the SHIs)
2017	Approximately 300 enrolled in CAPRI 2.0 between 2014 and 2017, ~70 patients per year	30	NA

DNPR = Danish National Patient Registry; GePaRD = German Pharmacoepidemiological Research Database; NA = not available; SHI = Statutory Health Insurance.

[a] Data extracted from approximately 20 hospitals.

[±] The number of radium-223 users has been estimated by dividing the number of dispensations by 6, as a patient can receive up to six dispensations.

[¥] In June 2018, there were approximately 175 men with prostate cancer and with a record of radium-223 treatment between 2014 and 2017. The table numbers show the approximate (rounded to nearest 5) number of users. These numbers are not expected to add up to the total of 175.

Study size will be determined by the "after" period, which will be shorter and have fewer radium-223 users than the "before" period. The estimated "after" study target is 50 to 100 new users of radium-223 in each country-specific data source. A study size between 50 and 100 new users per data source will provide an informative level of precision in the different scenarios when estimating the percentage of non-compliance with label change (Table 5).

Table 5. Binomial confidence intervals around possible estimated proportion of patients who are not compliant with the label indication or contraindication for different study sizes

Number of patients	95% Confidence intervals for different prevalence estimates, %[a]				
	2.5%	5%	10%	15%	20%
50	0.1-10.6	0.5-13.7	3.3-21.8	5.8-26.7	10.0-33.7
100	0.2-7.0	1.6-11.3	4.9-17.6	8.6-23.5	12.7-29.2
150	0.4-5.7	1.9-9.4	5.7-16.0	9.4-21.4	13.9-27.3
300	0.9-4.7	2.8-8.1	6.8-14.0	11.2-19.6	15.6-25.0
500	1.2-4.2	3.3-7.3	7.5-13.0	12.0-18.4	16.6-23.8

[a] Calculations were performed using Stata software.

9.6 Data management

Routine data management procedures in each participating data source will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control checks of all programs. Each research partner will maintain any patient-identifying information securely on site according to internal standard operating procedures (SOPs) or guidance documents. The individual patient and aggregated patient data will be kept separately at each research partner centre, and with no pooling of data will be performed. Only the results of the aggregated analysis will be shared and reported in the interim and final reports.

In the Netherlands, a web-based electronic data abstraction form will be used for data abstraction from electronic medical records. In the CAPRI 3.0 registry, in hospitals extraction modules will be built around the CTcue (software) extract, will be pseudonymised, and will conform required data for CAPRI. Data are sent every 24 hours to a Dutch trusted third party, taking into account General Data Protection Regulation (GDPR) compliance. The Netherlands Comprehensive Cancer Organization (IKNL) will test and accredit the data quality of these data extraction processes in a pilot process prior to go-live transmission. Twice a year, CAPRI registry released as a flat file to IKNL, and hence to academic research. The release process planned allows a 6-month delay to allow death record linkage maturity. The data collected for CAPRI can be part of the Netherlands Cancer Registry (NCR) in the near future.

Security processes will be in place to ensure the safety of all systems and data. Data will be kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM, DVD, secure servers), with periodic backup of files. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.7 Data analysis

For each of the primary endpoints, the main analysis will estimate the proportion of patients who used (1) radium-223 in combination with abiraterone acetate for mCRPC, (2) radium-223 in combination with other systemic therapies for mCRPC, and (3) radium-223 in the first line or second line of therapy without having received at least two previous therapies for mCRPC. The denominator for the proportions is the total number of new users of radium-223 during the study period (*p*), in each country-specific data source:

$$\widehat{p_m} = \frac{k_m}{n_m}$$

Where *n* is the number of patients who started radium-223 during the study period in each population, *m* and *k* is the number of patients who fulfilled one of the study outcomes: (1) received radium-223 in combination with abiraterone acetate, (2) in combination with other systemic therapies for mCRPC, or (3) in the first or second line of therapy without having received at least two previous therapies for mCRPC. We will provide 95% CIs computed with the exact method (Clopper-Pearson method) (19).

Based on the data, additional analysis of use in combination will describe the number of cycles in which radium-223 was used in combination with abiraterone acetate or other systemic therapies (e.g., in one, or in all 6 cycles) and the possible combination scenarios of concomitant use (see examples in Figure 2). In addition, to further characterise potential switching to abiraterone or other systemic therapies for mCRPC, rather than intention to combine therapies, the proportion of patients who use radium-223 in combination with abiraterone acetate during the 30 days after the last prescription of radium-223 will also be described.

The difference between the calculated proportion of patients in each of the primary outcomes before and after the label change will be calculated as an estimate of the change. The upper and lower limits of the 95% CI for the difference will be calculated using the most appropriate method described by Newcombe (20).

Those patients included in the before label-change period who do not have a 6-month follow-up after the first dispensing/administration of radium-223 will not be included in some of the analysis where this period is required to define the outcomes.

The secondary analysis will describe the variables in Section 9.3.3 in the study population. Continuous variables will be described estimating their means, and standard deviations and/or medians and quartiles. Categorical variables will be described providing their counts and estimating their proportions.

For prior use of therapies for mCRPC, in addition to the primary outcome (proportion of patients that did not receive at least two previous therapies), the study will also describe the number of prior systemic therapies for mCRPC and whether specific therapies (e.g., docetaxel, enzalutamide) had been used (yes/no) before the first radium-223 dispensing/administration.

Missing values will be described as such (i.e., no imputation will be performed). There will be no hypothesis testing.

The analysis will be programmed using SAS statistical software (SAS Institute, Cary, North Carolina) in Denmark and in GePaRD, and IBM SPSS in CAPRI. A common statistical analysis

plan will be generated and will include specifications to perform data source-specific analysis such as the specific code lists in the coding system used in each data source.

9.7.1 Sensitivity analysis

The following sensitivity analysis will be performed for the primary outcomes:

- The analysis of the primary outcomes will be performed among users of radium-223 with a confirmed diagnosis of mCRPC.
- In GePaRD, a sensitivity analysis will be performed by adding 5 days lag time after the last administration of abiraterone (see section 9.3.2).

9.8 Quality control

Investigators at each study site are required to archive documents and data sets, statistical programs, and study-relevant documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. Documents will be stored for a retention period of at least 10 years, unless local regulations define otherwise.

Data from the Netherlands will come from data already collected by the CAPRI 2.0 and 3.0 registry. As part of the CAPRI 3.0 registry, quality control of the electronic data collection will be performed by IKNL. Quality control concerns the three stages of data collection stated above and will be either performed manually or automatically. Quality of data is assured by (i) extensive education and regular training of data managers by professionals in the field of oncology and (ii) complex tumour specific decision support, (inter)national registry coding rules and automated quality checks incorporated in the information communication technology (ICT) solutions that are used by the data managers. There are also quality control processes at the source, i.e., in the process of patient identification, and quality control of the extracted data performed by IKNL ICT solutions that comply with national and international interoperability standards.

9.9 Limitations of the research methods

The design of the DUS will allow the description of new users of radium-223 and assessment of the extent to which radium-223 is prescribed in combination with abiraterone acetate. The main limitations of this planned research are as follows:

- The feasibility of capturing radium-223 use in European data sources is limited to a low number of data sources or registries because radium-223 must be administered in a hospital setting and is not reimbursed in all countries. In addition, because of the updated label indication and contraindication, the use of radium-223 across Europe is relatively reduced; therefore, the number of users in each data source is expected to be low (Table 4). This expected low number of radium-223 users can yield imprecise estimates, with wide CIs, if the proportion of patients who use radium-223 in combination with abiraterone acetate is high. However, the number of patients who will use radium-223 in combination with abiraterone acetate is unknown. In Denmark, results less than 5 will need to be clouded (i.e., masked) (see Section 10).
- The evaluation of off-label use in an inappropriate line of therapy requires assessment of "ineligibility for any available systemic mCRPC treatment" among patients using radium-223 in the first or second line, and this was not feasible in any of the data sources. Therefore,

the main objective of the study will be to describe "use in combination," and the proportion of patients that receive radium-223 in the first or second line of therapy as opposed to the third or fourth line, acknowledging that a subset (that may be the majority) of these patients may be receiving radium-223 in the first or second line because they are not eligible to receive other systemic therapies for mCRPC.

- The evaluation of off-label use in patients with mCRPC other than those with symptomatic bone metastasis but with no visceral metastasis requires that location(s) of metastasis and the symptomatic nature of bone metastasis be captured in the data, and this is not feasible in the current data sources. Only partial information on the presence of metastasis (yes/no), and potentially location, is available, although the degree of missingness is unknown. None of the data sources are able to identify whether or not metastases are symptomatic. Similarly, none of the data sources have information available on the number of bone metastases, which is a marker of osteoblastic activity. However, the total serum alkaline phosphatase level may be available in the CAPRI registry and in the Danish hospital data, from which it will be abstracted.
- Use among patients without a diagnosis of mCRPC will be described, although it is expected that the proportion of patients without a diagnosis will be low, and an absent diagnosis is more likely due to underrecording than to the use of radium-223 for treatment of other cancer types.
- Bias related to differential reporting of dispensings/administrations or impacts of contacts with patients and health care professionals will be minimised because the study will be conducted using health information recorded in at least two population-based databases and a CRPC registry in the Netherlands.
- Misclassification of duration of use of abiraterone and other drugs of interest, other than those dispensed intravenously in the hospital, may also occur in GePaRD given that the information will be ascertained from dispensings recorded in the outpatient setting (yes/no) and the amount dispensed.
- The quantity and quality of the data available might differ among the different databases.
- Misclassification of the clinical diagnoses of cancer is not expected in the Netherlands or in Denmark where medical record data abstraction is being performed, but it is a potential issue in GePaRD where diagnosis will be ascertained based on claims. However, studies evaluating data already collected, if combined with validation, are an efficient way to assess potential use in combination with abiraterone acetate. The availability of other information, such as cancer staging following the initial diagnosis, or other proxies of the cancer natural history, is limited in GePaRD and in the population registries in Denmark (21, 22). The degree of completeness in recording information for some variables will also vary across databases. A sensitivity analysis is planned among patients with a diagnosis of mCRPC.
- The population registries in Denmark and GePaRD have a time lag for data availability of up to 1 and 2 years, respectively; thus, a study that includes patients who start radium-223 and requires 6 months of follow-up will result in a final study report approximately 4 years after study start. However, as the time lag between data recording and data extraction will be shorter, i.e., approximately 2 months in the Netherlands, this will allow to have a first interim report containing information from the results using the CAPRI 3.0 registry data in Q3 2021.

9.10 Other aspects

This study will be conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (23) and applicable regulatory requirements including the EMA Guideline on Good Pharmacovigilance Practices: Module VIII – Post-Authorisation Safety Studies (1). The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols can be found in Annex 2.

10. Protection of human subjects

All data in the study are based on existing health records for which individual informed consent for study participation has been requested if required according to local requirements. The data will be or are already deidentified with no breach of confidentiality regarding personal identifiers or health information.

Researchers from each study site will apply for an independent ethics committee review or equivalent bodies, according to local regulations. Country-specific data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

In CAPRI, the study team will identify radium-223 users and will analyse electronic medical records of patients who used radium-223 in the study period. The team collecting the data will go through individual patient records. CAPRI will report to Bayer only aggregate data. As CAPRI has insight into individual patient records, patient consent is needed.

In Denmark, no individual patient consent is required according to local regulations. Approval from the Danish Patient Safety Board and from treating physicians/department heads is required to access to patients' hospital medical records to abstract data. In addition, in Denmark, "clouding" will be used as appropriate to prevent identification of individuals, i.e., any cell count below 5 and any complement count that would allow back-calculation will not be reported as an exact number.

In GePaRD, no individual patient consent is required according to local regulations. Approvals by SHI and their authorities (e.g., German Federal [Social] Insurance Office and the Senator for Science, Health, and Consumer Protection in Bremen) are required.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), individual reporting of adverse reactions is not required for non-interventional study designs that are based on secondary use of data (24).

Reports of the study endpoints will be summarised in aggregated format as part of the interim and final study reports.

12. Plans for disseminating and communicating study results

This study will be registered at www.clinicaltrials.gov and in in the EU PAS Register at http://www.encepp.eu/encepp_studies/indexRegister.shtml. Results will be disclosed in a publicly available database within the standard timelines.

Progress reports will be sent to the competent authorities on regular basis as part of Periodic Safety Update Reports (PSURs) or Periodic Benefit-Risk Evaluation Reports (PBRERs).

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. Current guidelines and recommendations on good publication practice, and The International Committee of Medical Journal Editors (ICMJE) criteria for authorship, will be followed (1, 25, 26). No individual investigator may publish on the results of this study, or their own patients, without prior review and comment by the MAH.

13. References

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Annex 1: List of stand-alone documents

Table 6: List of stand-alone documents

Document name	Final version and date (if available)
None	

Annex 2: ENCePP checklist for post-authorisation safety study (PASS) protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
DIRECT: **D**rug Utilizat**I**on Study of **R**adium 223 under Routin**E** **C**linical Prac**T**ice in Europe

EU PAS Register® number: Study not yet registered
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical data set is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1, 8.2
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

There will be no hypothesis testing. The a priori hypothesis is that the combination of radium-223 and abiraterone acetate is rare.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g., relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm [NNH])	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☒	☐	☐	9.2.1
	4.2.4 Disease/indication	☒	☐	☐	9.2.1
	4.2.5 Duration of follow-up	☒	☒	☐	9.2.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.2
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☒	☐	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) an appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQOL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

There will not be any comparison

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

There will not be any comparison

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.1

Comments:

There will not be any comparison

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7, 9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: PPD

Date:

Signature: _____

Annex 3: Additional information

Not applicable.

Annex 4: Signature pages