Post-Authorisation Safety Study (PASS) Report - Study Information

Acronym/Title	DIRECT: **D**rug Utilisat**I**on Study of **R**adium-223 Under Routin**E** **C**linical Prac**T**ice in Europe
Report version and date	Final study report V0.3, 1 June 2023
IMPACT study number	20702
Study type / Study phase	Observational Post-market surveillance, phase 4 (postmarketing clinical follow-up study) PASS Joint PASS: ☐ YES ☒ NO
EU PAS Register Number	EUPAS37163
Active substance	Various Therapeutic Radiopharmaceuticals (V10XX03), radium (^{223}Ra) dichloride
Medicinal product/Medical Device/Combination Product	Xofigo (Radium-223 [Ra-223])
Product reference	EU/1/13/873/001
Procedure number	EMEA/H/C/002653/MEA/014
Study Initiator and Funder	Bayer AG
Research question and objectives	The DIRECT drug utilisation study intended to answer the following question, "What proportion of users of radium-223 receive it in compliance with the new indication and contraindications introduced in October 2018?" To assess this, the primary objective of the study was 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 metastatic castration-resistant

	prostate cancer (mCRPC); and (3) the proportion who receive radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC. The secondary objectives of the study were to (1) estimate the difference before and after the 2018 label change in the proportions estimated in the primary objective and (2) characterise the population of new users of radium-223, irrespective of combination with other systemic therapies for castration-resistant prostate cancer, by describing the patients' characteristics, including the presence and, when available, location of metastases on the date of initiation of radium-223 (index date).
Country(-ies) of study	Denmark, Germany, The Netherlands
Author	Joan Fortuny (RTI Health Solutions) and PPD (RTI Health Solutions) on behalf of the DIRECT PASS team Contact information: PPD

Marketing authorisation holder

Marketing authorisation holder(s)	Bayer AG
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1. Abstract

Acronym/Title	DIRECT: **D**rug Utilisat**I**on Study of **R**adium-223 Under Routin**E** **C**linical Prac**T**ice in Europe
Report version and date **Author**	V0.3, 1 June 2023 Joan Fortuny and PPD (RTI Health Solutions) on behalf of the DIRECT PASS team Contact information: PPD
IMPACT study number	20702
Keywords	Xofigo, radium-223, drug utilisation study
Rationale and background	Radium-223 is a radioactive agent indicated for the treatment of adults with metastatic castration-resistant prostate cancer (mCRPC). The randomised controlled trial ERA-223 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 study arm treated with radium-223 and abiraterone acetate and prednisone/prednisolone than in the control arm. This outcome resulted in a change in the European Union (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 to use among patients who are in progression after at least 2 prior lines of systematic therapy for mCRPC (other than luteinising hormone–releasing hormone analogues) or who are ineligible for any other available systemic mCRPC treatment. Bayer performed this drug utilisation study (DUS) in Europe to evaluate the effectiveness of the risk minimisation measures by assessing compliance with the new indication and contraindications set after the 2018 EU label change.
Research question and objectives	This DIRECT post-authorisation safety study (PASS) was intended to answer the following question, "What proportion of users of radium-223 receive it in compliance with the new indication and contraindication introduced in October 2018?" To answer this question, the **primary objectives** of the DIRECT PASS were to estimate the following among the population of patients receiving radium-223 during the period *after* the 2018 European Medicines Agency (EMA) label change: (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 at least 2 prior lines of systemic therapy for mCRPC. The **secondary objectives** are to (4) estimate the difference before and after the label change in the proportions estimated in the primary objectives and (5) characterise the population of new users of radium-223, irrespective of combination with other systemic therapies for castration-resistant prostate cancer (CRPC) at treatment start for both study periods.
Study design	This was an observational, European prospective cohort DUS of new users of radium-223 in the Netherlands, Denmark, and Germany. The study used existing data sources (secondary data collection) through electronic medical records and medical record abstraction in the Netherlands, a combination of routinely collected data from national registries and data from electronic medical record abstraction in Denmark, and claims data from a population-based database in Germany. A period before the label change was assessed as a reference for a period after the label change. Compliance with the indication and contraindication introduced in the October 2018 EU label change was measured during these 2 periods. A common study design, protocol, and statistical analysis plan were followed in all 3 participating data sources. Each country-specific data source was managed, and country-specific data were analysed locally.
Setting	The study population included new users of radium-223 during the study periods captured in each data source. The study period included time periods before and after the label change. The “before” period started in November 2013, the month of radium-223 approval, and ended in November 2017, the month when the first Direct Healthcare Professional Communication letter was sent. The “after” period included an enrolment phase during which patients initiating radium-223 in each data source were identified. The enrolment phase started in April 2019 (6 months after the label change) and continued through a follow-up phase of at least 6 months after the last new user of radium-223 was identified. A 6-month follow-up allowed for the evaluation of radium-223 in combination with abiraterone acetate or other systemic therapies for mCRPC after the last radium-223 new user was identified, so that this patient could be followed during the approximately 6-month duration of radium-223 treatment.

Subjects and study size, including dropouts	For the main study period (i.e., the period after the 2018 EU label change for Xofigo [after–label change period]), a total of 184 patients exposed to radium-223 were included: 53 in the Netherlands, 68 in Germany, and 63 in Denmark. For the reference period before the label change, a total of 883 patients were included: 243 in the Netherlands, 580 in Germany, and 60 in Denmark.
Variables and data sources	The study was conducted using the following existing secondary data sources: • Electronic medical record data of all new users of radium-223 from an existing register of patients with CRPC in the Netherlands (CAPRI). CAPRI 1 and 2 were used to identify users of radium-233 before the label change from 20 hospitals, and CAPRI 3, to which 6 hospitals contributed data, was used after the label change. Users of radium-223 were identified through drug substance or product names identified in the electronic medical records of patients in CAPRI 2 and 3 from participating hospitals. • Data abstracted from existing medical records of all new users of radium-223 in 2 treating hospitals in Denmark. Initially, users of radium-223 were 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 were identified, data from hospital medical records for these patients were retrieved by trained employees of the Aarhus University Hospital. To supplement data from the medical record abstraction, additional data on comorbidities, cancer, and comedications were obtained through linkage to the DNPR and Danish Cancer Registry. 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 were captured in the German Pharmacoepidemiological Research Database (GePaRD), which is a population-based claims database. Users of radium-223 were identified based on dispensations of radium-223 recorded in the database. GePaRD covers approximately 15 to 17 million individuals per year from 4 statutory health insurance providers (SHIs) in Germany (2 large SHIs and 2 small SHIs) 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. Ultimately, reliable data on the prior use of systemic therapies for mCRPC were available from only 1 (large SHI) of the 4 participating SHIs. Therefore, the analyses of the second and third objectives were conducted in a restricted sample including only patients from this large SHI. Data on abiraterone use were available for all 4 SHIs.
Results	A total of 1 patient (1.9%) in the Netherlands, 3 patients (4.2%) in Germany, and $1 \leq n < 5$ patients in Denmark (exact number masked due to local privacy regulations) used radium-223 in combination with abiraterone in the after–label change period. A total of 5 patients (9.4%) in the Netherlands, 4 (11.8%) in Germany, and $1 \leq n < 5$ in Denmark used radium-223 in combination with other systemic therapies for mCRPC in the after–label change period. Use of radium-223 without at least 2 prior lines of systemic therapy for mCRPC occurred in 21 patients (39.6%) in the Netherlands, 9 (26.5%) in Germany, and $1 \leq n < 5$ in Denmark in the after–label change period.
Discussion	In patients covered by the participating data sources in the Netherlands, Germany, and Denmark, use of radium-223 with abiraterone or with other systemic therapies for mCRPC was very limited, in line with the prescription limitations imposed by the 2018 EU label change. In addition, many of the patients with combination use received abiraterone or other systemic therapies only at the last cycle, likely at the end of the treatment course with radium-223. Use of radium-223 without at least 2 prior lines of systemic therapy for mCRPC remained relatively common in the period after the 2018 EU label change in the Netherlands and Germany, but was uncommon in Denmark. It is important to note that the eligibility of patients to receive other systemic therapies for mCRPC could not be determined in this study; therefore, this finding reflects, at least in part, the proportion of patients in whom other systemic therapies were contraindicated. The relatively small number of patients enrolled in the after–label change period makes findings reported in this report prone to random variation.
Marketing Authorisation Holder(s)	Bayer AG

2. List of abbreviations

ATC	Anatomical Therapeutic Chemical (Classification System)
CAPRI	Castration-Resistant Prostate Cancer Registry
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRPC	Castration-Resistant Prostate Cancer
CSPC	Castration-Sensitive Prostate Cancer
DNPR	Danish National Patient Registry
DUS	Drug Utilisation Study
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Union Electronic Register of Post-Authorisation Studies
GePaRD	German Pharmacoepidemiological Research Database
GPP	Good Pharmacoepidemiology Practices
ICD-10	*International Classification of Diseases, Tenth Revision*
ICD-10-GM	*International Classification of Diseases, Tenth Revision, German Modification*
IV	intravenous
LHRH	Luteinising Hormone–Releasing Hormone
MAH	Marketing Authorisation Holder
mCRPC	Metastatic Castration-Resistant Prostate Cancer
N/A	Not Available
NA	Not Applicable
OS	Observational Study
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
Q*n* yyyy	Quarter of the Calendar Year
Q1, Q3	First and Third Quartiles
RTI-HS	RTI Health Solutions
SD	Standard Deviation
SHI	Statutory Health Insurance Provider

3. Investigators

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4. Other responsible parties

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Contact details of the responsible parties are available upon request.

5. Milestones

Table 1: Milestones

Milestone	Planned date (before COVID-19 pandemic)	Actual date	Comments
Protocol (version 2.0) endorsed by the EMA	October 2019	October 2019	
Start of data collection[a]	The Netherlands: Q4 2020 Germany: Q3 2022 Denmark: Q3-Q4 2021	The Netherlands: May 2021 Germany: 30 September 2022 Denmark: 5 July 2022	The COVID-19 pandemic introduced a 6-month delay to the start of data collection in the Netherlands because researchers had limited ability to enter hospitals to conduct chart abstraction.
End of data collection[b]	The Netherlands: Q1-Q2 2021 Germany: Q4 2022 Denmark: Q3 2022	The Netherlands: April 2022 Germany: 31 March 2023 Denmark: 30 May 2023	
Registration in the EU PAS Register	Q4 2020	13 October 2020	
Interim report	Q3 2021	13 September 2022	Overall, a 1-year delay in the preparation of the interim report occurred because of limitations imposed by the COVID-19 pandemic.
Final report	Q1-Q2 2023	Q2 2023	

COVID-19 = coronavirus disease 2019; EMA = European Medicines Agency; EU PAS Register = European Union Electronic Register of Post-Authorisation Studies; Q*n* yyyy = quarter of the calendar year.

[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).

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

6. Rationale and background

Radium-223 is a first-in-class alpha particle–emitting, radioactive agent used as monotherapy or in combination with a luteinising hormone–releasing hormone (LHRH) analogue for the treatment of adults with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least 2 prior lines of systemic therapy for mCRPC (other than LHRH analogues) or in those who are 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 doctor in a designated clinical setting, such as a licensed practice or a hospital outpatient setting, where a radiology infrastructure is available. Each radium-223 dose should be administered intravenously for at least 1 minute every 4 weeks, for up to a total of 6 injections, and the treatment may be completed in 5 to 6 months.

The ERA-223 randomised controlled trial was designed to evaluate the efficacy and safety of radium-223 in combination with abiraterone acetate and prednisone/prednisolone versus placebo in combination with abiraterone acetate and prednisone/prednisolone in asymptomatic, or mildly symptomatic, chemotherapy-naive subjects with bone-predominant mCRPC.

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 study arm treated with radium-223 in combination with abiraterone acetate and prednisone than in the control arm treated with abiraterone acetate and prednisone only (2). These results triggered an article 20 referral procedure led by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) and resulted in a change in the European Union (EU) product information in 2018. The updated radium-223 label indication and contraindication are as follows (3):

- 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."

Per the agreed risk management plan requirements, Bayer is performing 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 2 prior lines of systemic therapy for mCRPC (i.e., use of radium-223 as first- or second-line therapy). The assessment of whether use without 2 prior lines of systemic therapy for mCRPC represents on- or off-label use was not possible in the 3 data sources in Europe used in this study.

7. Research question and objectives

The **primary objectives** of the DIRECT post-authorisation safety study (PASS) were to estimate the following among the population of patients who received radium-223 during the period after the 2018 EU label change:

- The proportion of patients newly treated with radium-223 who receive at least 1 cycle of radium-223 in combination with abiraterone acetate. Only the first treatment episode consisting of up to 6 cycles of radium-223 will be considered.
- The proportion of patients newly treated with radium-223 who receive at least 1 cycle of radium-223 in combination with other systemic therapies for mCRPC, except LHRH analogues. Only the first treatment episode consisting of up to 6 cycles of radium-223 will be considered.
- The proportion of patients newly treated with radium-223 who start treatment with radium-223 without at least 2 prior lines of systemic therapy for mCRPC, except LHRH analogues. Only the first treatment episode consisting of up to 6 cycles of radium-223 will be considered.

The **secondary objectives** of the DIRECT PASS are as follows:

- To estimate the 3 primary objectives among the population of patients newly treated with radium-223 in the period before the 2018 EU label change and to estimate the resulting differences between the before and after periods.
- To characterise the population of new users of radium-223 at treatment start for both study periods.

Additional analyses report on the following:

- The number of cycles in which radium-223 was used in combination with abiraterone or other systemic therapies.
- The proportion of patients who use radium-223 in combination with abiraterone acetate or other systemic therapies for mCRPC during the 30 days after the last administration of a cycle of radium-223.

8. Amendments and updates

Table 2: Amendments

No.	Date	Section of study protocol	Amendment or update	Reason
1	30 April 2022	6. Milestones	Adapted timelines to reflect a 1-year delay in delivering the interim study report	The adapted timelines reflect the delays caused by the COVID-19 pandemic on enrolment and data extraction for CAPRI 3

COVID-19 = coronavirus disease 2019.

9. Research methods

9.1 Study design

This was an observational, European, cohort DUS of new users of radium-223. The study was conducted following a common statistical analysis plan in 3 existing data sources in the Netherlands, Denmark, and Germany.

Data from each country were managed and analysed locally by local investigators at Leibniz Institute for Prevention Research and Epidemiology (BIPS) in Germany, CAPRI in the Netherlands, and Aarhus University in Denmark, with the support from epidemiologists and biostatisticians from RTI Health Solutions (RTI-HS).

9.2 Setting

The study population consisted of men with castration-resistant prostate cancer (CRPC) enrolled in one of the participating data sources. All users of radium-223 identified in each data source during the before or after periods defined for each data source were eligible to be included in the study.

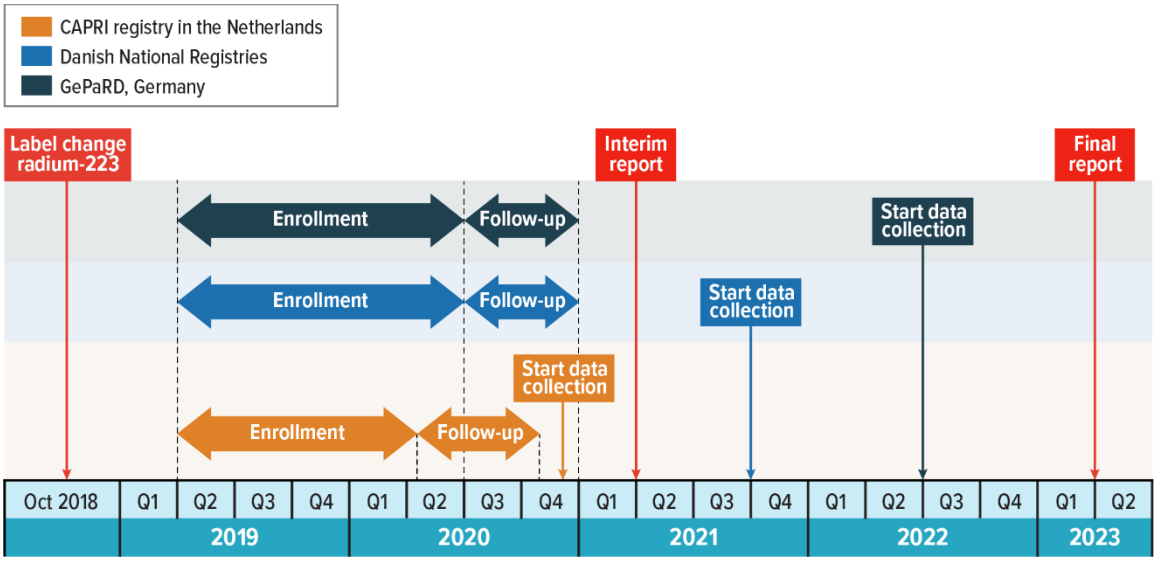
The study comprised the following 2 separate periods:

- The "period before the 2018 EU label change" [before–label change period] started on 13 November 2013, the date when radium-223 was marketed, and ended on 30 November 2017, the day when the first Direct Healthcare Professional Communication letter was sent. Patients were allowed to enrol through 31 May 2017, so that a minimum of 6 months of follow-up for study outcomes for a patient enrolling on the last day of the enrolment period was possible.
- The "period after the 2018 EU label change" [after–label change period] started on 30 April 2019 (i.e., 6 months after the label change). In CAPRI, patients were allowed to enrol through 30 April 2020, and the study period extended through 31 October 2020 to allow for at least 6 months of follow-up for study outcomes for a patient enrolling on the last day of the enrolment period. In Denmark and the Netherlands, the enrolment phase extended through June 2020; given that data extraction occurred annually for the full calendar year in these data sources, at the time of data extraction, the study period would include a minimum of 6 months of follow-up, i.e., data through December 2020 were available.

Follow-up (patient observation time): Patients were 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 occurred first.

Compliance with the indication and contraindications introduced at the time of the label change was measured during these 2 periods. The period after the 2018 label change was the period of interest, and the period before the 2018 label change was used as the reference. Figure 1 details the timeframe.

Figure 1: Study overview



Q*n* yyyy = quarter of the calendar year.

9.3 Subjects

The study population included new users of radium-223 who were captured in each data source during the study periods before and after the label change.

New users were defined as men of any age who initiated treatment with radium-223 during 1 of the 2 study periods (Section 9.2) and who had no previous record of an administration of radium-223. Therefore, users identified before the label change were not eligible for inclusion in the period after the label change.

The index date for patients meeting all the inclusion criteria was defined as the date of the first ever administration of radium-223 within either of the 2 study periods (Section 9.2).

Inclusion criteria:

- Male sex.
- In Denmark or Germany, 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) or, in the Netherlands, uninterrupted enrolment in CAPRI after the diagnosis of CRPC. Patient characteristics were obtained retrospectively from the medical records after the patient joined CAPRI at progression to CRPC.
- A first ever recorded use of radium-223 during either of the 2 study periods that were defined by the label change (Section 9.2).

Exclusion criterion:

- Prior use of radium-223.

Considerations on the application of inclusion and exclusion criteria:

- To allow for the characterisation of users of radium-223, including its potential off-label use, no age restrictions or additional exclusion criteria were applied.
- Patients were assessed to identify the use of radium-223 for which they qualified as new users within the 2 study periods of interest (Section 9.2). A patient could qualify as a new user only once and therefore could be included in only 1 of the 2 study periods.
- If all criteria were not met at the time of a patient's first use of radium-223, subsequent uses of radium-223 were not considered as new use and were thus disregarded; such patients were not included in the study.

9.4 Variables

9.4.1 Exposure definitions

For both study periods (i.e., before and after the label change), the main exposure of interest was new use of radium-223, which defined the study population.

In CAPRI, the drug substance or product name recorded in the electronic medical records was used to capture data on exposure to the study medications. CAPRI 1 and 2 were used to obtain exposure data for radium-223 for the before–label change period. Manual extraction of the medical records was performed to collect information in the registry electronic case report form on the type of systemic therapy for mCRPC. This included available information on date of administration, prescribed cycles, and dose administered. CAPRI 3 was used to obtain the semiautomated exposure data for radium-223 for the after–label change period. Semiautomated extraction of the relevant exposure data from the electronic medical records provided information similar to the manual extraction conducted for CAPRI 1 and 2, with improved efficiency. This semiautomated extraction underwent satisfactory pilot testing for completeness and accurateness.

In Denmark, all cancer therapies are administered in hospitals. Hospital-administered therapies are not available in the Danish National Prescription Registry (DNPR) because it captures only outpatient dispensings in community pharmacies (4). Selected hospital-administered therapies are assigned local procedure codes, which can be used to document treatment in the DNPR. Potential users of radium-223 were identified based on a hospital procedure code available in the DNPR): BWGG5, "Isotope therapy with radium-223 dichloride." Once potential users of radium-223 were identified via this code, use of radium-223 was confirmed during the abstraction of hospital medical records. The completeness and consistency of use of any given code are unknown, although the positive predictive value is expected to be high (5).

In Germany, use of radium-223 was 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 [Anatomical Therapeutic Chemical] code V10XX03) in the German Pharmacoepidemiological Research Database (GePaRD).

9.4.1.1 Important definitions

- **New user of radium-223:** a patient who was dispensed or administered a first cycle of radium-223 during the enrolment period for 1 of the 2 study periods and who had no prior evidence of having used radium-223. Concurrent administration of abiraterone or other systemic therapies for mCRPC did not affect the status of new user of radium-223.

- **Index date:** date of the first recorded use of radium-223 during a study period (i.e., index use of radium-223).
- **Exposure to radium-223:** a patient was considered exposed to radium-223 and at risk of meeting the criteria for a study outcome during the 30 days after each valid administration of radium-223 (Figure 2 in Section 9.4.2.1 and Figure 3 in Section 9.4.2.2).

9.4.1.2 Main exposure of interest

Radium-223 (ATC code: V10XX03; Xofigo) was the main exposure of interest. Radium-223 is administered intravenously over at least 1 minute, and a dose should be administered once every 4 weeks, up to a total of 6 injections. Typically, the treatment may be completed in 5 to 6 months.

9.4.1.3 Other exposures of interest

The following exposures were recorded, described, and used to describe patients and define the study outcomes, as appropriate (Section 9.4.2):

- Systemic therapies for mCRPC are as follows:
  - Abiraterone acetate (ATC: L02BX03): taken orally, usually at a dose of 1,000 mg per day in combination with prednisone until disease progression
  - Enzalutamide (ATC: L02BB04): taken orally, usually at a dose of 160 mg per day until disease progression
  - Docetaxel (ATC: L01CD02): administered intravenously every 3 weeks until disease progression
  - Cabazitaxel (ATC: L01CD04): administered intravenously every 3 weeks until disease progression
  - Sipuleucel-T (ATC: L03AX17): administered intravenously every 2 weeks for 3 cycles (this drug was available only briefly in the EU and was never available in Denmark)
  - Pembrolizumab (ATC: L01FF02): administered intravenously every 3 weeks until disease progression
- Concomitant use of prednisone (ATC: H02AB07), prednisolone (ATC: H02AB06), or methylprednisolone (ATC: H02AB04) administered orally in conjunction with other systemic therapies for mCRPC. Of note, use of corticosteroids was ultimately not available in CAPRI.
- LHRH analogues:
  - Leuprolide (ATC: L02AE02)
  - Goserelin (ATC: L02AE03)
  - Triptorelin (ATC: L02AE04)
  - Histrelin (ATC: L02AE05)
  - Buserelin (ATC: L02AE01)
  - Nafarelin (ATC: H01CA02)
  - Gonadorelin (ATC: H01CA01)
- LHRH antagonists:
  - Degarelix (ATC: L02BX02)

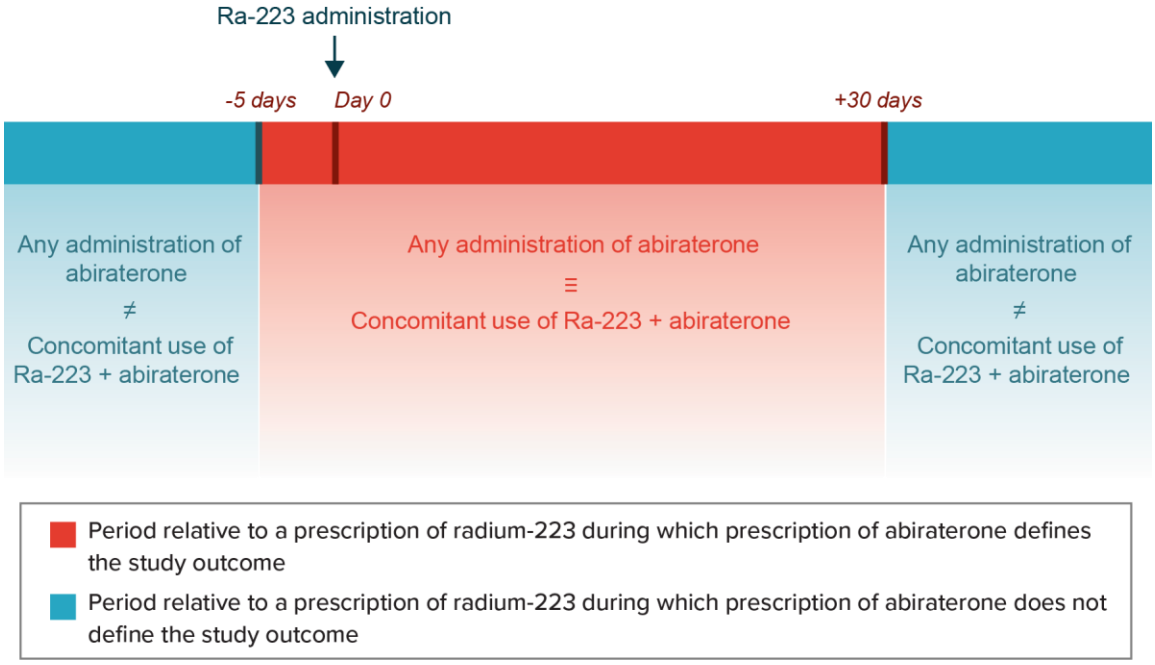
- Other medications of interest used in the description of patients participating in the study:
  - Cytotoxic drug: mitoxantrone (ATC: L01DB07)
  - Antiandrogen drugs: apalutamide (ATC: L02BB05), bicalutamide (ATC: L02BB03), darolutamide (ATC: L02BB06), flutamide (ATC: L02BB01), nilutamide (ATC: L02BB02)
  - Bone-health agents:
    - Bisphosphonates: etidronate (ATC: M05BA01), clodronate (ATC: M05BA02), tiludronate (ATC: M05BA05), pamidronate (ATC: M05BA03), alendronate (ATC: M05BA04), ibandronate (ATC: M05BA06), risedronate (ATC: M05BA07), zoledronate (ATC: M05BA08)
    - Denosumab (ATC: M05BX04)
    - Bone morphogenetic proteins (ATC: M05BC)
  - Drugs affecting bone structure and mineralisation:
    - Ipriflavone (ATC: M05BX01)
    - Aluminium chlorohydrate (ATC: M05BX02)
    - Strontium ranelate (ATC: M05BX03)
    - Burosumab (ATC: M05BX05)
    - Romosozumab (ATC: M05BX06)
    - Strontium ranelate and cholecalciferol (ATC: M05BX53)

9.4.2 Outcome definitions

9.4.2.1 Use of radium-223 in combination with abiraterone

The outcome “use of radium-223 in combination with abiraterone acetate” was defined as a patient having at least 1 administration of abiraterone acetate on the same date or within 30 days after an administration of radium-223. Because radium-223 is given at 4-week intervals for a total of 6 or more cycles, an administration of abiraterone within the 30 days after a radium-223 administration would be considered to have occurred within 1 cycle of radium-223 (3). Use in combination was also defined when an administration of radium-223 occurred within 5 days after the last administration of abiraterone. This 5-day period is based on the elimination half-life of abiraterone (Figure 2). Overall, an at-risk period of 36 days was defined by each administration of radium-223.

Figure 2: Definition of the outcome "use of radium-223 in combination with abiraterone"



Ra-223 = radium-223.

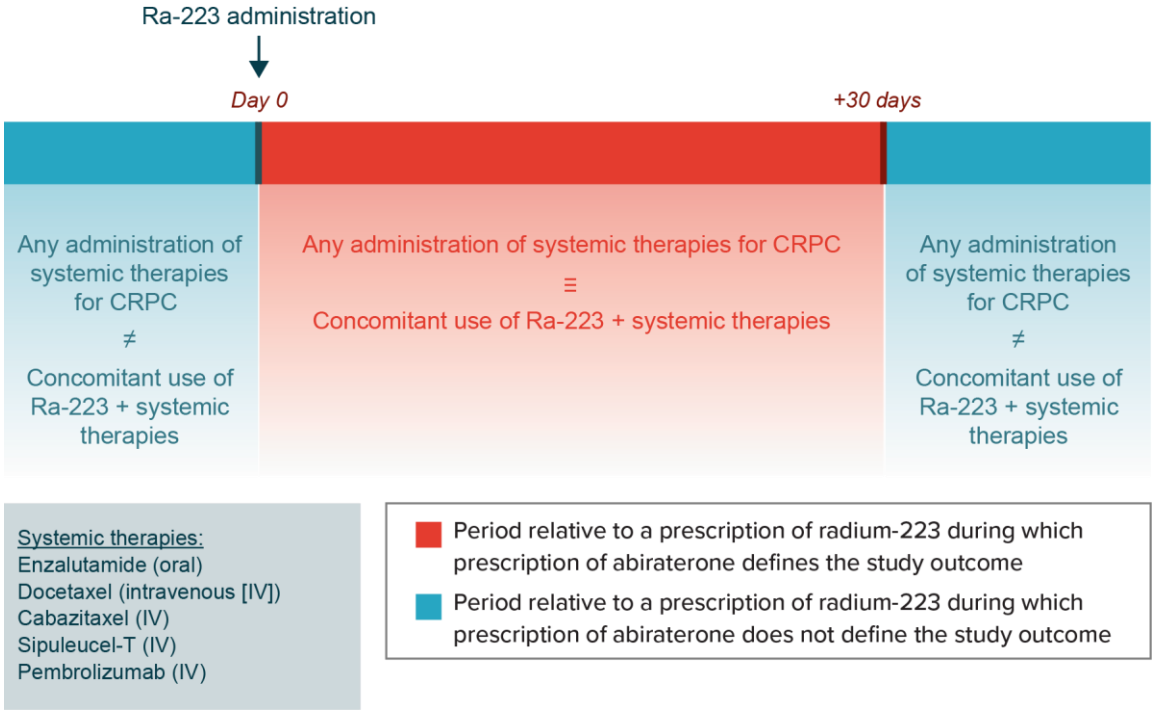
When abiraterone was last administered more than 5 days before the index date for radium-223, use in combination of abiraterone acetate and radium-223 was not assumed, even if the abiraterone drug supply or recorded treatment plan overlapped with the use of radium-223. In this situation, a switch from abiraterone acetate to radium-223 was assumed.

This outcome was assessed in the periods before and after the label change.

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

The outcome "use of radium-223 in combination with other systemic therapies for mCRPC, except LHRH analogues" was defined as a patient having at least 1 administration of systemic therapy for mCRPC, other than abiraterone acetate, on the same date or within 30 days after an administration of radium-223. Having an administration of radium-223 after the last administration of other systemic therapies for mCRPC was not considered use in combination, even if the drug supply or recorded treatment plan overlapped with the use of radium-223 (Figure 3).

Figure 3: Definition of the outcome "use of radium-223 in combination with other systemic therapies for mCRPC"



CRPC = castration-resistant prostate cancer; IV = intravenous; Ra-223 = radium-223.

Administration of other systemic therapies for mCRPC that occurs more than 30 days after the last administration of radium-223 was not considered use in combination.

The following medications were included as other systemic therapies for mCRPC:

- Enzalutamide (ATC: L02BB04)
- Docetaxel (ATC: L01CD02)
- Cabazitaxel (ATC: L01CD04)
- Sipuleucel-T (ATC: L03AX17)
- Pembrolizumab (ATC: L01FF02)

This outcome was assessed in the periods before and after the label change.

9.4.2.3 Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC

New users of radium-223 included in the study were classified as receiving this drug in first, second, third, or fourth or subsequent therapy line for mCRPC based on having used any of the following medications at least once before the index date:

- Abiraterone (ATC: L02BX03)
- Enzalutamide (ATC: L02BB04)
- Docetaxel (ATC: L01CD02)
- Cabazitaxel (ATC: L01CD04)
- Sipuleucel-T (ATC: L03AX17)
- Pembrolizumab (ATC: L01FF02)

A single use of each drug counted as 1 prior line, irrespective of the completeness or number of cycles received of the specific drug.

This outcome was assessed in the periods before and after the label change.

9.4.2.4 Characterisation of new users of radium-223

To characterise new users of radium-223, the demographic and clinical characteristics listed below were described at treatment start for both study periods.

- Age.
- Calendar year of radium-223 start.
- Time since first (i.e., incident primary) prostate cancer diagnosis (in months).
- Time since surgical castration, if applicable (in months).
- Time since first use of an antiandrogen medication (in months).
- Confirmed diagnosis of mCRPC:
  - The Netherlands: as recorded in CAPRI (yes/no). The type of progression, including presence and location of metastases, was recorded in CAPRI at the date of CRPC diagnosis. If no radiologic assessment was performed, the metastatic status was considered unknown (missing). Patients who had known metastasis before progression to CRPC were considered metastatic upon progression to CRPC irrespective of the presence or not of a radiologic assessment at CRPC progression
  - Denmark: As recorded in the hospitals and identified through medical record abstraction (in-hospital medications)
  - Germany: confirmation of castration-resistant versus castration-sensitive status was not possible in GePaRD; therapies were assumed to have been administered for mCRPC
- Time since first confirmed diagnosis of mCRPC (in months) (not available in GePaRD).
- Prior use of therapies for CRPC and castration-sensitive prostate cancer (CSPC): i.e., cytotoxic drugs, immunotherapies, antiandrogens, LHRH agonists/analogues, LHRH antagonists, and corticosteroids. Prior use of these therapies was defined as having at least 1 administration (see list of drug substances and ATC codes in Section 9.4.1.3) at any time before the index date.
- Level of serum alkaline phosphatase at the index date or the closest measurement before the index date: as U/L and categorised as above or below a threshold (e.g., < 220 U/L and ≥ 220 U/L). Only measurements up to 2 months before or 1 week after the index date were considered. Measurements were hierarchically prioritised as follows:
  - The closest measurement before the index date if it occurred 1 week or less before the index date.
  - The closest measurement within 1 week after the index date if the closest measurement before the index date is more than 1 week before the index date.
  - The closest measurement within 2 months before the index date if no measurements within 1 week after the index date were available.
- Prior use of bone-health agents (i.e., bisphosphonates, denosumab) (see list of drug substances and ATC codes in Section 9.4.1.3): defined as having at least 1 dispensing or

administration of bone-health agents at any time during the 6 months before but not including the index date.

- Prior diagnosis of osteoporosis before the index date.

9.5 Data sources and measurement

9.5.1 CAPRI, the Netherlands

CAPRI is a disease-specific registry in the Netherlands available for observational research (6). An initial registry (CAPRI 1 and 2) was completed between 2010 and 2017 and included patients diagnosed with CRPC between 1 January 2010 and 31 December 2015. A second registry (CAPRI 3) was started in 2021 and included patients diagnosed with either metastatic CSPC or mCRPC diagnosed after 1 January 2016.

Data for CAPRI 1 and 2 were obtained from 20 hospitals. Based on the participating hospitals, it is estimated that around 20% of patients with CRPC in the Netherlands were included in CAPRI 1 and 2. The study data from CAPRI 3 were obtained from 6 hospitals: 4 reference hospitals, 1 academic hospital, and 1 general hospital from various geographical regions of the country. Of the 6 hospitals contributing data to CAPRI 3, 5 also contributed patients to CAPRI 1 and 2. The number of hospitals that contributed data to CAPRI 3 during the study period was smaller than originally expected due to the limitations imposed by the coronavirus disease 2019 (COVID-19) pandemic. This prompted extension of the data collection period originally planned for CAPRI 3 to allow as many hospitals as possible to contribute data to the after–label change period.

Data from CAPRI used in the present study were identified and abstracted from patient records in participating hospitals by trained data managers using a web-based electronic data abstraction form. This process was partially automated in CAPRI 3.

Data from the before–label change period were retrieved from CAPRI 1 and 2, which included patients diagnosed with CRPC who were new users of radium-223 at any time between 13 November 2013 and 31 May 2017. Follow-up of patients to identify study outcomes extended through 30 November 2017.

Data from the after–label change period were retrieved from the CAPRI 3 and covered patients diagnosed with CRPC who were new users of radium-223 at any time between 30 April 2019 and 30 April 2020. Follow-up of patients to identify study outcomes extended through 31 October 2020.

9.5.2 Danish National Health Registries and other data sources

Potential users of radium-223 were identified using data from the DNPR, including departments administering radium-223 treatment. Of 3 treating departments in Denmark in which potential patients treated with radium-233 were identified, 2 agreed to participate. As the actual number of the potentially eligible patients exceeded the planned number, all patients in the after–label change period were included, and a sample of those in the before–label change period were selected to reach the number of patients planned in the protocol. For these patients, data from hospital medical records were abstracted to establish dates of treatment with radium-223 and other relevant treatments. The data collection form was created in collaboration with the Aarhus University investigators based on study needs and available data.

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 and the Danish Cancer Registry, among others. Data collected in these registries are available for research purposes.

9.5.3 German Pharmacoepidemiological Research Database (GePaRD)

GePaRD is a population-based database of claims obtained from 4 statutory health insurance providers (SHIs) in Germany (2 large SHIs and 2 small SHIs) and currently includes information on about 25 million persons who have been insured with one of the participating providers since 2004 or later (7). 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 20% 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. Outpatient services are registered according to EBM (Einheitlicher Bewertungsmaßstab) codes, which were developed for payment of physicians for the outpatient treatment of German SHI patients.

Ultimately, detailed data on the prior use of systemic therapies for mCRPC were available from only 1 large SHI of the 4 participating SHIs. Until 2010, information on parenteral preparations of chemotherapies and monoclonal antibodies in German claims data was restricted to the dispensation of such a preparation including the date, but without details on the substances included in the preparation. Since 2010, the substances included in the preparations also have to be recorded, but only 1 SHI contributing to GePaRD included this information in the standard data set transferred to BIPS. As long as there were no projects based on GePaRD requiring this information, it was not recognised that the other SHIs did not provide this information. Once this was recognised, the BIPS study team tried to get this data retrospectively but was only partly successful: the 2 small SHIs provided some data but not for all the data years that would be required for the Xofigo DUS project; the other large SHI did not provide the data. Therefore, the analyses of the second and third objectives were conducted in a restricted sample including patients from only 1 SHI.

9.6 Bias

Misclassification of exposure to the study drugs, including dose and duration of use, was theoretically possible but unlikely in the Netherlands and Denmark because information was obtained from the patients' medical records by trained personnel in those 2 countries. For the same reason, misclassification of the clinical diagnosis of cancer was not expected in these 2 data sources either.

In the Netherlands, if patients enrolled in CAPRI were not representative of the overall population of patients with mCRPC in the country, the study results may not be generalisable. Patients enrolled in CAPRI 1 and 2 were deemed representative of the CRPC patients in the Netherlands based on comparisons with the nationwide registry on prostate cancer. However, because CAPRI 3 data came from only 6 hospitals, the results are reflective of the patients treated in these hospitals, and possible differences with the clinical practices in other hospitals cannot be ruled out.

In Germany, misclassification of the duration of exposure to drugs used in outpatient settings, including abiraterone, may have occurred given that the information was ascertained from drug

dispensing and the amount dispensed. As diagnoses in Germany were ascertained based on insurance claims, and mCRPC status could not be confirmed, misclassification of the clinical diagnosis may have occurred. All systemic therapies for prostate cancer were assumed to have been administered for CRPC.

9.7 Study size

The size of the study was driven by the uptake of radium-223 in the study population and included all new users of radium-223 captured in the participating data sources. Overall, CAPRI 1 and 2 enrolled 243 patients from 20 hospitals. CAPRI 3 enrolled 53 patients from 6 hospitals. GePaRD included 580 patients before the label change and 71 patients after the label change. In the Danish National Health Registries, 205 patients before the label change and 74 patients after the label change were identified from the 3 hospitals in Denmark that administered radium-223 during the study period. The chart abstraction was performed in 2 hospitals that agreed to participate in the study. All 63 patients treated with radium-223 identified during the after–label change period from those 2 hospitals were included in the analyses. For the before–label change period, a sample of 100 patients was selected; of those, 60 charts could be abstracted.

9.8 Data transformation

All the following variables were ascertained:

- Age (years): mean; median; quartiles 1 and 3 (Q1, Q3); minimum; maximum; and < 50, 50 to 59, 60 to 69, 70 to 79, 80 to 89, and ≥ 90 years
- Calendar year at the prescription date: 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020
- Time since first prostate cancer diagnosis (months): mean, median, Q1, Q3, minimum, maximum
- Time since first use of an antiandrogen medication (months): mean, median, Q1, Q3, minimum, maximum
- Confirmed diagnosis of mCRPC: yes, no (not available in GePaRD)
- Time since first mCRPC confirmed diagnosis (months): mean, median, Q1, Q3, minimum, maximum (from patient charts in Denmark and CAPRI; based on an algorithm in GePaRD)
- Prior use of therapies for CRPC: yes, no, for each therapy of interest (incomplete capture in GePaRD)
- Prior use of therapies for CSPC: yes, no, for each therapy of interest (not available in GePaRD; as castration-resistant or castration-sensitive status was not ascertainable in GePaRD, all therapies were assumed to have been administered for CRPC)
- Presence of metastases: bone metastases, visceral metastases, unknown location
- Levels of serum alkaline phosphatase: percentage < 220 U/L and ≥ 220 U/L (not available in GePaRD)
- Prior use of bone-health agents during the 6 months before the index date: yes, no, for each therapy of interest
- Prior use of other drugs affecting bone structure and mineralisation: yes, no, for each therapy of interest (not available in CAPRI)
- Prior history of osteoporosis: yes, no (not available in CAPRI 1 and 2)

9.8.1 Data management

In Germany, the study involved an analysis of the GePaRD insurance claims database, i.e., secondary data. The database combines reimbursement information from different sources (outpatient setting, inpatient setting, pharmacy data, demographic data), which can be linked through pseudonymised patient identifiers. All this information is provided on an annual basis by the SHIs, i.e., there is no linkage of different registries.

In the Netherlands, this study involved a secondary analysis of data from CAPRI 1 and 2 and from CAPRI 3, previously described in Section 9.5. Data from the enrolled patients' medical charts were abstracted via a web-based electronic data abstraction form that incorporated a semiautomated process in CAPRI 3. The present study was conducted using the CAPRI network and study infrastructure. Data abstraction forms were created by CAPRI investigators and were based on the study needs and prior experience in CAPRI 1 and 2.

In Denmark, potential users of radium-223 were identified in the Danish National Patient Register, and then relevant variables for the study were abstracted from the medical records of these patients using an electronic data abstraction form developed in collaboration with the study team and programmed in REDCap (8). Following the chart abstraction, the data retrieved from hospitals were uploaded to a centralised government server to be merged with national registry data, including the DNPR, and the Danish Cancer Registry.

9.9 Statistical methods

Analyses of GePaRD data and Danish data were performed using SAS statistical software (SAS Institute, Cary, North Carolina). Analyses of CAPRI data were performed using IBM SPSS Statistics 25.

Small cell count regulations: in Denmark, cell counts of 1 to 4, and cells with which back-calculation within or across tables can be performed to lead to a result of 1 to 4, cannot be reported due to the local privacy protection policies. Therefore, in such situations, results are reported as ranges.

9.9.1 Main summary measures

Data were summarised using means, standard deviations, quartiles, and minimum and maximum values for continuous variables and frequencies and percentages for categorical variables. Outcome descriptive statistics consisted of the frequency of each outcome (i.e., use of radium-223 in combination with abiraterone, use of radium-223 in combination with other systemic therapies for mCRPC, use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC) for the periods before and after the label change.

9.9.2 Main statistical methods

The main analyses estimated the proportion of patients who used radium-223 (1) in combination with abiraterone acetate for mCRPC, (2) in combination with other systemic therapies for mCRPC, and (3) without having received at least 2 previous therapies for mCRPC.

For all main outcomes, the denominator for the proportions was the total number of new users of radium-223 during the study period:

$$\widehat{p_{im}} = \frac{k_{im}}{n_i}$$

where *n* is the number of patients who started radium-223 during the *i* study period, and *k* is the number of patients who fulfilled the corresponding *m* outcome.

We provide 95% confidence intervals (CIs) computed with the exact method (Clopper-Pearson method) (9). The Clopper-Pearson estimation method is based on the exact binomial distribution instead of on a large-sample normal approximation. The formula for the CI is

$$\left(1 + \frac{n - x + 1}{x * F(1 - \frac{\alpha}{2}; 2x, 2(n - x + 1)}\right)^{-1} < p < \left(1 + \frac{n - x}{(x + 1) * F(\frac{\alpha}{2}; 2(x + 1), 2(n - x)}\right)^{-1}$$

where *x* is the number of events, *n* is the total number of radium-223 prescriptions, *P* is the proportion of events (*x/n*), α is the level of significance, *F(α, b, c)* is the specified αth percentile of the *F* distribution with *b* and *c* degrees of freedom.

Because of a relationship between the cumulative binomial distribution and the beta distribution, the Clopper-Pearson interval has an alternate format that uses quantiles from the beta distribution:

$$B\left(\frac{\alpha}{2}; x, (n - x + 1)\right) < p < B\left(1 - \frac{\alpha}{2}; (x - 1), (n - x)\right)$$

where *x* is the number of events, *n* is the number of radium-223 prescriptions, and *B(p; v, w)* is the *p*th quantile from a beta distribution with shape parameters *v* and *w*. The lower bound is set to 0 when $x = 0$, and the upper bound is set to 1 when $x = n$.

9.9.2.1 Proportion of patients who received radium-223 in combination with abiraterone acetate

The proportion of new users of radium-223 with at least 1 administration of radium-223 in combination with abiraterone acetate during the after–label change period was described, along with the following:

- The number and proportion of cycles where radium-223 was used in combination with abiraterone
- Use of radium-223 in combination with abiraterone by calendar year of administration of the first cycle of radium-223
- Use of radium-223 in combination with abiraterone only at the last cycle

9.9.2.2 Proportion of patients who received radium-223 in combination with other systemic therapies for mCRPC, except LHRH analogues

The proportion of new users of radium-223 with at least 1 administration of radium-223 in combination with other systemic therapies, except combination with LHRH analogues, during the study period was described. Three additional analyses were conducted for this main objective:

- Use of radium-223 in combination with other systemic therapies, except combinations with LHRH analogues, by calendar year (where the unit of analysis was radium-223 administrations or dispensings)
- A description of the proportions of cycles used in combination, by specific type of other systemic therapy
- Use of radium-223 in combination with other systemic therapies, except combinations with LHRH analogues

9.9.2.3 Proportion of patients who received radium-223 without at least 2 prior lines of systemic therapy for mCRPC, except LHRH analogues

The proportion of new users of radium-223 with at least 1 administration of radium-223 during the study period who had received fewer than 2 prior lines of systemic therapy for mCRPC, except LHRH analogues, was described.

The following 2 additional analyses were conducted for this main objective:

- Use of radium-223 in patients who had received fewer than 2 prior lines of systemic therapy for mCRPC, except LHRH analogues, by calendar year (where the unit of analysis was radium-223 administrations or indications)
- A description of the proportions of cycles used without at least 2 prior lines of systemic therapy for mCRPC, except LHRH analogues

As secondary analyses, the same main objectives (i.e., use of radium-223 in combination with abiraterone acetate for mCRPC, use of radium-223 in combination with other systemic therapies for mCRPC, and use of radium-223 without at least 2 previous therapies for mCRPC) were assessed in the before–label change period. The same analytical approach described above was used for the after–label change period.

9.9.2.4 Characterisation of the population at each study period

Characteristics of new users of radium-223 were presented separately for patients included in the periods before and after the label change.

9.9.2.5 Description of follow-up of radium-223 new users by study period

Follow-up of the new users was described, including the reason for end of follow-up.

9.9.2.6 Comparison of the periods before and after the 2018 EU label change

The difference in the proportions in the periods before and after the label change estimated in the primary objectives was calculated. The upper and lower limits of the 95% CI for the difference were calculated using the method described by Newcombe (10). Additionally, the relative risk of the outcomes of interest, using the before–label change period as the reference, was calculated along with the 95% CI using the Wald method.

9.9.3 Missing values

Missing values were described as separate categories for each applicable variable.

9.9.4 Sensitivity analyses

To account for those cycles dispensed or administered after the 6-month follow-up period of the main analysis, a sensitivity analysis was conducted that extended follow-up until 1 month after the date of the last administration of radium-223. The last administration was defined as an administration of radium-223, up to the sixth one, that was not followed by a subsequent administration within 2 months.

In GePaRD and Denmark, to estimate the proportion of patients who received radium-223 in combination with systemic corticosteroids (i.e., prednisone or methylprednisolone), an assessment of the proportion of all study patients who had at least 1 administration of radium-223 in combination with systemic corticosteroids was performed (see Section 9.4.2.2). In CAPRI, contrary to initial expectations, the date of the end of corticosteroid prescriptions was not available, and this sensitivity analysis could not be conducted.

9.9.4.1 Sensitivity analyses performed in GePaRD only

To account for uncertainty surrounding the actual administration date of a dispensing of abiraterone in GePaRD, the analysis on "use of radium-223 in combination with abiraterone" was repeated adding an additional 5 days lag time after the last dispensing of abiraterone. The outcome was defined as having at least 1 dispensing of abiraterone acetate on the same date or within 30 days after a prescription for radium-223 or when a dispensing or administration of radium-223 occurred within 10 days after the last dispensing or administration of abiraterone.

To account for the possibility that a 30-day dispensing of abiraterone would continue to be used when treatment with radium-223 started, the analysis on "use of radium-223 in combination with abiraterone" was repeated with an additional 30 days lag time after the last dispensing of abiraterone. For this sensitivity analysis, the outcome of interest also included patients with a dispensing of radium-223 occurring within 30 days after the last dispensing or administration of abiraterone (in addition to the cases identified through the main analysis).

In GePaRD, where clinical information on castration sensitivity or resistance is lacking, use of docetaxel was considered to have occurred as treatment of CRPC. A "worst-case scenario" sensitivity analysis was performed that considered docetaxel use as a line of treatment of CSPC and therefore did not count towards the lines of treatment for CRPC.

9.9.5 Amendments to the statistical analysis plan

The start of data collection in CAPRI was delayed from the planned Q4 2020 through May 2021 due to the COVID-19 pandemic preventing researchers from entering hospitals to perform chart abstraction. For the same reason, the data collection period was extended by 6 months, through April 2021, to maximise the number of hospitals contributing to CAPRI 3.

In the analysis comparing the proportion of patients using radium-223 before and after the 2018 EU label change, a relative risk calculation was added in addition to the planned absolute difference.

The analysis on "use of radium-223 in combination with abiraterone" was planned to be repeated among patients with a confirmed diagnosis of mCRPC; however, in CAPRI and Denmark all

patients included in the study had a confirmed diagnosis of mCRPC, and in GePaRD confirmed diagnosis was not available; therefore, this sensitivity analysis was the same as the main analysis.

9.10 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 specify otherwise.

To ensure the integrity and quality of the study results, a programming validation life cycle process that includes quality checking of analysis programs, logs, and output for accuracy according to relevant standard operating procedures or internal guidance documents was followed for all analyses. The study analysis adhered to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* of the International Society for Pharmacoepidemiology (11) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (12).

In CAPRI, all data were checked against medical records by CAPRI researchers centrally and were manually validated in participating hospitals in case of any discrepancies.

10. Results

10.1 Participants

For the **before–label change period**, the following numbers of patients were identified who had a first radium-223 prescription and met inclusion and exclusion criteria (Table 3):

- 243 patients from 20 hospitals in CAPRI 1 and 2 (the Netherlands)
- 580 patients in the 4 SHIs from GePaRD (Germany) and 245 patients in the sample restricted to 1 SHI with full data on CRPC systemic treatments (data not shown in Table 3)
- 205 patients in Denmark; of these, 60 patients from 2 hospitals that contributed to chart abstraction were included

Table 3: Cohort attrition, population before the 2018 EU label change

Inclusion criteria	CAPRI 1 and 2 N (%)	GePaRD N (%)	Denmark N (%)
Total patients with a first administration of radium-223	285	988	526
First administration of radium-223 within the enrolment period before the label change[a]	243 (85.3%)	581 (58.8%)	205 < n < 210[b]
At least 6 months of continuous enrolment before the first radium-223 administration	243 (85.3%)	580 (58.7%)	205 (39.0%)
Treated at a hospital that contributed to chart abstraction	NA	NA	60 (11.4%)[c]

EU = European Union; NA = not applicable.
[a] Enrolment period was 13 November 2013 through 31 May 2017.
[b] Actual number masked due to small cell policy when the difference between cells is 1 ≤ n < 5 patients.
[c] From the 2 hospitals that agreed to participate in the study, 100 patients were sampled for chart abstraction; of those, charts of 60 patients could be abstracted.

For the **after–label change period**, the following numbers of patients were identified who had a first radium-223 prescription and met inclusion and exclusion criteria (Table 4):

- 53 patients from 6 hospitals in the Netherlands, 5 of which also contributed data to CAPRI 1 and 2
- 71 patients in the 4 SHIs from GePaRD (Germany) and 34 patients from the sample restricted to 1 SHI with full data on CRPC systemic treatments (data not shown in Table 4)
- 74 patients in Denmark; of these, 63 patients from 2 hospitals that contributed to chart abstraction were included

Table 4: Cohort attrition, population after the 2018 EU label change

Inclusion criteria	CAPRI 3 N (%)	GePaRD N (%)	Denmark N (%)
Total patients with a first administration of radium-223	68	988	526
First administration of radium-223 within the enrolment period after the label change[a]	53 (77.9%)	71 (7.2%)	74 (14.1%)
At least 6 months of continuous enrolment before the first radium-223 administration	53 (77.9%)	71 (7.2%)	74 (14.1%)
Treated at a hospital that contributed to chart abstraction	NA	NA	63 (12.0%)

EU = European Union; NA = not applicable.
[a] Enrolment period was 30 April 2019 through 30 April 2020 for CAPRI 3 and 30 April 2019 through 30 June 2020 in Germany and Denmark.

10.2 Descriptive data

In the Netherlands, the mean age of participants was similar in both study periods at 73.9 years and 73.1 years in the after– and before–label change periods, respectively. Patients were enrolled in the after–label change period after a median of 52.2 months after diagnosis of prostate cancer, and patients were enrolled in the before–label change period after a median of 59.3 months after diagnosis of prostate cancer. All patients had a confirmed diagnosis of mCRPC at enrolment in both study periods, with diagnosis occurring a median of 23.3 months before enrolment in the after–label change period and 27.5 months before enrolment in the before–label change period. Among those enrolled in the after–label change period, 17.0% had undergone surgical castration; the corresponding figure for those enrolled in the before–label change period was 11.9%. Most patients had previous use of medications for CRPC at enrolment in the after– and before–label change periods (94.3% and 97.9%, respectively).

In Germany, in patients from the 4 SHIs participating in GePaRD, the mean age was also similar across study periods at 74.2 years and 72.4 years in the after– and before–label change periods, respectively. Patients were enrolled in the after–label change period a median of 50 months after diagnosis of prostate cancer and patients were enrolled in the before–label change period a median of 57 months after diagnosis of prostate cancer. None of the patients enrolled in the after–label change period had undergone surgical castration, but 1.9% in the before–label change period had undergone surgical castration. Most patients had previous use of medications for CRPC at enrolment in the after– and before–label change periods (100% and 98.6%, respectively).

Characteristics between patients from the 4 SHIs and those from the restricted sample from GePaRD were similar on most variables. However, there were some differences in proportions of some characteristics. In the after–label change period, the median time since prostate cancer diagnosis was slightly shorter in the restricted sample: 48 months versus 50 months in the full sample (characteristics from the restricted sample are presented as additional information in Annex 2,

Table A-1). As expected due to the lack of information on substances included in systemic therapies for CRPC in 3 of 4 SHIs, in the restricted sample, a higher proportion of patients had prior use of cytotoxic drugs (cabazitaxel and docetaxel). The proportion of patients exposed to abiraterone was similar in both samples for both study periods (full sample: 56.4% and 73.2% and restricted sample: 58% and 79.4%, in the before– and after–label change periods, respectively).

In Denmark, due to time and pandemic constraints, the collection of data on each study outcome (combinations with abiraterone and other systemic therapies, and prior lines of treatment) was prioritised; therefore, not all baseline characteristics were available. The mean age of participants in both study periods was 71.9 years. Patients were enrolled in the after–label change period a median of 55.0 months after diagnosis of prostate cancer, and in the before–label change period, a median of 59.8 months after diagnosis of prostate cancer.

Table 5 presents the clinical characteristics of the enrolled patients at baseline for both study periods.

Table 5: Clinical characteristics at baseline of each study period

Characteristic	After label change			Before label change		
	CAPRI 3 N (%)	GePaRD N (%)	Denmark[a] N (%)	CAPRI 1 and 2 N (%)	GePaRD N (%)	Denmark[a] N (%)
Age (years)						
Mean (SD)	73.9 (8.0)	74.2 (8.5)	71.9 (6.3)	73.1 (8)	72.4 (7.9)	71.9 (7.8)
Median (Q1, Q3)	74 (70, 80)	76 (69, 81)	72 (68, 76)	73 (68,79)	74 (68, 77)	72 (66, 77)
Min, max	53, 90	53, 91	Masked	51, 92	48, 98	Masked
Missing n (%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0
Age group (years), n (%)						
< 50	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	3 (0.5%)	0
50-59	3 (5.7%)	5 (7.0%)	1 ≤ n < 5	12 (4.9%)	41 (7.1%)	6 (10.0%)
60-69	7 (13.2%)	16 (22.5%)	17 (27.0%)	69 (28.4%)	130 (22.4%)	15 (25.0%)
70-79	28 (52.8%)	27 (38.0%)	38 (60.3%)	107 (44.0%)	312 (53.8%)	29 (48.3%)
80-89	14 (26.4%)	22 (31.0%)	1 ≤ n < 10	53 (21.8%)	91 (15.7%)	10 (16.7%)
90 and more	1 (1.9%)	1 (1.4%)	0	2 (0.8%)	3 (0.5%)	0
Calendar year at the prescription date/ index date, n (%)						
2013	NA	NA	NA	6 (2.5%)	1 (0.2%)	0
2014	NA	NA	NA	32 (13.2%)	14 (2.4%)	5 (8.3%)
2015	NA	NA	NA	71 (29.2%)	238 (41.0%)	16 (26.7%)
2016	NA	NA	NA	99 (40.7%)	245 (42.2%)	27 (45.0%)
2017	NA	NA	NA	35 (14.4%)	82 (14.1%)	12 (20.0%)
2019	34 (64.2%)	46 (64.8%)	38 (60.3%)	NA	NA	NA
2020	19 (35.8%)	25 (35.2%)	25 (39.7%)	NA	NA	NA
Time since first prostate cancer diagnosis, months						
Mean (SD)	75.3 (57.2)	71.8 (53.7)	71.5 (50.7)	77.4 (54.0)	69.1 (46.6)	68.2 (44.7)
Median (Q1, Q3)	52.2 (32, 108)	50 (28, 94)	55.0 (32.9, 96.5)	59.3 (39, 101)	57 (28, 108)	59.8 (31.2, 102.0)
Min, max	10.3, 237.2	7, 196	Masked	9.8, 262.9	1, 163	Masked
Missing n (%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0
Time since surgical castration (if applicable)						
Patients who underwent surgical castration (n, %)	9 (17.0%)	0	N/A	29 (11.9%)	11 (1.9%)	N/A
Mean (SD), months	24.5 (20.3)	NA	N/A	60.4 (44.0)	21.3 (20.8)	N/A
Median (Q1, Q3), months	18.5 (6.9, 38.3)	NA	N/A	48.7 (32.0, 69.0)	15 (10, 21)	N/A
Min, max, months	4.7, 63.3	NA	N/A	17.0, 229.0	5, 77	N/A
Unknown time, n	1	NA	N/A	0	N/A	N/A
Time since first use of an antiandrogen medication[b]						
Mean (SD), months	57.8 (38.6)	56.5 (44.3)	N/A	52.6 (35)	57.9 (41.1)	N/A
Median (Q1, Q3), months	46.6 (29.7, 79.6)	41 (25, 69)	N/A	46.1 (28, 65)	47 (24, 84)	N/A
Min, max, months	9.5, 168.7	4, 189	N/A	2.5, 229.0	2, 160	N/A
Unknown time, n	3	0 (0.0%)	N/A	0	8 (1.4%)	N/A
Confirmed diagnosis of mCRPC, n (%)						
Yes	53 (100.0%)	N/A	N/A	243 (100.0%)	N/A	N/A
No	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A	N/A

Characteristic	After label change			Before label change		
	CAPRI 3 N (%)	GePaRD N (%)	Denmark[a] N (%)	CAPRI 1 and 2 N (%)	GePaRD N (%)	Denmark[a] N (%)
Time since first mCRPC confirmed diagnosis, months						N/A
Mean (SD)	28.7 (20.9)	N/A	N/A	30.1 (17)	N/A	N/A
Median (Q1, Q3)	23.3 (11.6, 39.2)	N/A	N/A	27.5 (17, 41)	N/A	N/A
Min, max	1.3, 103.2	N/A	N/A	0.7, 76.7	N/A	N/A
Date of mCRPC diagnosis missing, n (%)	0 (0.0)	N/A	N/A	4 (1.6)	N/A	N/A
Any prior use of a LHRH analogue, n (%)						
Yes	49 (92.5)	71 (100%)	N/A	218 (89.7)	569 (98.1%)	N/A
No	4 (7.5)	0 (0.0%)	N/A	25 (10.3)	11 (1.9%)	N/A
Prior use of therapies for CRPC, n (%)[c]	50 (94.3)	71 (100%)		238 (97.9)	572 (98.6%)	N/A
Cytotoxic drugs						
Cabazitaxel	11 (20.8%)	9 (12.7%)	N/A	38 (15.6%)	31 (5.3%)	N/A
Docetaxel	15 (28.3%)	22 (31.0%)	N/A	146 (60.1%)	94 (16.2%)	N/A
Mitoxantrone	0 (0.0%)	0 (0.0%)	N/A	0 (0.0%)	1 (0.2%)	N/A
Immunotherapies						
Sipuleucel-T	0 (0.0%)	0 (0.0%)	N/A	0 (0.0%)	0 (0.0%)	N/A
Pembrolizumab	1 (1.9%)	0 (0.0%)	N/A	0 (0.0%)	0 (0.0%)	N/A
Antiandrogens						
Abiraterone	24 (45.3%)	52 (73.2%)	N/A	109 (44.9%)	327 (56.4%)	N/A
Apalutamide[d]	1 (1.9%)	1 (1.4%)	N/A	0 (0.0%)	0 (0.0%)	N/A
Bicalutamide[d]	15 (28.3%)	53 (74.6%)	N/A	145 (59.7%)	483 (83.3%)	N/A
Darolutamide[d]	0 (0.0%)	0 (0.0%)	N/A	0 (0.0%)	0 (0.0%)	N/A
Enzalutamide	30 (56.6%)	37 (52.1%)	N/A	103 (42.4%)	235 (40.5%)	N/A
Flutamide[d]	0 (0.0%)	10 (14.1%)	N/A	4 (1.6%)	128 (22.1%)	N/A
Nilutamide[d]	0 (0.0%)	0 (0.0%)	N/A	9 (3.7%)	0 (0.0%)	N/A
LHRH analogues[d]						
Leuprolide/ leuprorelin	1 (1.9%)	53 (74.6%)	N/A	57 (23.5%)	445 (76.7%)	N/A
Goserelin	2 (3.8%)	10 (14.1%)	N/A	53 (21.8%)	56 (9.7%)	N/A
Histrelin	N/A	0 (0.0%)	N/A	N/A	1 (0.2%)	N/A
Triptorelin	0 (0.0%)	19 (26.8%)	N/A	3 (1.2%)	84 (14.5%)	N/A
Buserelin	0 (0.0%)	12 (16.9%)	N/A	2 (0.8%)	119 (20.5%)	N/A
Nafarelin	N/A	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A
Gonadorelin	0 (0.0%)	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A
Degarelix	0 (0.0%)	7 (9.9%)	N/A	53 (21.8%)	80 (13.8%)	N/A
Prednisone/ (methyl) prednisolone[e,e,f]	N/A	65 (91.5%)	N/A	N/A	424 (73.1%)	N/A
Corticosteroids for noncancer indications since first diagnosis of CRPC[d,e,f]	N/A	N/A	N/A	N/A	N/A	N/A
Prior use of therapies for CSPC, n (%)	49 (92.5%)	N/A	N/A	162 (66.7%)	N/A	N/A
Cytotoxic drugs		N/A	N/A		N/A	N/A
Cabazitaxel	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A	N/A
Docetaxel	20 (37.7%)	N/A	N/A	0 (0.0%)	N/A	N/A
Mitoxantrone[d]	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A	N/A
Immunotherapies						
Sipuleucel-T	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A	N/A
Pembrolizumab	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A	N/A

Characteristic	After label change			Before label change		
	CAPRI 3 N (%)	GePaRD N (%)	Denmark[a] N (%)	CAPRI 1 and 2 N (%)	GePaRD N (%)	Denmark[a] N (%)
Antiandrogens						
Abiraterone	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A	N/A
Apalutamide[d]	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A	N/A
Bicalutamide[d]	38 (71.7%)	N/A	N/A	88 (36.2%)	N/A	N/A
Darolutamide[d]	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A	N/A
Enzalutamide[d]	1 (1.9%)	N/A	N/A	0 (0.0%)	N/A	N/A
Flutamide[d]	0 (0.0%)	N/A	N/A	1 (0.4%)	N/A	N/A
Nilutamide[d]	0 (0.0%)	N/A	N/A	3 (1.2%)	N/A	N/A
LHRH analogues[d]						
Leuprolide/ leuprorelin	25 (47.2%)	N/A	N/A	57 (23.5%)	N/A	N/A
Goserelin	17 (32.1%)	N/A	N/A	53 (21.8%)	N/A	N/A
Histrelin	N/A	N/A	N/A	N/A	N/A	N/A
Triptorelin	1 (1.9%)	N/A	N/A	3 (1.2%)	N/A	N/A
Buserelin	2 (3.8%)	N/A	N/A	2 (0.8%)	N/A	N/A
Nafarelin	N/A	N/A	N/A	N/A	N/A	N/A
Gonadorelin	0 (0.0%)	N/A	N/A	N/A	N/A	N/A
Degarelix	1 (1.9%)	N/A	N/A	53 (21.8%)	N/A	N/A
Prednisone/ (methyl) prednisolone[d,e,f]	N/A	N/A	N/A	N/A	N/A	N/A
Corticosteroids for noncancer indications since first diagnosis of CSPC[d,e,f]	N/A	N/A	N/A	N/A	N/A	N/A
Presence of metastases, ever before[g]						
Bone metastases[h]	53 (100.0%)	32 (45.1%) *(inpatient)* 39 (54.9%) *(outpatient)*	N/A	229 (94.2%)	284 (49.0%) *(inpatient)* 267 (46.0%) *(outpatient)*	N/A
Visceral metastases[h]	1 (1.9%)	1 (1.4%) *(inpatient)* 1 (1.4%) *(outpatient)*	N/A	18 (7.4%)	10 (1.7%) *(inpatient)* 21 (3.6%) *(outpatient)*	N/A
Unknown metastatic location[h]	0 (0.0%)	1 (1.4%) *(inpatient)* 19 (26.8%) *(outpatient)*	N/A	13 (5.3%)	9 (1.6%) *(inpatient)* 153 (26.4%) *(outpatient)*	N/A
Levels of serum alkaline phosphatase, n (%)[i,j]						
< 220 U/L	25 (47.2%)	N/A	N/A	140 (57.6%)	N/A	N/A
≥ 220 U/L	8 (15.1%)	N/A	N/A	69 (28.4%)	N/A	N/A
Prior use of bone-health agents during the 180 days before the index date, n (%)[d]						
Bisphosphonates	3 (5.7%)	19 (26.8%)	N/A	32 (13.2%)	215 (37.1%)	N/A
Denosumab	13 (24.5%)	30 (42.3%)	N/A	13 (5.3)	221 (38.1%)	N/A
Bone morphogenetic proteins	N/A	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A

Characteristic	After label change			Before label change		
	CAPRI 3 N (%)	GePaRD N (%)	Denmark[a] N (%)	CAPRI 1 and 2 N (%)	GePaRD N (%)	Denmark[a] N (%)
Prior use of other drugs affecting bone structure and mineralisation[d]	N/A	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A
Ipriflavone	N/A	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A
Aluminium chlorohydrate	N/A	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A
Strontium ranelate	0 (0.0%)	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A
Burosumab	N/A	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A
Romosozumab	N/A	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A
Strontium ranelate and cholecalciferol	N/A	0 (0.0%)	N/A	N/A	0 (0.0%)	N/A
Prior history of osteoporosis ever before,[e] n (%)						
Yes[h]	2 (3.8%)	0 (0.0%) *(inpatient)* 7 (9.9%) *(outpatient)*	N/A	N/A	9 (1.6%) *(inpatient)* 68 (11.7%) *(outpatient)*	N/A
No	49 (92.5%)	64 (90.1%)	N/A	N/A	503 (86.7%)	N/A

CRPC = castration-resistant prostate cancer; CSPC = castration-sensitive prostate cancer; EU = European Union; ICD-10 = *International Classification of Diseases, Tenth Revision*; LHRH = luteinising hormone–releasing hormone; max = maximum; mCRPC = metastatic castration-resistant prostate cancer; min = minimum; N/A = not available; NA = not applicable; Q1, Q3 = first and third quartiles; SD = standard deviation; SHI = statutory health insurance provider.

Notes: CAPRI 3 had data from 6 hospitals, CAPRI 1 and 2 had data from 20 hospitals, GePaRD data were from 4 SHIs, and data from Denmark were from 2 hospitals. The period before the 2018 EU label change was 13 November 2013 through 31 May 2017 and the period after the 2018 EU label change was 30 April 2019 through 30 April 2020 in CAPRI and 30 April 2019 through 30 June 2020 in GePaRD and Denmark; 2013 data are from 13 November through 31 December 2013; 2017 data are from January through 30 November 2017; 2019 data are from 30 April through 31 December 2019; and 2020 data are from January through 30 April 2020 in CAPRI and 30 June 2020 in the GePaRD and Denmark.

[a] Per Danish data privacy requirements, if the number of individuals in a cell is from 1 to 4, or would allow back-calculation of cells to lead to a result of 1 to 4, the value is reported as a range. Cells with values originating from 1 to 4 patients are masked.

[b] "Antiandrogen medication" is defined as "first evidence of prescription of an LHRH analogue or antiandrogen medication, whichever comes first."

[c] In GePaRD, because castration-resistant status was not available, all systemic therapies were assumed to have been administered for CRPC.

[d] Outpatient use only in GePaRD.

[e] Information not available in CAPRI for the before–label change period.

[f] Information on indication of corticosteroids not available for GePaRD.

[g] Individual patients may contribute to both bone and visceral metastasis. Assessed any time before the index date. Information assessed through ICD-10 codes C79.88 and C79.9 in GePaRD.

[h] In GePaRD, inpatient and outpatient diagnoses of metastases and osteoporosis were reported separately.

[i] Only measurements up to 2 months before or 1 week after the index date were considered.

[j] Information not available in GePaRD.

10.3 Outcome data

See Section 10.4.

10.4 Main results

Table 6 shows the follow-up (with reasons for censoring) and number of radium-223 cycles accumulated in the after–label change period (main study period) and the before–label change period (reference period).

Table 6: Follow-up during each study period

Variable	Period after the 2018 EU label change			Period before the 2018 EU label change		
	CAPRI N (%)	GePaRD N (%)	Denmark N (%)[a]	CAPRI N (%)	GePaRD N (%)	Denmark N (%)[a]
Follow-up (months)						
Total	251.1	390.5	240	1,304	3,248	271
Mean (SD)	4.7 (1.1)	5.5 (1.1)	3.8 (1.5)	5.4 (1.3)	5.6 (1.0)	4.5 (1.6)
Median (Q1, Q3)	4.6 (4.6, 5.7)	6 (6, 6)	3.4 (2.9, 5.7)	6.0 (6.0, 6.0)	6 (6, 6)	5.7 (3.0, 5.7)
Min, max	1.6, 6.0	2, 6	Masked, Masked	0.2, 6.0	1, 6	Masked, 6.0
Number of cycles						
Total	257	281	246	989	2,551	276
Mean (SD) (per patient)	4.8 (1.6)	4.0 (1.7)	3.9 (1.7)	4.1 (2.0)	4.4 (1.8)	4.6 (1.7)
Median (Q1, Q3) (per patient)	6 (3.5, 6)	4 (3, 6)	3 (3, 6)	5 (2, 6)	5 (3, 6)	6 (3, 6)
Min, max (per patient)	1, 6	1, 6	Masked, 6	1, 6	1, 6	Masked, 6
Reason to end follow-up						
End of treatment[b]	28 (52.8%)	52 (73.2%)	58 < n < 63	180 (74.1%)	452 (77.9%)	55 < n < 60
Death	9 (17.0%)	18 (25.4%)	1 ≤ n < 5	51 (21.0%)	128 (22.1%)	1 ≤ n < 5
Disenrolment/lost to follow-up	4 (7.5%)	1 (1.4%)	1 ≤ n < 5	9 (3.7 %)	0 (0.0%)	1 ≤ n < 5
End of study period	12 (22.6%)	0 (0.0%)	0 (0.0%)	3 (1.2%)	0 (0.0%)	0 (0.0%)

EU = European Union; max = maximum; min = minimum; Q1, Q3 = first and third quartiles; SD = standard deviation; SHI = statutory health insurance provider.

Note: CAPRI 3 had data from 6 hospitals, CAPRI 1 and 2 had data from 20 hospitals, GePaRD data were from 4 SHIs, and data from Denmark were from 2 hospitals. The period before the 2018 EU label change was 13 November 2013 through 31 May 2017, with follow-up through 30 November 2017. The period after the 2018 EU label change was 30 April 2019 through 30 April 2020 in CAPRI and 30 April 2019 through 30 June 2020 in GePaRD and Denmark, with follow-up through 31 October 2020 in CAPRI and through 31 December 2020 in GePaRD and Denmark.

[a] Per Danish data privacy requirements, if the number of individuals in a cell is from 1 to 4, or would allow back-calculation of cells to lead to a result of 1 to 4, the value is reported as a range. Cells with values originating from 1 to 4 patients are masked.

[b] End of treatment was defined as use of radium-223 up to the sixth cycle or within 6 months after the first cycle, whichever came first.

In the **after–label change period**, median follow-up was 4.6 months with a median of 6 cycles of radium-223 administered per patient in the Netherlands, 6 months of follow-up and 4 cycles in Germany (full sample), and 3.4 months of follow-up and 3.0 cycles in Denmark. End of follow-up was due to end of treatment in most patients (52.8%, 73.2%, and 94%-98% in the Netherlands, Germany, and Denmark, respectively). Death during follow-up occurred in 17.0% of patients in the Netherlands, 25.4% in Germany, and 2% to 6% in Denmark.

In the **before–label change period**, the median follow-up of patients was 6 months with a median of 5 radium-223 cycles administered per patient in the Netherlands and Germany and 5.7 months with a median of 6 cycles in Denmark. End of follow-up was due to end of treatment in most patients (74.1%, 77.9%, and 93%-98% in the Netherlands, Germany, and Denmark, respectively). Death during follow-up occurred in 21.0% of patients in the Netherlands, 22.1% in Germany, and 2% to 7% in Denmark.

Table 7 shows the use of radium-223 in combination with abiraterone in the after–label change period (main study period) and the before–label change period (reference period).

Table 7: Use of radium-223 in combination with abiraterone

	Period after the 2018 EU label change[a]			Period before the 2018 EU label change[a]		
	CAPRI N (%)	**GePaRD N (%)**	**Denmark N (%)[b]**	**CAPRI N (%)**	**GePaRD N (%)**	**Denmark N (%)**
Number of patients, n	53	71	63	243	580	60
Use of radium-223 in combination with abiraterone, number of patients	1 (1.9%)	3 (4.2%)	1 ≤ n < 5[c]	16 (6.6%)	133 (22.9%)	0 (0.0%)
By calendar year of the first administration of radium-223						
2013	NA	NA	NA	2 (0.8%)	0 (0.0%)	0 (0.0%)
2014	NA	NA	NA	3 (1.2%)	3 (0.5%)	0 (0.0%)
2015	NA	NA	NA	6 (2.4%)	51 (8.8%)	0 (0.0%)
2016	NA	NA	NA	5 (2.0%)	61 (10.5%)	0 (0.0%)
2017	NA	NA	NA	0 (0.0%)	18 (3.1%)	0 (0.0%)
2019	1 (1.9%)	2 (2.8%)	1 ≤ n < 5	NA	NA	NA
2020	0 (0.0%)	1 (1.4%)	0	NA	NA	NA
Number of radium-223 cycles, n	257	281	246	989	2,551	276
Use of radium-223 in combination with abiraterone, number of cycles	2 (0.8%)	3 (1.1%)	1 ≤ n < 5	37 (3.7%)	467 (18.3%)	0 (0.0%)
Use of radium-223 in combination with abiraterone only at last cycle	0 (0.0%)	1 (1.4%)	1 ≤ n < 5	N/A	16 (2.8%)	0 (0.0%)

EU = European Union; N/A = not available; NA = not applicable; SHI = statutory health insurance provider.
Note: CAPRI 3 had data from 6 hospitals, CAPRI 1 and 2 had data from 20 hospitals, GePaRD data were from 4 SHIs, and data from Denmark were from 2 hospitals. When assessing cycles, the denominator is the total number of radium-223 cycles administered per period.
[a] The period before the 2018 EU label change was 13 November 2013 through 31 May 2017, with follow-up through 30 November 2017. The period after the 2018 EU label change was 30 April 2019 through 30 April 2020 in CAPRI and 30 April 2019 through 30 June 2020 in GePaRD and Denmark, with follow-up through 31 October 2020 in CAPRI and through 31 December 2020 in GePaRD and Denmark.
[b] Per Danish data privacy requirements, if the number of individuals in a cell is from 1 to 4, or would allow back-calculation of cells to lead to a result of 1 to 4, the value is reported as a range. Cells with values originating from 1 to 4 patients are masked.
[c] All of these patients received radium-223 in combination with abiraterone only by receiving abiraterone at least 20 days after the administration of the last cycle of radium-223.

During the after–label change period, 1 patient (1.9%) in the Netherlands, 3 patients (4.2%) in Germany (1 patient at the last cycle of radium-223), and 1 ≤ n < 5 patients in Denmark used at least 1 cycle of radium-223 in combination with abiraterone. In Denmark, all of these patients received radium-223 in combination with abiraterone only when abiraterone was administered at least 20 days after the administration of the last cycle of radium-223. In the 1 patient in the Netherlands, 2 radium-223 cycles (all the cycles this patient received) were used in combination with abiraterone, representing 0.8% of all radium-223 cycles administered to the study patients in CAPRI during the after–label change period. In Germany, radium-223 was used in combination with abiraterone in 3

cycles, representing 1.1% of all cycles administered in GePaRD patients during the after–label change period. In Denmark, use in combination with abiraterone occurred in 1 ≤ n < 5 cycles, in all cases, after the last cycle of radium-223, representing less than 2% of all radium-223 cycles.

During the before–label change period, 16 patients (6.6%) in the Netherlands, 133 (22.9%) in Germany, and no patients in Denmark had at least 1 cycle of radium-223 administered in combination with abiraterone. In the Netherlands, 3.7% of all radium-223 cycles were administered in combination with abiraterone during the before–label change period. By year, the coadministration of radium-223 and abiraterone occurred in 0% to 2.4% of all patients across the before–label change period. In the full sample of GePaRD, Germany, 18.3% of all radium-223 cycles occurred in combination with abiraterone during the before–label change period. By year, the coadministration of radium-223 and abiraterone occurred in 0% to 10.5% of all patients across the before–label change period.

Table 8 shows the use of radium-223 in combination with other systemic therapies for mCRPC in the after–label change period (main study period) and the before–label change period (reference period).

Table 8: Use of radium-223 in combination with other systemic therapies for mCRPC

Outcomes	Period after the 2018 EU label change[a]			Period before the 2018 EU label change[a]		
	CAPRI N (%)	GePaRD[b] N (%)	Denmark[c] N (%)	CAPRI N (%)	GePaRD[b] N (%)	Denmark[c] N (%)
Number of patients, n	53	34	63	243	245	60
Use of radium-223 in combination with other systemic therapies for mCRPC[d], number of patients	5 (9.4%)	4 (11.8%)	1 ≤ n < 5	35 (14.4%)	67 (27.3%)	0 (0.0%)
By calendar year of the first administration of radium-223[e]						
2013	NA	NA	NA	14 (5.7%)	0 (0.0%)	0 (0.0%)
2014	NA	NA	NA	10 (4.1%)	3 (1.2%)	0 (0.0%)
2015	NA	NA	NA	3 (1.2%)	20 (8.2%)	0 (0.0%)
2016	NA	NA	NA	2 (0.8%)	32 (13.1%)	0 (0.0%)
2017	NA	NA	NA	6 (2.6%)	12 (4.9%)	0 (0.0%)
2019	3 (5.7%)	4 (11.8%)	1 ≤ n < 5	NA	NA	NA
2020	2 (3.8%)	0 (0.0%)	0	NA	NA	NA
Number of radium-223 cycles, n	257	142	246	989	1,047	276
Use of radium-223 in combination with other systemic therapies for mCRPC[d], number of cycles	13 (5.1%)	4 (2.8%)	1 ≤ n < 5	38 (3.8%)	241 (23.0%)	0 (0.0%)
Number of radium-223 cycles with enzalutamide	7 (2.7%)	2 (1.4%)	1 ≤ n < 5	28 (2.8%)	59 (24.1%)	0 (0.0%)
Number of radium-223 cycles with docetaxel	6 (2.3%)	2 (1.4%)	0	5 (0.5%)	5 (2.0%)	0 (0.0%)
Number of radium-223 cycles with cabazitaxel	0 (0.0%)	0 (0.0%)	0	5 (0.5%)	6 (2.4%)	0 (0.0%)
Number of radium-223 cycles with sipuleucel-T[f,g]	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of radium-223 cycles with pembrolizumab	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)

Outcomes	Period after the 2018 EU label change[a]			Period before the 2018 EU label change[a]		
	CAPRI N (%)	GePaRD[b] N (%)	Denmark[c] N (%)	CAPRI N (%)	GePaRD[b] N (%)	Denmark[c] N (%)
Use of radium-223 in combination with other systemic therapies only at last cycle	2 (3.8%)	3 (8.8%)	1 ≤ n < 5	NA	11 (4.5%)	0 (0.0%)

EU = European Union; LHRH = luteinising hormone–releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; NA = not applicable; SHI = statutory health insurance provider.

Note: CAPRI 3 had data from 6 hospitals, CAPRI 1 and 2 had data from 20 hospitals, GePaRD data were from one SHI, and data from Denmark were from 2 hospitals. When assessing cycles, the denominator is the total number of radium-223 cycles administered per period.

[a] The period before the 2018 EU label change was 13 November 2013 through 31 May 2017, with follow-up through 30 November 2017. The period after the 2018 EU label change was 30 April 2019 through 30 April 2020 in CAPRI and 30 April 2019 through 30 June 2020 in GePaRD and Denmark, with follow-up through 31 October 2020 in CAPRI and through 31 December 2020 in GePaRD and Denmark.

[b] Because information on the substances included in previous systemic therapies was available from only 1 of the 4 participating SHIs, this outcome was analysed in a restricted sample including only patients from that SHI.

[c] Per Danish data privacy requirements, if the number of individuals in a cell is from 1 to 4, or would allow back-calculation of cells to lead to a result of 1 to 4, the value is reported as a range. Cells with values originating from 1 to 4 patients are masked.

[d] Except LHRH analogues.

[e] 2013 data were from 13 November through 31 December 2013; 2017 data were from January through 30 November 2017. 2019 data were from 30 April through 31 December 2019; 2020 data were from January through 31 October for CAPRI and through 31 December 2020 for Denmark and GePaRD. Other years had data for the full year.

[f] Sipuleucel-T is not available in Denmark.

[g] In GePaRD, only outpatient use of sipuleucel-T was captured.

During the after–label change period, 5 patients (9.4%) in the Netherlands, 4 patients (11.8%) in the sample restricted to the single SHI contributing data to GePaRD that was able to provide data for this objective, and 1 ≤ n < 5 patients (2%-6%) in Denmark used at least 1 cycle of radium-223 in combination with other systemic therapies for mCRPC. By specific systemic therapy for mCRPC, enzalutamide and docetaxel were the most commonly co-administered systemic therapies in the Netherlands and Germany. Overall, the number of radium-223 cycles co-administered with other systemic therapies for mCRPC represented 5.1%, 2.8% and < 2% of all radium-223 cycles to the study patients during the before–label change period in the Netherlands, Germany, and Denmark, respectively. The coadministration of radium-223 and other systemic therapies for mCRPC was less common in 2020 compared with 2019 in the 3 countries. Among the patients who received a radium-223 cycle with another systemic therapy for mCRPC, 2 patients (40%) in the Netherlands, 3 patients (75%) in Germany, and all patients in Denmark received it at their last cycle of radium-223.

During the before–label change period, 35 patients (14.4%) in the Netherlands, 67 patients (27.3%) in Germany, and no patients in Denmark had at least 1 cycle of radium-223 administered in combination with other systemic therapies for mCRPC. By specific systemic therapy for mCRPC, enzalutamide was the most commonly co-prescribed systemic therapy in the 3 countries. Overall, the number of radium-223 cycles that were co-administered with other systemic therapies for mCRPC represented 3.8% and 23.0% of all radium-223 cycles administered to study patients in the Netherlands and Germany, respectively, during the before–label change period.

Table 9 shows the use of radium-223 without at least 2 prior lines of systemic therapy for mCRPC in the after–label change period (main study period) and the before–label change period (reference period).

Table 9: Use of radium-223 without at least 2 prior lines of systemic therapy for mCRPC

Outcomes	Period after the 2018 EU label change[a]			Period before the 2018 EU label change[a]		
	CAPRI N (%)	GePaRD[b] N (%)	Denmark[c] N (%)	CAPRI N (%)	GePaRD[b] N (%)	Denmark[c] N (%)
Number of patients, n	53	34	63	243	245	60
Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC,[d, e] number of patients	21 (39.6%)	9 (26.5%)	1 ≤ n < 5	113 (46.5%)	137 (55.9%)	16 (26.7%)
By calendar year of the first administration of radium-223[f]						
2013	NA	NA	NA	2 (0.8%)	0 (0.0%)	0 (0.0%)
2014	NA	NA	NA	16 (6.6%)	4 (1.6%)	0 (0.0%)
2015	NA	NA	NA	32 (13.2%)	53 (21.6%)	7 (11.7%)
2016	NA	NA	NA	46 (18.9%)	60 (24.5%)	1 ≤ n < 10
2017	NA	NA	NA	17 (7.0%)	20 (8.2%)	1 ≤ n < 5
2019	10 (18.9%)	6 (17.6%)	1 ≤ n < 5	NA	NA	NA
2020	11 (20.8%)	3 (8.8%)	0 (0.0%)	NA	NA	NA
Number of radium-223 cycles, n	257	142	246	989	1,047	276
Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC,[d] number of cycles	103 (40.1%)	40 (28.2%)	1 ≤ n < 5	490 (49.5%)	600 (57.3%)	80 (29.0%)

EU = European Union; LHRH = luteinising hormone–releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; NA = not applicable; SHI = statutory health insurance provider.

Note: CAPRI 3 had data from 6 hospitals, CAPRI 1 and 2 had data from 20 hospitals, GePaRD data were from one SHI, and data from Denmark were from 2 hospitals. When assessing cycles, the denominator is the total number of radium-223 cycles administered per period.

[a] The period before the 2018 EU label change was 13 November 2013 through 31 May 2017, with follow-up through 30 November 2017. The period after the 2018 EU label change was 30 April 2019 through 30 April 2020 in CAPRI and 30 April 2019 through 30 June 2020 in GePaRD and Denmark, with follow-up through 31 October 2020 in CAPRI and through 31 December 2020 in GePaRD and Denmark.

[b] Because information on the substances included in prior systemic therapies was available from only 1 of the 4 participating SHIs, this outcome was analysed in a restricted sample including only patients from that SHI.

[c] Per Danish data privacy requirements, if the number of individuals in a cell is from 1 to 4, or would allow back-calculation of cells to lead to a result of 1 to 4, the value is reported as a range. Cells with values originating from 1 to 4 patients are masked.

[d] Except LHRH analogues.

[e] "Systemic therapy for mCRPC" is defined as any use of abiraterone, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, or pembrolizumab (each drug substance counted as a prior line, irrespective of the number of administrations of the specific drug substance).

[f] 2013 data were from 13 November through 31 December 2013; 2017 data were from January through 30 November 2017. 2019 data were from 30 April through 31 December 2019; 2020 data were from January through 31 October for CAPRI and through 31 December 2020 for Denmark and GePaRD. Other years had data for the full year.

During the after–**label change period**, 21 patients (39.6%) in the Netherlands, 9 (26.5%) in Germany in the sample restricted to 1 SHI, and 1 ≤ n < 5 (2%-6%) patients in Denmark used at least 1 cycle of radium-223 without at least 2 prior lines of systemic therapy for mCRPC. Overall, this represented 40.1% and 28.2% of all radium-223 cycles in the Netherlands and Germany, respectively, and 0% to 2% in Denmark.

During the before–**label change period**, 113 patients (46.5%) in the Netherlands, 137 (55.9%) in Germany, and 16 patients (26.7%) in Denmark used at least 1 cycle of radium-223 without at least 2 prior lines of systemic therapy for mCRPC. Overall, this represented 49.5%, 57.3%, and 29.0% of

all radium-223 cycles in the Netherlands, Germany, and Denmark, respectively. The percentage of patients who received radium-223 cycles before 2 prior lines of systemic therapies was larger in years 2015 (13.2% in the Netherlands and 21.6% in Germany) and 2016 (18.9% in the Netherlands and 24.5% in Germany) than in other years of the before–label change period.

10.5 Other analyses

10.5.1 Comparison of the study main outcomes before and after the 2018 EU label change

Table 10 shows the difference and relative risk between study periods in the proportion of patients meeting the criteria for the 3 main outcomes of interest with the corresponding relative risks. All 3 outcomes in all 3 countries occurred less frequently in the after–label change period than during the before–label change period. The difference between the 2 periods was largest in Germany.

When assessing the risk ratios using the before–label change period as the reference, the relative risk of using radium-223 in combination with abiraterone in the after–label change period was 0.29 (95% CI, 0.04-2.11) in the Netherlands and 0.18 (95% CI, 0.06-0.56) in Germany. The relative risk of using radium-223 in combination with other systemic therapies for mCRPC in the after–label change period was 0.65 (95% CI, 0.02-1.59) in the Netherlands and 0.43 (95% CI, 0.17-1.11) in Germany, and the relative risk of using radium-223 without at least 2 prior lines of systemic therapy for mCRPC in the after–label change period was 0.85 (95% CI, 0.59-1.22) in the Netherlands and 0.47 (95% CI, 0.27-0.84) in Germany. In Denmark, relative risk and absolute differences could not be estimated due to masking of small cell counts for patient privacy.

Table 10: Difference and relative risk for the proportion of patients using radium-223 before and after the 2018 EU label change

Outcomes	Period before the 2018 EU label change			Period after the 2018 EU label change			Absolute difference, % (95% CI)			Relative risk(95% CI)[a]		
	CAPRI 3 N (%)	GePaRD N (%)	Denmark N (%)	CAPRI 1 and 2 N (%)	GePaRD N (%)	Denmark[e] N (%)	CAPRI[b]	GePaRD	Denmark	CAPRI[b]	GePaRD	Denmark
Use of radium-223 in combination with abiraterone	16 (6.6%)	133 (22.9%)	0 (0.0%)	1 (1.9%)	3 (4.2%)	1 ≤ n < 5	−4.7 (−7.6 to 3.7)	−17.9 (−5.0 to −23.9)	Masked	0.29 (0.04-2.11)	0.18 (0.06-0.56)	Masked
Use of radium-223 in combination with other systemic therapies for mCRPC[c,d]	35 (14.4%)	67 (27.3%)	0 (0.0%)	5 (9.4%)	4 (11.8%)	1 ≤ n < 5	−5.0 (−11.6 to 6.5)	−15.6 (0.2 to −24.8)	Masked	0.65 (0.02-1.59)	0.43 (0.17-1.11)	Masked
Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC[c,d]	113 (46.5%)	137 (55.9%)	16 (26.7%)	21 (39.6%)	9 (26.5%)	1 ≤ n < 5	−6.9 (−20.4 to 7.9)	−29.4 (−11.7 to −42.8)	Masked	0.85 (0.59-1.22)	0.47 (0.27-0.84)	Masked

CI = confidence interval; EU = European Union; LHRH = luteinising hormone–releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; SHI = statutory health insurance provider.

Note: The period before the 2018 EU label change was 13 November 2013 through 31 May 2017, with follow-up through 30 November 2017 for all data sources. The period after the 2018 EU label change was 30 April 2019 through 30 April 2020, with follow-up through 31 October 2020 in CAPRI and through 31 December 2020 in GePaRD and Denmark.

[a] The reference was the period before the 2018 EU label change.

[b] Difference and relative risk for CAPRI 3 with data from CAPRI 1 and 2 as the reference.

[c] Except LHRH analogues. Drugs included enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, and pembrolizumab.

[d] In GePaRD, use of radium-223 in combination with other systemic therapies for mCRPC and use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC were calculated in the restricted sample from the one SHI that could provide information on the substances included in prior systemic therapies (245 patients in the before–label change period and 34 patients in the after–label change period).

[e] Per Danish data privacy requirements, if the number of individuals in a cell is from 1 to 4, or would allow back-calculation of cells to lead to a result of 1 to 4, the value is reported as a range. Cells with values originating from 1 to 4 patients are masked. Differences were not assessable due to small cell counts.

10.5.2 Use of radium-223 in combination with abiraterone adding 5 days of lag time after dispensing abiraterone; period after the 2018 EU label change

The sensitivity analysis reported in Table 11 was performed only in Germany. Adding 5 days of lag time after the dispensing of abiraterone yielded the same results as the main analysis: 3 patients (4.2%) used radium-223 in combination with abiraterone at any cycle in the after–label change period.

Table 11: Sensitivity analysis: use of radium-223 in combination with abiraterone adding 5 days of lag time after dispensing abiraterone; period after the 2018 EU label change

	GePaRD N (%)
Use of radium-223 in combination with abiraterone at any cycle, number of patients	3 (4.2%)
By calendar year of the first dispensing/administration of radium-223 b	
2019	2 (2.8%)
2020	1 (1.4%)

EU = European Union; SHI = statutory health insurance provider.
Note: GePaRD data were from 4 SHIs.
[a] 2019 data were from 30 April through 31 December 2019; 2020 data were from January through 31 December 2020 for GePaRD.

10.5.3 Use of radium-223 in combination with abiraterone adding 30 additional days of lag time after dispensing abiraterone; period after the 2018 EU label change

The sensitivity analysis reported in Table 12 was performed only in Germany. In the analysis adding 30 days of lag time after dispensing abiraterone, additional use in combination was captured: 8 patients (11.3%) used radium-223 in combination with abiraterone at any cycle during the after–label change period (compared with 3 patients in the main analysis). Of these, 5 patients (7.0%) were from 2019, and 3 patients (4.2%) were from 2020.

Table 12: Sensitivity analysis: use of radium-223 in combination with abiraterone adding 30 additional days of lag time after dispensing abiraterone; period after the 2018 EU label change

	GePaRD N (%)
Use of radium-223 in combination with abiraterone at any cycle	8 (11.3%)
By calendar year of the first dispensing/administration of radium-223[a]	
2019	5 (7.0%)
2020	3 (4.2%)

EU = European Union; SHI = statutory health insurance provider.
Note: GePaRD data were from 4 SHIs.
[a] 2019 data were from 30 April through 31 December 2019; 2020 data were from January through 31 December 2020 for GePaRD.

10.5.4 Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC, assuming all docetaxel use was for CSPC

This "worst-case" sensitivity analysis (Table 13) was performed in Germany and Denmark, where castration-resistant status was not recorded, and all treatments were assumed to have been administered for CRPC in the main analyses. As in the main analysis for this outcome, in Germany this analysis was performed in the restricted sample including only patients from one large SHI. Under the assumption that all docetaxel use was for CSPC, 18 patients (52.9%) in Germany and 16 (25.4%) in Denmark used radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC. This is roughly twice the number of patients that meet the outcome in the main analysis in Germany, and over 3 times as many as the $1 \leq n < 5$ patients that meet this outcome in the main analysis in Denmark.

Table 13: Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC, Germany and Denmark, restricted sample

	GePaRD N (%)	Denmark N (%)
Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC[a], assuming all docetaxel use was for CSPC	18 (52.9%)	16 (25.4%)
By calendar year of the first dispensing/administration of radium-223[b]		
2019	12 (35.3%)	9 (14.3%)
2020	6 (17.6%)	7 (11.1%)
Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC, number of cycles	77 (54.2%)	76 (30.9%)

CSPC = castration-sensitive prostate cancer; LNRH = luteinising hormone–releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; SHI = statutory health insurance provider.
Note: Because information on the substances included in prior systemic therapies was available from only 1 of the 4 participating SHIs, this outcome was analysed in a restricted sample including only patients from that SHI.
[a] Except LHRH analogues.
[b] 2019 data were from 30 April through 31 December 2019; 2020 data were from January through 31 December 2020 for GePaRD and Denmark.

10.5.5 Use of radium-223 in combination with abiraterone among patients with a confirmed diagnosis of mCRPC

This sensitivity analysis was not performed because all patients in CAPRI and all patients in the after–label change period in Denmark had a confirmed diagnosis of mCRPC. In GePaRD, mCRPC status was not available and all abiraterone use was assumed to have been among patients with mCRPC.

10.5.6 Proportion of patients who received radium-223 in combination with systemic corticosteroids

The sensitivity analysis reported in In Denmark, combinations with prednisone or methylprednisolone were available only for a subset of 61 out of the total of 63 patients. Of the 61 patients, 25 (41.0%) received radium-223 in combination with systemic corticosteroids during the after–label change period. Among the 25 patients, use during only 1 or 2 cycles was recorded for 64% of the patients (data not shown).

Table 14 was restricted to the after–label change period. In CAPRI, Netherlands, contrary to initial expectations, the information on the date of end of corticosteroid use was not reliable. Therefore, the proportion of patients who used radium-223 in combination with corticosteroids could not be calculated.

In Germany, one patient (1.4%) received radium-223 in combination with systemic corticosteroids (prednisone/methylprednisolone) during the after–label change period.

In Denmark, combinations with prednisone or methylprednisolone were available only for a subset of 61 out of the total of 63 patients. Of the 61 patients, 25 (41.0%) received radium-223 in combination with systemic corticosteroids during the after–label change period. Among the 25 patients, use during only 1 or 2 cycles was recorded for 64% of the patients (data not shown).

Table 14: Sensitivity analysis: proportion of patients who received radium-223 in combination with systemic corticosteroids; period after the 2018 EU label change

	CAPRI 3	GePaRD N (%)	Denmark N (%)
Use of radium-223 in combination with systemic prednisone/(methyl) prednisolone	N/A	1 (1.4%)	25 (41.0%)

EU = European Union; N/A = not available; SHI = statutory health insurance provider.
Note: CAPRI 3 had data from 6 hospitals, GePaRD data were from 4 SHIs, and data from Denmark were from 2 hospitals. The period after the 2018 EU label change was 30 April 2019 through 31 October 2020 for CAPRI and 30 April 2019 through 31 December 2020 for GePaRD and Denmark.

10.5.7 Use of radium-223 in combination with abiraterone and use in combination with other systemic therapies for mCRPC using an alternative follow-up period

The sensitivity analysis reported in Table 15 was restricted to the after–label change period. Use of radium-223 in combination with abiraterone and use in combination with other systemic therapies for mCRPC with extended follow-up until 1 month after the date of the last administration of radium-223 (as opposed to censoring follow-up 6 months after the index date) was assessed. In the Netherlands (CAPRI) and in Germany, compared with the main analyses, no additional cycles of radium-223 were administered in combination with abiraterone or with other systemic therapies for mCRPC when considering all cycles of radium-223. In Denmark, implementing the alternative follow-up period, between 1 and 4 patients used radium-223 in combination with abiraterone and with other systemic therapies. Due to small numbers, results are masked and cannot be compared with the main analysis results.

Table 15: Sensitivity analysis: use of radium-223 in combination with abiraterone and use in combination with other systemic therapies for mCRPC using an alternative follow-up period; period after the 2018 EU label change

	CAPRI 3 N (%)	GePaRD[a] (4 SHIs) N (%)	GePaRD[a] (1 SHI) N (%)	Denmark[b] N (%)
Use of radium-223 in combination with abiraterone				
At any cycle, number of patients	1 (1.9%)	3 (4.2%)	N/A	1 ≤ n < 5
At any cycle, number of cycles	2 (0.8%)	3 (1.1%)	N/A	1 ≤ n < 5
Only at the last cycle	0 (0.0%)	1 (1.4%)	N/A	1 ≤ n < 5
Use of radium-223 in combination with other systemic therapies for mCRPC				
At any cycle, number of patients	5 (9.4%)	N/A	4 (11.8%)	1 ≤ n < 5
At any cycle, number of cycles	13 (5.1%)	N/A	4 (2.8%)	1 ≤ n < 5
Only at the last cycle	2 (0.8%)	N/A	3 (8.8%)	1 ≤ n < 5

EU = European Union; mCRPC = metastatic castration-resistant prostate cancer; N/A = not available; SHI = statutory health insurance provider.

Note: CAPRI 3 had data from 6 hospitals, and data from Denmark were from 2 hospitals (see footnote [a] for GePaRD). The period after the 2018 EU label change was 30 April 2019 through 31 October 2020 for CAPRI 3 and 30 April 2019 through 31 December 2020 for GePaRD and Denmark. However, follow-up lasted until 1 month after the date of the last administration of radium-223. The last administration was defined as an administration of radium-223, up to the sixth one, that was not followed by a subsequent cycle within 2 months.

[a] In GePaRD, "use of radium-223 in combination with abiraterone" was assessed in 4 (SHIs), whereas "use of radium-223 in combination with other systemic therapies for mCRPC" was assessed in the sample restricted to 1 SHI.

[b] Per Danish data privacy requirements, if the number of individuals in a cell is from 1 to 4, or would allow back-calculation of cells to lead to a result of 1 to 4, the value is reported as a range. Cells with values originating from 1 to 4 patients are masked.

10.6 Safety data (adverse events/adverse reactions)

Not applicable.

11. Discussion

11.1 Key results

Analyses in CAPRI in the Netherlands and in national health registries in Denmark were conducted among patients with confirmed mCRPC. In Germany, all patients receiving radium-223 were assumed to have mCRPC since castration sensitivity status could not be assessed. Nearly all patients in CAPRI and around half of patients in Germany had evidence of bone metastases in both study periods. Patient characteristics were in line with the expectations for this type of patient population.

Overall, during the after–label change period, only 1 patient in the Netherlands, 3 patients in Germany (in the 4 SHIs) (representing 1.9% and 4.2% of all study patients in the Netherlands and Germany, respectively), and between 1 and 4 patients in Denmark (representing 1.9%, 4.2%, and 2%-6% of all study patients in the Netherlands, Germany, and Denmark, respectively) used radium-223 in combination with abiraterone (all use of abiraterone was after the last cycle of radium-223). Use of radium-223 in combination with other systemic therapies for mCRPC occurred in 5 patients in the Netherlands, 4 patients in Germany (in the sample restricted to 1 SHI) (representing 9.4% and 11.8% of all patients in the Netherlands, Germany, respectively), and between 1 and 4 patients in Denmark (representing 9.4%, 11.8%, and 2%-6% of all patients in the Netherlands, Germany, and Denmark, respectively). Use of radium-223 without at least 2 prior lines of systemic therapy for mCRPC occurred in 21 patients in the Netherlands, 9 patients in Germany (in the restricted sample), and $1 \leq n < 5$ patients in Denmark (representing 39.6%, 26.5% and 2%-6% of all patients in the Netherlands, Germany and Denmark, respectively).

In brief, in Germany and the Netherlands, the prevalence of all study outcomes decreased in the study period after the 2018 EU label change relative to the prevalence in the study before–label change period. In Denmark, use of radium-223 in combination with abiraterone and in combination with other systemic therapies for mCRPC was very rare, occurring in few patients during the after–label change period and not at all during the before–label change period. Use of radium-223 without at least 2 prior lines of systemic therapy for mCRPC was less common in Denmark than in the other 2 countries and decreased in the after–label change period.

11.2 Limitations

In the Netherlands, enrolment of participating hospitals was lower than anticipated in CAPRI 3 due to the limitations imposed by the COVID-19 pandemic on the chart abstraction process in several hospitals. Nevertheless, despite the exceptional situation caused by the pandemic, the extension of

the data-extraction period allowed the enrolment of 53 patients, which was within the pre-pandemic range of expected participants in the after–label change period.

In Germany, contrary to initial expectations, 3 of the 4 SHIs contributing data to the GePaRD database could not provide detailed information on the type of systemic therapy used to treat mCRPC other than abiraterone. Results for the study outcomes on the use of radium-223 in combination with systemic therapies for mCRPC other than abiraterone and on the use of radium-223 without having used at least 2 prior lines of treatment for mCRPC were based on data from 1 SHI that accounted for about half of the total number patients prescribed radium-223 in the 4 SHIs. Results for the use of radium-223 in combination with abiraterone could be based on all 4 SHIs.

In Denmark, only 2 of the 3 hospitals that administered radium-223 during the study period contributed to the study. Moreover, for the before–label change period, only a limited number of medical records could be abstracted from the 2 participating hospitals. Finally, policies on the reporting of small cell counts to protect patient privacy prevented an understanding of the true proportions of each outcome of interest.

The small number of patients in the study implies that the results were prone to random variation, especially in the after–label change period. Lower participation of hospitals in CAPRI and Denmark, and the restriction to one SHI in Germany for 2 of the 3 outcomes, could have introduced selection bias if participating hospitals/SHIs treated patients with characteristics different from patients at hospitals/SHIs that did not participate. However, when comparing the periods before and after the label change, results suggest that, as expected, doctors tended to align their prescription habits with the updated indication and new contraindication introduced in the label for radium-223 in October 2018.

The study outcomes of interest are dependent on the quality of the information on use of systemic therapies for mCRPC. If this information was poorly recorded, the results observed could be biased. However, because recording the use of the study treatments of interest is one of the key drivers of CAPRI, and in Denmark chart abstraction was performed to extract the key variables needed for this study, it is unlikely that this problem affected the study in the Netherlands and Denmark. In Germany, where claims data were used, some variables could have been undercaptured in the claims. However, the fact that for most study variables, good alignment was observed across the 3 data sources suggests that the quality of data from GePaRD was also good.

Contrary to initial expectations, information in CAPRI on use of systemic corticosteroids during the after–label change period was not available due to lack of reliable information on stop date of corticosteroid prescriptions. Therefore, the planned sensitivity analysis to assess the concomitant use of radium-223 with systemic corticosteroids was conducted only in the Danish National Registries and in GePaRD.

Use of LHRH analogues in patients in CAPRI was recorded, but the indication (CSPC or CRPC) was often unavailable. In addition, the specific type of LHRH analogue was missing in several instances. This detailed information was part of the planned description of patients who use radium-223. To partially circumvent this lack of information, we reported data on “Any prior use of a LHRH analogue” in Table 5 so that prior use of LHRH analogues was described, irrespective of the exact indication and type of LHRH analogue. However, because LHRH analogues were not part of the outcome definitions, this did not affect the estimation of the key target outcomes.

In Germany, castration-resistant or castration-sensitive status was not captured in the data source, and in Denmark, mCRPC status was available only for a subset of patients in the before–label change period. Therefore, all patients were assumed to have mCRPC, and all systemic therapies administered—including docetaxel, which can be prescribed in both CSPC and CRPC—were assumed to have been given for mCRPC. This assumption, if incorrect, could have inflated the number of patients who were considered to have received 2 prior lines of systemic therapy for mCRPC and led to an underestimate of the number of patients with use of radium without at least 2 prior lines of treatment. To assess this possibility, in a sensitivity analysis, we assumed a "worst-case scenario" under which all docetaxel use was assumed to be for CSPC.

The collected data did not allow for assessment of patients' lack of tolerance, frailty, or other eligibility factors for receiving other systemic therapies for mCRPC. In the after–label change period, this likely resulted in an overestimation of the proportion of patients whose use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC represented a true deviation from the guidelines.

11.3 Interpretation

The administration of radium-223 in the 3 countries took place mostly in line with the current label in Europe with respect to coadministration with other study drugs. Only 1.9% (1 patient) in the Netherlands, 4.2% (3 patients) in Germany, and less than 6% ($1 \leq n < 5$ patients) of the study patients in Denmark used it in combination with abiraterone. Radium-223 was used in combination with other systemic therapies for mCRPC during the after–label change period in 9.4% (5 patients) in the Netherlands, 11.8% (4 patients) in Germany, and less than 6% ($1 \leq n < 5$ patients) of the study patients in Denmark. Furthermore, on some occasions, patients received abiraterone or other systemic therapies at the last cycle of radium-223, possibly after the end of the treatment course, which may represent a treatment switch rather than concomitant use of the medications. Of the cycles of radium-223 that were administered in combination with abiraterone, 0% in the Netherlands, 33% in Germany, and 100% in Denmark were last cycles.

The number of cases when Ra-223 was used in combination with abiraterone and with other systemic therapies for mCRPC decreased after the label change, compared with the before–label change period in the Netherlands and Germany (absolute differences of 4.7% and 18.5%, respectively, for use in combination with abiraterone and 5.0% and 15.6%, respectively, for use in combination with other systemic therapies). Among the limited number of patients that could be assessed in the before–label change period in Denmark, no use in combination with abiraterone or with other systemic therapies was identified. This limited use of radium-223 in combination with systemic therapies for mCRPC (i.e., abiraterone and others) in both study periods may be related to a lack of evidence at that time on combination therapy from clinical trials to guide physicians' prescribing practices.

However, use of radium-223 before at least 2 prior lines of systemic therapy for mCRPC remained relatively common after the label change in the Netherlands and Germany (39.6% and 26.5%, respectively), even if the frequency decreased compared with the before–label change period (46.5% and 55.9%, respectively). In Denmark, less than 6% of patients in the after–label change period used radium-223 before at least 2 prior lines of systemic therapy, a decrease from 26.7% in the before–label change period. Importantly, the collected data did not allow for assessment of the eligibility of patients to receive other systemic therapies for mCRPC, and this finding likely reflects, at least in part, the proportion of patients in whom other systemic therapies are contraindicated. In addition,

this relatively high proportion of patients in Germany and the Netherlands may relate to the fact that clinical guidelines before the label change recommended the use of radium-223 as a first-line option in mCRPC, especially in frail patients in whom chemotherapy could be seen as too aggressive (13-16), and may still lead doctors to consider its use as a first-line medication in frail patients. The PRECISE Xofigo study conducted in Sweden (2013-2018) found that 64.9% of patients used radium-223 as a first- or second-line treatment for mCRPC (17), which is higher than the observed use in the Netherlands, Germany, and Denmark in the before–label change period (46.5%, 55.9%, and 26.7% respectively). Similarly to the other 2 study main outcomes, the prevalence of this outcome also decreased in the after–label change period.

Use of radium-223 in combination with corticosteroids was uncommon in Germany (1 patient) and could not be assessed in the Netherlands. In Denmark, of the 61 patients assessed for this analysis, 25 patients (41.0%) used both drugs in combination, however for most of these patients it was only for a limited period during the radium-223 treatment.

In the sensitivity analysis that extended follow-up to include radium-223 administrations beyond the 6 months after the index date, no additional cycles were administered in combination with abiraterone or with other systemic therapies for mCRPC in the Netherlands or Germany (in Denmark, masking due to small numbers did not allow comparisons).

11.4 Generalisability

All patients in the study had prostate cancer cared for in the Netherlands, Germany, or Denmark. Therefore, results reflect prescription habits of radium-223 among patients in those countries in the defined periods before and after the label change for radium-223.

The representativeness of the hospitals that contributed data to CAPRI with regard to all hospitals in the Netherlands that administer radium-223 is not known. Overall, 20 hospitals contributed data to the period before the label change in CAPRI 1 and 2, but only 6 hospitals could contribute data to CAPRI 3 in the period after the label change, 5 of which also contributed to CAPRI 1 and 2. Because different types of centres (i.e., larger tertiary hospitals and smaller general hospitals) contributed data to CAPRI 3 and because patient characteristics were similar in the before and after period in the Netherlands, a variety of prescription habits may have been assessed that can be representative of all hospitals in the Netherlands that administer radium-223.

In Germany, only 1 SHI provided detailed data on the administration of systemic cancer therapies, so the analyses of radium-223 use in combination with other systemic therapies and without at least 2 lines of prior therapy were restricted to a smaller sample of patients belonging only to that SHI. Nevertheless, because patient characteristics were similar between the 4 SHIs and the sample restricted to 1 SHI, the likelihood of bias is low. Furthermore, a core property of the German SHI system is uniform access to all levels of care, i.e., the care of patients is expected to be similar across the different SHIs.

The representativeness of the 2 participating hospitals in Denmark with regards to all hospitals in Denmark that administer radium-223 is expected to be high, as health care in Denmark is delivered according to centralised evidence-based guidelines (18).

Overall, despite being based on relatively small numbers, results appear to be representative of the nationwide radium-223 prescribing practices in each participating country in both study periods.

12. Other information

None.

13. Conclusion

In the patients covered by data sources in the Netherlands, Germany, and Denmark, use of radium-223 in combination with abiraterone or with other systemic therapies for mCRPC was uncommon and became less common in the after–label change period, which was in line with the updated indication and new contraindication introduced in the EU in 2018. A substantial proportion of this use was observed at the end of the radium-223 treatment course and therefore may represent switching rather than coadministration. The use of radium-223 without at least 2 prior lines of systemic therapy for mCRPC remained relatively common in the period after the 2018 EU label change in the Netherlands and Germany, which may relate to the fact that clinical guidelines before the label change recommended the use of radium-223 as a first-line option in mCRPC, especially in frail patients in whom chemotherapy could be seen as too aggressive, and may still lead doctors to consider its use as a first-line medication in frail patients. Of note, the eligibility of patients to receive other systemic therapies for mCRPC could not be determined in this study; therefore, this finding reflects, at least in part, the proportion of patients in whom other systemic therapies were contraindicated. The relatively small number of patients enrolled in the period after the label change make the reported findings more prone to random variation. Nevertheless, despite being based on relatively small numbers, results can be considered representative of the nationwide radium-223 prescribing practices in each participating country in both study periods.

14. References

1. EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – post-authorisation safety studies (EMA/813938/2011 Rev 3). European Medicines Agency; 9 October 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed 29 March 2023.
2. Bayer. Phase III trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone for patients with metastatic castration-resistant prostate cancer unblinded early. PR News Wire; 30 November 2017. Available at: https://www.prnewswire.com/news-releases/phase-iii-trial-of-radium-ra-223-dichloride-in-combination-with-abiraterone-acetate-and-prednisoneprednisolone-for-patients-with-metastatic-castration-resistant-prostate-cancer-unblinded-early-300564844.html. Accessed 29 March 2023.
3. Xofigo SmPC. Xofigo 1100 kBq/mL solution for injection (summary of product characteristics). Bayer AG; 18 May 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/xofigo-epar-product-information_en.pdf. Accessed 29 March 2023.
4. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. Int J Epidemiol. 2017 Jun;46(3):798-f.
5. Nielsson MS, Erichsen R, Frøslev T, Taylor A, Acquavella J, Ehrenstein V. Positive predictive values of the coding for bisphosphonate therapy among cancer patients in the Danish National Patient Registry. Clin Epidemiol. 2012;4:233-6.
6. Netherlands Trial Register. Castration-resistant prostate cancer registry: an observational study in the Netherlands. 3 October 2022. Available at: https://trialsearch.who.int/Trial2.aspx?TrialID=NTR3591. Accessed 13 June 2023.
7. Pigeot I, Ahrens W. Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. Pharmacoepidemiol Drug Saf. 2008 Mar;17(3):215-23.
8. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377-81.
9. Rosner B. Estimation. In: Rosner B, editor. Fundamentals of biostatistics. 7th ed. Boston, MA: Brooks/Cole; 2011. p. 186.
10. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998 Apr;17(8):873-90.
11. ISPE. Guidelines for good pharmacoepidemiology practices (GPP). Revision 3. International Society for Pharmacoepidemiology; June 2015. Available at: https://www.pharmacoepi.org/resources/policies/guidelines-08027/. Accessed 29 March 2023.

12. ENCePP. Guide on methodological standards in pharmacoepidemiology (EMA/95098/2010 Rev. 10). European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; July 2022. Available at: https://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml. Accessed 29 March 2023.

13. Cookson MS, Roth BJ, Dahm P, Engstrom C, Freedland SJ, Hussain M, et al. Castration-resistant prostate cancer: AUA guideline. J Urol. 2013 1 August;190(2):429-38.

14. Omlin A, Pezaro C, Gillessen Sommer S. Sequential use of novel therapeutics in advanced prostate cancer following docetaxel chemotherapy. Ther Adv Urol. 2014;6(1):3-14.

15. Basch E, Loblaw DA, Oliver TK, Carducci M, Chen RC, Frame JN, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2014 20 October;32(30):3436-48.

16. Parker C, Gillessen S, Heidenreich A, Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 September;26 Suppl 5:v69-77.

17. Stattin P, Westerberg M, Lissbrant IF, Eriksson MH, Kjellman A, Ullén A, et al. Real world outcomes in patients with metastatic, castration-resistant prostate cancer treated with radium-223 in routine clinical practice in Sweden. Clin Genitourin Cancer. 2023 Feb;21(1):107.e1-.e9.

18. Schmidt M, Schmidt SAJ, Adelborg K, Sundboll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol. 2019;11:563-91.

Appendices

Annex 1: List of stand-alone documents

Not applicable

Annex 2: Additional information

Refer to protocol in EU PAS Register - https://www.encepp.eu/encepp/viewResource.htm?id=46942.

Table A-1: Clinical characteristics at baseline of each study period, restricted sample from 1 SHI in Germany for which detailed data on the prior use of systemic therapies for mCRPC were available

	After label change N (%)	Before label change N (%)
Age (years)		
Mean (SD)	74.2 (9.7)	72.7 (7.7)
Median (Q1, Q3)	77 (67, 81)	74 (68, 78)
Min, max	53, 91	52, 98
Missing n (%)	0 (0.0%)	0 (0.0%)
Age group (years), n (%)		
< 50	0 (0.0%)	0 (0.0%)
50-59	3 (8.8%)	16 (6.5%)
60-69	8 (23.5%)	59 (24.1%)
70-79	12 (35.3%)	127 (51.8%)
80-89	10 (29.4%)	42 (17.1%)
90 and more	1 (2.9%)	1 (0.4%)
Calendar year at the prescription date/ index date, n (%)		
2013	NA	0 (0.0%)
2014	NA	8 (3.3%)
2015	NA	104 (42.4%)
2016	NA	101 (41.2%)
2017	NA	32 (13.1%)
2019	25 (73.5%)	NA
2020	9 (26.5%)	NA
Time since first prostate cancer diagnosis, months		
Mean (SD)	65.6 (46.9)	69.2 (44.5)
Median (Q1, Q3)	48 (27, 94)	58 (33, 107)
Min, max	7, 170	3, 157
Missing n (%)	0 (0.0%)	0 (0.0%)
Time since surgical castration (if applicable)		
Patients who underwent surgical castration (n, %)	0	5 (2.0%)
Mean (SD), months	NA	31.8 (28.2)
Median (Q1, Q3), months	NA	19 (18, 40)
Min, max, months	NA	5, 77
Unknown time, n	NA	NA
Time since first use of an antiandrogen medication[a]		
Mean (SD), months	50.9 (36.4)	59.3 (39.5)
Median (Q1, Q3), months	42 (24, 69)	50 (27, 85)
Min, max, months	4, 134	2, 160
Unknown time, n	0 (0.0%)	5 (2.0%)
Confirmed diagnosis of mCRPC, n (%)		
Yes	N/A	N/A
No	N/A	N/A
Time since first mCRPC confirmed diagnosis, months		
Mean (SD)	N/A	N/A
Median (Q1, Q3)	N/A	N/A
Min, max	N/A	N/A
Date of mCRPC diagnosis missing, n (%)	N/A	N/A
Any prior use of a LHRH analogue, n (%)		
Yes	34 (100%)	239 (97.6%)
No	0 (0.0%)	6 (2.4%)

	After label change N (%)	Before label change N (%)
Prior use of therapies for CRPC, n (%)[b]	34 (100%)	240 (98.0%)
Cytotoxic drugs		
Cabazitaxel	8 (23.5%)	29 (11.8%)
Docetaxel	22 (64.7%)	93 (38.0%)
Mitoxantrone	0 (0.0%)	1 (0.4%)
Immunotherapies		
Sipuleucel-T	0 (0.0%)	0 (0.0%)
Pembrolizumab	0 (0.0%)	0 (0.0%)
Antiandrogens		
Abiraterone	27 (79.4%)	142 (58.0%)
Apalutamide[c]	1 (2.9%)	0 (0.0%)
Bicalutamide[c]	25 (73.5%)	203 (82.9%)
Darolutamide[c]	0 (0.0%)	0 (0.0%)
Enzalutamide	17 (50.0%)	93 (38.0%)
Flutamide[c]	4 (11.8%)	57 (23.3%)
Nilutamide[c]	0 (0.0%)	0 (0.0%)
LHRH analogues[c]		
Leuprolide/ leuprorelin	27 (79.4%)	186 (75.9%)
Goserelin	5 (14.7%)	26 (10.6%)
Histrelin	0 (0.0%)	1 (0.4%)
Triptorelin	9 (26.5%)	32 (13.1%)
Buserelin	5 (14.7%)	44 (18.0%)
Nafarelin	0 (0.0%)	0 (0.0%)
Gonadorelin	0 (0.0%)	0 (0.0%)
Degarelix	3 (8.8%)	33 (13.5%)
Prednisone/ (methyl) prednisolone[c,d,e]	31 (91.2%)	179 (73.1%)
Corticosteroids for noncancer indications since first diagnosis of CRPC [c,d,e]	N/A	N/A
Prior use of therapies for CSPC, n (%)	N/A	N/A
Cytotoxic drugs	N/A	N/A
Cabazitaxel	N/A	N/A
Docetaxel	N/A	N/A
Mitoxantrone[c]	N/A	N/A
Immunotherapies	N/A	N/A
Sipuleucel-T	N/A	N/A
Pembrolizumab	N/A	N/A
Antiandrogens	N/A	N/A
Abiraterone	N/A	N/A
Apalutamide[c]	N/A	N/A
Bicalutamide[c]	N/A	N/A
Darolutamide[c]	N/A	N/A
Enzalutamide[c]	N/A	N/A
Flutamide[c]	N/A	N/A
Nilutamide[c]	N/A	N/A
LHRH analogues[c]	N/A	N/A
Leuprolide/ leuprorelin	N/A	N/A
Goserelin	N/A	N/A
Histrelin	N/A	N/A
Triptorelin	N/A	N/A
Buserelin	N/A	N/A
Nafarelin	N/A	N/A
Gonadorelin	N/A	N/A
Degarelix	N/A	N/A
Prednisone/(methyl)prednisolone [c,d]	N/A	N/A

	After label change N (%)	Before label change N (%)
Corticosteroids for noncancer indications since first diagnosis of CSPC [c,d]	N/A	N/A
Presence of metastases, ever before[e]		
Bone metastases, inpatient diagnoses	17 (50.0%)	120 (49.0%)
Bone metastases, outpatient diagnoses	17 (50.0%)	111 (45.3%)
Visceral metastases, inpatient diagnoses	1 (2.9%)	2 (0.8%)
Visceral metastases, outpatient diagnoses	1 (2.9%)	12 (4.9%)
Unknown metastatic location, inpatient diagnoses	1 (2.9%)	4 (1.6%)
Unknown metastatic location, outpatient diagnoses	8 (23.5%)	60 (24.5%)
Levels of serum alkaline phosphatase, n (%) [f,g]		
< 220 U/L	N/A	N/A
≥ 220 U/L	N/A	N/A
Prior use of bone-health agents during the 180 days before the index date, n (%)[c]		
Bisphosphonates	7 (20.6%)	97 (39.6%)
Denosumab	16 (47.1%)	88 (35.9%)
Bone morphogenetic proteins	0 (0.0%)	0 (0.0%)
Prior use of other drugs affecting bone structure and mineralisation[c]		
Ipriflavone	0 (0.0%)	0 (0.0%)
Aluminium chlorohydrate	0 (0.0%)	0 (0.0%)
Strontium ranelate	0 (0.0%)	0 (0.0%)
Burosumab	0 (0.0%)	0 (0.0%)
Romosozumab	0 (0.0%)	0 (0.0%)
Strontium ranelate and cholecalciferol	0 (0.0%)	0 (0.0%)
Prior history of osteoporosis ever before,[d] n (%)		
Yes, inpatient diagnoses	0 (0.0%)	2 (0.8%)
Yes, outpatient diagnoses	3 (8.8%)	25 (10.2%)
No	31 (91.2%)	218 (89.0%)

CRPC = castration-resistant prostate cancer; CSPC = castration-sensitive prostate cancer; EU = European Union; ICD-10 = *International Classification of Diseases, Tenth Revision*; LHRH = luteinising hormone–releasing hormone; max = maximum; mCRPC = metastatic castration-resistant prostate cancer; min = minimum; N/A = not available; NA = not applicable; Q1, Q3 = first and third quartiles; SD = standard deviation; SHI = statutory health insurance provider.

Notes: The period before the 2018 EU label change was 13 November 2013 through 31 May 2017 and the period after the 2018 EU label change was 30 April 2019 through 30 June 2020; 2013 data are from 13 November through 31 December 2013; 2017 data are from January through 30 November 2017; 2019 data are from 30 April through 31 December 2019; and 2020 data are from January through 30 June 2020.

[a] "Antiandrogen medication" is defined as "first evidence of prescription of an LHRH analogue or antiandrogen medication, whichever comes first."

[b] In GePaRD, because castration-resistant status was not available, all systemic therapies were assumed to have been administered for CRPC.

[c] Outpatient use only in GePaRD.

[d] Information on indication of corticosteroids not available for GePaRD.

[e] Individual patients may contribute to both bone and visceral metastasis. Assessed any time before the index date. Information assessed through ICD-10 codes C79.88 and C79.9 in GePaRD.

[f] Only measurements up to 2 months before or 1 week after the index date were considered.

[g] Information not available in GePaRD.

Three of 4 SHIs in GePaRD lacked information on substances included in systemic therapies for mCRPC. Results for use of radium-223 in combination with other systemic therapies for mCRPC and use of radium-223 without 2 prior lines of systemic therapy for mCRPC are presented in the main body of the report restricted to the one SHI that had full information. These 2 outcomes calculated among all 4 SHIs constituting the GePaRD data source are presented in Table A-2 and Table A-3 for transparency. However, results are based on incomplete data and should not be used to draw conclusions about the objectives of the study.

Table A-2: Use of radium-223 in combination with other systemic therapies for mCRPC, data from 4 SHIs in GePaRD

Outcomes	Period after the 2018 EU label change[a] N (%)	Period before the 2018 EU label change[a] N (%)
Number of patients, n	71	580
Use of radium-223 in combination with other systemic therapies for mCRPC[b], number of patients	5 (7.0%)	152 (26.2%)
By calendar year of the first administration of radium-223[c]		
2013	NA	0 (0.0%)
2014	NA	3 (0.5%)
2015	NA	56 (9.7%)
2016	NA	69 (11.9%)
2017	NA	24 (4.1%)
2019	5 (7.0%)	NA
2020	0 (0.0%)	NA
Number of radium-223 cycles, n	281	2,551
Use of radium-223 in combination with other systemic therapies for mCRPC[c], number of cycles	6 (2.1%)	503 (19.7%)
Number of radium-223 cycles with enzalutamide	4 (1.4%)	492 (19.3%)
Number of radium-223 cycles with docetaxel	2 (0.7%)	5 (0.2%)
Number of radium-223 cycles with cabazitaxel	0 (0.0%)	7 (0.3%)
Number of radium-223 cycles with sipuleucel-T[d]	0 (0.0%)	0 (0.0%)
Number of radium-223 cycles with pembrolizumab	0 (0.0%)	0 (0.0%)
Use of radium-223 in combination with other systemic therapies only at last cycle	3 (4.2%)	17 (2.9%)

EU = European Union; LHRH = luteinising hormone–releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; NA = not applicable; SHI = statutory health insurance provider.

Note: When assessing cycles, the denominator is the total number of radium-223 cycles administered per period.

[a] The period before the 2018 EU label change was 13 November 2013 through 31 May 2017, with follow-up through 30 November 2017. The period after the 2018 EU label change was 30 April 2019 through 30 June 2020, with follow-up through 31 December 2020.

[b] Except LHRH analogues.

[c] 2013 data were from 13 November through 31 December 2013; 2017 data were from January through 30 November 2017. 2019 data were from 30 April through 31 December 2019; 2020 data were from January 31 December 2020. Other years had data for the full year.

[d] In GePaRD, only outpatient use of sipuleucel-T was captured.

Table A-3: Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC, data from 4 SHIs in GePaRD

Outcomes	Period after the 2018 EU label change[a] N (%)	Period before the 2018 EU label change[a] N (%)
Number of patients, n	71	580
Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC,[b,c] number of patients	31 (43.7%)	381 (65.7%)
By calendar year of the first administration of radium-223[d]		
2013	NA	1 (0.2%)
2014	NA	8 (1.4%)
2015	NA	157 (27.1%)
2016	NA	158 (27.2%)
2017	NA	57 (9.8%)
2019	18 (25.4%)	NA
2020	13 (18.3%)	NA
Number of radium-223 cycles, n	281	2,551
Use of radium-223 without having received at least 2 prior lines of systemic therapy for mCRPC,[b] number of cycles	124 (44.1%)	1,717 (67.3%)

EU = European Union; LHRH = luteinising hormone–releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; NA = not applicable; SHI = statutory health insurance provider.

Note: When assessing cycles, the denominator is the total number of radium-223 cycles administered per period.

[a] The period before the 2018 EU label change was 13 November 2013 through 31 May 2017, with follow-up through 30 November 2017. The period after the 2018 EU label change was 30 April 2019 through 30 June 2020, with follow-up through 31 December 2020.

[b] Except LHRH analogues.

[c] "Systemic therapy for mCRPC" is defined as any use of abiraterone, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, or pembrolizumab (each drug substance counted as a prior line, irrespective of the number of administrations of the specific drug substance).

[d] 2013 data were from 13 November through 31 December 2013; 2017 data were from January through 30 November 2017. 2019 data were from 30 April through 31 December 2019; 2020 data were from January through 31 December 2020. Other years had data for the full year.

Annex 3: Signature pages

Signature Page - Coordinating Centre, on behalf of DIRECT PASS team

Title	DIRECT: Drug UtilisatIon Study of Radium-223 Under RoutinE Clinical PracTice in Europe
Report version and date	Final study report; V0.3, 1 June 2023
IMPACT study number	20702
Study type / Study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS Register number	EUPAS37163
Medicinal product	Various Therapeutic Radiopharmaceuticals (V10XX03), radium (^{223}Ra) dichloride
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: Joan Fortuny

Date, Signature: _____, _____

Signature Page – MAH Study Responsible

Title	DIRECT: Drug UtilisatIon Study of Radium-223 Under RoutinE Clinical PracTice in Europe
Report version and date	Final study report; V0.3, 1 June 2023
IMPACT study number	20702
Study type / Study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS Register number	EUPAS37163
Medicinal product	Various Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: _____, _____

Signature Page – MAH Regulatory Lead

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