Post-Authorisation Safety Study (PASS) Information

Acronym/title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant **PR**ostate cancer (mCRPC) Pati**E**nts treated with Radium-223 in routine **C**linical pract**I**ce in **S**wed**E**n
Protocol version and date	v 2.1, 6 SEP 2019
IMPACT study number	20437
Study type/study phase	PASS ☒ PASS Joint PASS: ☐ YES ☒ NO>
EU PAS register number	Study not yet registered
Active substance	Various Therapeutic Radiopharmaceuticals (V10XX03), radium (^{223}Ra) dichloride
Medicinal product	Radium-223 (Ra-223)
Product reference	EU/1/13/873/001
Procedure number	EMEA/H/C/PSP/S/0076
Comparator/reference therapy	Docetaxel, abiraterone, enzalutamide, cabazitaxel, and other chemotherapies that are standard of care in Sweden.
Study initiator and funder	Bayer AG
Research question and objectives	The research questions are: • Does the use of radium-223 (Ra-223) increase the risk of bone fractures compared with other treatments for metastatic castration-resistant prostate cancer (mCRPC) in routine clinical practice? • Does the use of Ra-223 increase the risk of death compared with other treatments for mCRPC in routine clinical practice? • Does the use of Ra-223 increase the risk of prostate cancer–specific death compared with other treatments for mCRPC in routine clinical practice? The primary objective of this study is to estimate the effect of Ra-223 on the incidence of bone fractures compared with other standard treatments for mCRPC. The secondary objectives are to

	estimate the effect of Ra-223 on overall survival and prostate cancer–specific survival compared with other standard treatments for mCRPC and to estimate heterogeneity of the estimates by line of treatment (first, second, and subsequent).
Country(-ies) of study	Sweden
Author	PPD PPD PPD PPD on behalf of the Ra-223 PRECISE team

Marketing authorisation holder

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

The study will be conducted in compliance with the protocol

and any applicable regulatory requirements.

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

1. Table of contents

2. List of abbreviations

ADT	Androgen-Deprivation Therapy
AEFUP	Administrative End of Follow-up
CRPC	Castration-Resistant Prostate Cancer
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ICD	*International Classification of Diseases, 10th Revision*
ISPE	International Society for Pharmacoepidemiology
HR	Hazard Ratio
MAH	Marketing Authorisation Holder
mCRPC	Metastatic Castration-Resistant Prostate Cancer
NPCR	National Prostate Cancer Registry
OS	Overall Survival
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PCBaSe	Prostate Cancer data Base Sweden
PPC	Patient-overview Prostate Cancer, a subregister of the PCBaSe
PSA	Prostate-Specific Antigen
PSUR	Periodic Safety Update Report
QOL	Quality of Life
Ra-223	Radium-223
RCT	Randomised Controlled Trial
RR	Relative Risk
WHO	World Health Organization

3. Responsible parties

3.1 Study initiator and funder

Role:
Name:
E-mail:

Role:
Name:

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

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

This study will be conducted in collaboration with academic institutions in Sweden and RTI-HS as a collaborating centre.

The Prostate Cancer data Base Sweden (PCBaSe) principal investigator and lead statistician responsible for the conduct of this study are PPD and PPD, respectively. Contact details on the coordinating and/or principal investigators and coinvestigators participating in the study are listed in a stand-alone document (Annex 1), which is available upon request.

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

4. Abstract

Acronym/title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant **PR**ostate cancer (mCRPC) Pati**E**nts treated with Radium-223 in routine **C**linical pract**I**ce in **S**wed**E**n
Protocol version and date	v 2.1, 6 SEP 2019
IMPACT study number	20437
Study type/study phase	PASS ☒ PASS Joint PASS: ☐ YES ☒ NO>
Author	PPD PPD PPD
Rationale and background	Radium-223 (Ra-223) is an alpha particle–emitting radioactive agent approved for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC). The ALSYMPCA trial showed that Ra-223 prolonged median overall survival (OS) by 3.6 months when compared with placebo in patients with mCRPC, symptomatic bone metastases, and no visceral metastases. The safety profile was favourable, with a low incidence of myelosuppression. The ERA 223 trial was designed to evaluate the efficacy and safety of Ra-223 in combination with abiraterone acetate plus prednisone/prednisolone versus placebo in combination with abiraterone acetate plus prednisone/prednisolone in asymptomatic or mildly symptomatic chemotherapy-naive patients with bone-predominant metastatic mCRPC. The trial was unblinded in November 2017 per an independent data monitoring committee's recommendation because of the observation of an imbalance of more fractures and deaths in the treatment arm, treated with Ra-223 in combination with abiraterone and prednisone, when compared with the control arm, treated with placebo in combination with abiraterone and prednisone.
Research questions and objectives	This study will address the following research questions: • Does the use of Ra-223 increase the risk of bone fractures compared with other treatments for mCRPC in routine clinical practice?

	• Does the use of Ra-223 increase the risk of death compared with other treatments for mCRPC in routine clinical practice? • Does the use of Ra-223 increase the risk of prostate cancer–specific death compared with other treatments for mCRPC in routine clinical practice? The primary objective in this study is to estimate the effect of Ra-223 on the incidence of bone fractures compared with other standard treatments for mCRPC. The secondary objectives are to estimate the effect of Ra-223 as on OS and prostate cancer–specific survival compared with other standard treatments for mCRPC and to estimate heterogeneity of the estimates by line of treatment (first, second, and subsequent).
Study design	Observational retrospective comparative cohort study. The effect of Ra-223 will be addressed in different lines of treatment for mCRPC (first, second, third/fourth). The cohort of first-line treatment will include patients meeting the eligibility criteria when they start a first line of treatment for mCRPC. The cohort of second-line treatment will include patients meeting the eligibility criteria described when they start a second line of treatment. The same approach will be used for third- and fourth-line treatment cohorts. Cohorts will be analysed together if there is no evidence of effect heterogeneity between first and subsequent lines of treatment. The comparator cohorts will be patients using standard of care.
Population	Patients receiving treatment for mCRPC recorded in the Prostate Cancer data Base Sweden (PCBaSe) during the study period, without evidence of having received Ra-223 before the study period. Patients will be identified from the "Patient-overview Prostate Cancer" (PPC), a subregistry of the PCBaSe. The study period will start in November 2013, the month of Ra-223 launch in Sweden, and end in December 2018, the latest data covering full information including cause of death available at the time of data extraction.
Variables	The main analysis will compare the following two groups: A. Ra-223 initiators. Patients can stop Ra-223 after 6 cycles—or earlier—in the event of toxicity, cancer progression, or worsening of the overall health status. Patients can start other drugs for mCRPC (docetaxel, cabazitaxel, enzalutamide, abiraterone, others) after the initiation of Ra-223, when clinically indicated, but never at the same time as Ra-223. Androgen-deprivation therapy (ADT) with first-generation antiandrogens can be used at any time.

	B. Initiators of other standard of care (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients are allowed to stop the standard of care and continue with other lines of treatment, with the exception of Ra-223, when clinically indicated. ADT with first-generation antiandrogens can be used at any time. The primary outcome will be the cumulative incidence of bone fractures. Bone fractures will be identified based on ICD-10 diagnosis codes in the hospital or in outpatient hospital clinics. Thus, the study will capture only fractures that prompted a diagnostic work-up in this environment because of symptoms. Asymptomatic bone fractures incidentally diagnosed through routine imaging and not requiring attention at a hospital or outpatient level may not be captured. The secondary outcomes will be OS and prostate cancer–specific survival. The date and cause of death will be identified from the Cause of Death Register that is linked to the PCBaSe. The following variables will be adjusted for to attain conditional exchangeability: age; calendar year of inclusion; time from diagnosis to baseline; history of skeletal-related events; tumour, node, metastasis staging; tumour grade; Eastern Cooperative Oncology Group Performance Status; prostate-specific antigen; haemoglobin; alkaline phosphatase; osteoporosis; Charlson comorbidity index; site of metastasis (visceral; bone; lymph nodes); history of spinal cord compression; use of bone-health agents and steroids; time on ADT; line of treatment for mCRPC; and type of drugs for mCRPC used in the past (taxanes, second generation antiandrogens).
Data sources	This study will use the database PPC, which is a subregistry of the PCBaSe. The PCBaSe consists of the linkage of the National Prostate Cancer Registry (NPCR) with a number of other health care registers, including the Swedish National Cancer Register, the National Patient Register (with hospital and outpatient hospital clinic diagnoses), the Cause of Death Register, the Prescribed Drug Register with filled prescription since July 2005, the Multi Generation Register, and the LISA database, a socioeconomic database. The NPCR captures cancer data around the date of diagnosis. Treatments initiated at a later stage of the disease, such as treatments for mCRPC, are not captured in the NPCR. These treatments are captured in the PPC, which collects data on men from initiation of ADT treatment to death. Currently, the PPC contains data on approximately 6,800 men from 33 health care providers. The PPC population has been enriched recently with patients from newly added centres.

Study size	Approximately 800 patients will be registered to have received Ra-223 and 3,000 patients will be registered to have received standard of care other than Ra-223 during the study period.
Data analysis	Patients will be assigned to each exposure group that is consistent with their observed data at the baseline date, as follows for the main analysis: A. Patients will be assigned to the Ra-223 arm when they start Ra-223. Patients will be artificially censored if and/or when they combine other mCRPC-specific treatment with Ra-223. Patients will be followed from Ra-223 initiation until the artificial censoring because of treatment combination, death, or the administrative end of follow-up, whichever occurs first. B. Patients will be assigned to the comparator group when they start a standard of care treatment other than Ra-223 (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients will be artificially censored if and/or when they start Ra-223. Patients will be followed from the initiation of standard of care until artificial censoring because of Ra-223 initiation, death, or the administrative end of follow-up, whichever is first. The primary outcome will be the cumulative incidence of bone fractures. Time to bone fracture will be defined as the time from the baseline date until the occurrence of the first bone fracture event. For patients without bone fractures, the censoring date is defined as the earlier of date of death and the end of follow-up. The secondary outcomes will be as follows: • OS, which will be defined as the time from the baseline date until death. For patients alive at the end of follow-up, the censoring date is defined as the last available date of follow-up. • Prostate cancer–specific survival, which will be defined as the time from the baseline date until death because of prostate cancer. For patients that do not die because of prostate cancer, the censoring date is defined as the earlier of date of death (for causes other than prostate cancer) and the end of follow-up. The main effect estimates will be reported as hazard ratios and as adjusted absolute risk differences at 6-month intervals of follow-up for all the available follow-up. All effect estimates will be bounded with 95% confidence intervals. We will use inverse probability weighting to adjust for baseline and postbaseline variables.

Milestones	The start of data collection will be Q1 2020. Data collection will end 3 months after study start. The final report of study results will be delivered in Q2 2021, 12 months after the end of data collection.

5. Amendments

Prior to start of data collection:

Version number	Date	Section(s) of protocol	Change	Reason
2.1	6 SEPT 2019	6. Milestones	Updated milestones with final report of study results: Q2 2021	Following PRAC communications 14 JUL 2019
2.1	6 SEPT 2019	9. Research methods; Annex 3	Additional details on the data sources has been added to the "Data sources" section; the full list of contributing centres was provided in Annex 3	Following PRAC communications 14 JUL 2019
2.1	6 SEPT 2019	9.6 Data management	A data management plan was included as Annex 4	Following PRAC communications 14 JUL 2019
2.1	6 SEPT 2019	9.7 Data analysis	A sensitivity analysis to estimate the effect of Ra-223 alone or in combination with other treatments for mCRPC compared with standard of care was added. A sensitivity analysis where patients can be eligible for the analysis only through June 2017 and thus can have a potential follow-up of at least 18 months was added.	Following PRAC communications 14 JUL 2019
2.0	12 MAY 2019	6. Milestones	Update of milestones with final report of study results: 27 NOV 2020	Following PRAC communications 14 MAR 2019
2.0	12 MAY 2019	7. Rationale and background	A reference to the Article 20 Referral restricting the use of the cancer medicine Xofigo was added. A summary of the feasibility evaluation that was done prior to the design of the study was added	Following PRAC communications 14 MAR 2019

Version number	Date	Section(s) of protocol	Change	Reason
2.0	12 MAY 2019	8. Research question and objectives	The research questions were updated as follows: • Does the use of Ra-223 increase the risk of bone fractures compared with other treatments for mCRPC in routine clinical practice? • Does the use of Ra-223 increase the risk of death compared with other treatments for mCRPC in routine clinical practice? • Does the use of Ra-223 increase the risk of prostate cancer–specific death compared with other treatments for mCRPC in routine clinical practice?	Following PRAC communications 14 MAR 2019
2.0	12 MAY 2019	4. Abstract 8. Research question and objectives 9. Research methods	The study design has been changed from descriptive to comparative: patients treated with Ra-223 will be compared with patients treated with a contemporaneous standard of care (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Methods have been changed accordingly.	Following PRAC communications 14 MAR 2019
2.0	12 MAY 2019	9. 2 Setting	Administrative end of follow-up updated from OCT 2018 to DEC 2018.	Following PRAC communications 14 MAR 2019
2.0	12 MAY 2019	9.3 Variables	Cause of death has been added as an outcome.	Following PRAC communications 14 MAR 2019
2.0	12 MAY 2019	9.4 Data sources	The primary data source, PCBaSe, has been expanded with additional centres.	Following PRAC communications 14 MAR 2019
2.0	12 MAY 2019	9.5 Study size	Estimated study size and precision of the main effect estimates was added.	Following PRAC communications 14 MAR 2019

Version number	Date	Section(s) of protocol	Change	Reason
2.0	12 MAY 2019	9.6 Data management	A data management plan was developed.	Following PRAC communications 14 MAR 2019
2.0	12 MAY 2019	9.7 Data analysis	Effect estimates will be computed by line of treatment. New definition of patient follow-up, which starts at baseline and ends at death or administrative end of follow-up). Description of the number of doses of Ra-223 has been added.	Following PRAC communications 14 MAR 2019
2.0	12 MAY 2019	9.9 Limitations of the research methods	The Limitations section was expanded	Following PRAC communications 14 MAR 2019

PRAC = Pharmacovigilance Risk Assessment Committee; mCRPC = metastatic castration-resistant prostate cancer; PCBaSe = Prostate Cancer data Base Sweden.

6. Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation, data release from authorities that hold health care registers, and analysis do not require amendments to the protocol. Revised study timelines and milestones that do not constitute a need for a formal protocol amendment are kept as a stand-alone document (Annex 1) that is available upon request.

Table 1: Milestones

Milestone	Planned date
Protocol endorsement by EMA	Q1 2020
Registration in the EU PAS Register	Following EMA endorsement and prior to start of data collection
Start of data collection[1]	Q1 2020
End of data collection[2]	Q2 2020
Study progress report(s)	Q4 2020
Final report of study results	Q2 2021 (12 months after end of data collection)

EMA = European Medicines Agency; EU PAS Register = European Union electronic register of post-authorisation studies.

1. Start of data collection: the date from which information on the first study patient 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).
2. End of data collection: the date from which the analytical data set is completely available [IR Art 37(2)]. The analytical data set: the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study (1).

7. Rationale and background

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

Ra-223 dichloride is a first-in-class therapeutic alpha particle–emitting pharmaceutical with targeted antitumour effect on bone metastases, developed for the treatment of men with mCRPC, symptomatic bone metastases, and no known visceral metastatic disease. ALSYMPCA, the pivotal phase 3, randomised, double-blind, placebo-controlled trial (RCT) compared treatment with Ra-223 dichloride plus best standard of care versus placebo plus best standard of care in patients that either had received docetaxel, were not fit enough to receive docetaxel, declined to receive docetaxel, or for whom docetaxel was not available. Ra-223 prolonged median overall survival (OS) by 3.6 months (14.9 vs. 11.3 months; $P < 0.001$) (4), regardless of previous docetaxel exposure (5) and the median time to first symptomatic skeletal event by 5.8 months (15.6 vs. 9.8 months; $P < 0.001$) (6). Ra-223 was well tolerated and associated with a low incidence of grade 3 or 4 myelosuppression (Ra-223 vs. placebo: anaemia, 13% vs. 13%; neutropenia, 2% vs. 1%; and thrombocytopenia, 7% vs. 2%). A 3-year follow-up of the ALSYMPCA trial confirmed a good safety profile (7). Quality-of-life (QOL) data from the ALSYMPCA RCT demonstrated that Ra-223 provides significant QOL benefits, including a higher percentage of patients with meaningful improvement in QOL and an overall slower decline in QOL over time (8).

The ERA 223 RCT (study 15396, NCT02043678) was designed to evaluate the efficacy and safety of Ra-223 dichloride in combination with abiraterone acetate plus prednisone/prednisolone (APP) versus placebo in combination with APP in asymptomatic or mildly symptomatic chemotherapy-naive patients with bone-predominant mCRPC. Subjects had at least two bone metastases, an Eastern Cooperative Oncology Group performance status of 0 or 1, and no known brain metastasis or visceral metastasis. The primary endpoint was *symptomatic* skeletal event–free survival (i.e., time from randomisation to the first of the following: use of external beam radiotherapy to relieve skeletal symptoms, new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgery) (9). The trial was unblinded in November 2017, following an independent data monitoring committee's recommendation based on the observation of an unexpected increase of bone fractures and deaths in the arm with Ra-223 in combination with APP when compared with the control arm with placebo and APP (10). Median symptomatic skeletal event–free survival was 22.3 months (95% CI, 20.4-27.8) in the Ra-223 group and 26.0 months (95% CI, 21.8-28.3) in the placebo group (hazard ratio [HR], 1.12; 95% CI, 0.92-1.37). Median OS was 30.7 months (95% CI, 25.8-not estimable) in the Ra-223 group and 33.3 months (95% CI, 30.2-41.1) in the placebo group (HR, 1.20; 95% CI, 0.95-1.51) (11).

On 01 December 2017, a Pharmacovigilance Risk Assessment Committee (PRAC) review under Article 20 of Regulation (EC) No. 726/2004 (EMEA/H/A-20/1459/C/002653/0028) was initiated at the request of the European Commission for Xofigo (radium Ra223 dichloride). As a result of this Referral procedure, the PRAC recommended that the indication of radium-223 should be restricted to the use as monotherapy or in combination with a luteinising hormone releasing hormone (LHRH) analogue, for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases, and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment. The PRAC further considered that radium-223 should be contraindicated in combination with abiraterone acetate and prednisone/prednisolone, and further warnings and precautions should be added to the product information.

In addition, the PRAC recommended imposing as conditions to the marketing authorisation of Xofigo (Radium-223-dichloride) the conduct of a randomised controlled clinical trial, a biodistribution study, and a non-interventional post-authorisation safety study (PASS), in order to further characterise the safety and efficacy of Ra-223, including the mechanisms responsible for the increased risk of fracture and possible risk of increased mortality reported in ERA 223. The outcome was adopted with EC decision (C(2018) 6459 final) on September 28, 2018.

This protocol is for a non-interventional PASS, intended to cover the requested non-interventional post-authorisation safety study (Category 1 study, annex II condition). The protocol adheres to the European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices (GVP). Module VIII – Post-authorisation safety studies* (EMA/813938/2011 Rev 3) and proposes using an observational comparative cohort design to evaluate the risk of bone fractures, death, and prostate cancer–specific death among patients treated with Ra-223 in routine clinical practice. No specific treatment will be mandated in the study, and information will be obtained through secondary data collection from an existing and well-established resource for prostate cancer research, the Prostate Cancer data Base Sweden (PCBaSe) (12). The PCBaSe is based on linkages between the National Prostate Cancer Register (NPCR) of Sweden, a nationwide population-based quality database, and other nationwide registers. Over 180,000 cases of prostate cancer have been recorded in PCBaSe since the establishment of the Swedish National Cancer Register in 1998.

The feasibility of conducting the PRECISE study was explored in a range of European data sources in addition to PCBaSe, all of which were determined unlikely to be feasible for the specific data needs of this observational PASS for different reasons. We administered a feasibility questionnaire to candidate data sources that included questions on the capture of variables on prostate cancer diagnoses, ADT drugs, CRPC drugs, bone-targeted drugs, skeletal fractures and complications, and bone metastases, as well as a consideration of the number of anticipated users of Ra-223 and the ability to identify use of Ra-223 specifically. We followed-up by phone or e-mail with the data liaisons when further communication was needed.

Several of the European data sources that were considered do not capture the required exposure variables on prostate cancer therapy, including specific information on Ra-223 dispensing or administration. For example, in the System National de Données de Santé database in France, because the treatment codes identify only isotope administration, and are not isotope-specific, Ra-223 use is identifiable only before March 2015, when no other isotopes were present in the coding system. Data in the Dutch PHARMO Database Network and associated registries, the Clinical Practice Research Datalink (CPRD) database in the United Kingdom, the German Cancer Registry, the Swiss NICER database, and the EpiChron database in Spain are subject to similar limitations. There have been no publications on treatments specifically for advanced prostate cancer from more general cancer and patient registries, such as those in Belgium and Norway.

Other data sources anticipate an insufficient number of users of Ra-223 to be able to conduct the study. In Denmark's national population registers, the study cannot be conducted because Ra-223 is scarcely used in the country and requires primary data collection. The use of Ra-223 is also very low in France as it is not reimbursed by the French medical system.

Two Italian regional claims databases were considered, the Toscana Regional Health Agency and UNIMIB in Milan. However, prostate cancer patients in these databases can be identified only from hospital discharge episodes, and outpatient episodes are not captured. A significant proportion of prostate cancer patients, those treated in outpatient settings, would be missed if these data sources were included.

8. Research questions and objectives

There are no a priori hypotheses. This study will address the following research questions:

- Does the use of Ra-223 increase the risk of bone fractures compared with other treatments for mCRPC in routine clinical practice?
- Does the use of Ra-223 increase the risk of death compared with other treatments for mCRPC in routine clinical practice?
- Does the use of Ra-223 increase the risk of prostate cancer–specific death compared with other treatments for mCRPC in routine clinical practice?

8.1 Primary objective

The primary objective of this study is to estimate the effect of Ra-223 on the incidence of bone fractures compared with other standard treatments for mCRPC.

8.2 Secondary objective

The secondary objectives are as follows:

- To estimate the effect of Ra-223 on OS compared with other standard treatments for mCRPC.
- To estimate the effect of Ra-223 on prostate cancer–specific survival compared with other standard treatments for mCRPC.

9. Research methods

9.1 Study design

The study will be an observational comparative cohort study.

Ra-223 can be administered in clinical practice in different lines of treatment. We will consider a "line of treatment" to be the initiation of a new mCRPC-specific drug (i.e., Ra-223, docetaxel, cabazitaxel, abiraterone, enzalutamide, and other chemotherapy combinations used in Sweden) administered because of tumour progression or intolerance (e.g., toxicity) to a previous treatment. Because the line of treatment reflects the natural evolution of the disease (i.e., patients receiving later lines of treatment are more frail, have a higher baseline risk of bone fractures, and have a worse prognosis than those receiving initial lines of treatment), we will create cohorts specific for each line of treatment. For each cohort, baseline will be considered the time of initiation of the line of treatment that is specific for that cohort. At the baseline of each cohort, we will apply the selection criteria, extract the baseline variables, and assign patients to the exposure strategy that is consistent with their baseline data (13). In this sequence of cohorts, patients can contribute person-time to several cohorts if eligible (14-16).

A priori, there is not biological reason to expect a differential effect of Ra-223 on the risk of fracture or death by line of treatment (effect modification). We will pool the cohorts unless we find heterogeneity of the effect in the first and second line of treatment versus subsequent lines of treatment (Section 9.7.5).

Our main analysis will estimate the effect of starting Ra-223 (with or without ADT) and continuing it until toxicity or disease progression, without combining it with another drug for mCRPC, compared with starting any other treatment for mCRPC (with or without ADT) and never receiving Ra-223. We will estimate the effect corresponding to *full adherence* to the treatment strategies (i.e., the observational analogue of a per-protocol effect in a RCT), as opposed to the effect of initiating the strategy regardless of treatment received afterwards (i.e., the observational analogue of an intention-to-treat effect in a RCT). We focus on estimating the effect of full adherence to the treatment strategy because an intention-to-treat–like comparison can bias the effect estimate towards the null if there is lack of compliance (17).

The estimation of the per-protocol effect is very similar in a RCT (18) and in an observational cohort analysis (15) and requires artificial censoring to emulate full adherence and the use of g-methods to adjust for baseline differences and for the potential bias introduced by the artificial censoring. In the current study, we will use inverse-probability-of-treatment weighting. The analytic approach is described in detail in Section 9.7.

9.2 Setting

9.2.1 Study population

The study population comprises men with mCRPC in the PCBaSe data set during the study time frame. No sampling will be performed.

9.2.2 Study time frame

The study period will start in November 2013, the month of Ra-223 launch in Sweden, and end in December 2018, which is the latest available date of data covering full information including cause of death at the time of data extraction in Q1 2020.

Data for men on Ra-223 will include a start of treatment up to 31 December 2018, and follow-up will also be until this date. To have a complete capture in the Patient Registry and the Registry for the total population and population changes (Folkbokföringen) a linkage with these registries should be done in fall 2019 and we will then capture all events up to 31 December 2018.

9.2.3 Selection criteria

Selection criteria are applied at baseline in each of the four cohorts (first to fourth line of treatment). The selection criteria have been chosen to select a population as similar as possible to the one included in the ALSYMPCA and ERA 223 trials.

- Inclusion criteria (*all* of the following must be present):
    - Histologically confirmed adenocarcinoma of the prostate, i.e., the patient is registered in the NPCR (histology other than adenocarcinomas are not registered in the NPCR).
    - Start of any systemic treatment for mCRPC as an *n*th line of treatment, where *n* goes from 1 to 4. The following will be considered systemic treatment for mCRPC: Ra-223, docetaxel, cabazitaxel, enzalutamide, abiraterone, and the following group of less commonly used drugs in Sweden, which will be labelled as “others”—cisplatin, cyclophosphamide, doxorubicin, estramustine, etoposide, gemcitabine, carboplatin, methotrexate, mitoxantrone.
    - Prostate cancer progression to ADT or subsequent lines of therapy. Prostate cancer progression will be surrogated by the initiation of a drug specific for mCRPC in the first or later lines of treatment.
    - Eastern Cooperative Oncology Group performance status of 0-2 at treatment initiation. We will assume that patients starting any of the systemic therapies under study have a performance status of 0-2.
    - Presence of bone metastasis. We will assume that all patients receiving Ra-223 have bone metastasis and will select for the comparator group those with recorded bone metastasis.
- Exclusion criterion (includes either of the following):
    - Prior use of Ra-223
    - Patients that have participated in a Ra-223 RCT

9.2.4 Representativeness

PCBaSe is a population-based database (12). Thanks to its linkage to the NPCR, it is expected that the database captures more than 98% of all newly diagnosed, biopsy-confirmed prostate cancers registered in the Swedish National Cancer Register, to which registration is compulsory and mandated by law (12). Most of the treatment information will be based on data from the PPC (Section 9.3.2), which we expect will capture approximately 60% to 70% of the Ra-223 use in Sweden, based on distribution information for Ra-223 provided by Bayer.

9.3 Variables

9.3.1 Exposure definition

The following two groups will be compared:

A. Ra-223 initiators. Patients can stop Ra-223 after 6 cycles, or earlier in the event of toxicity, cancer progression, or worsening of the overall health status. Patients can start other systemic drugs for mCRPC (docetaxel, cabazitaxel, enzalutamide, abiraterone, others) after the initiation of Ra-223, when clinically indicated, but never at the same time of Ra-223. ADT with first-generation antiandrogens can be used at any time.

B. Initiators of other standard of care (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients are allowed to stop the standard of care and continue with other lines of treatment, with the exception of Ra-223, when clinically indicated. ADT with first-generation antiandrogens can be used at any time.

Section 9.7.2 describes how these two exposures are assigned and operationalised.

Note: although docetaxel has been shown to improve survival in castration-sensitive prostate cancer (19), it is not approved for that indication by the EMA (20). Therefore, we assume that docetaxel users have a mCRPC.

9.3.2 Outcomes definition

The *primary outcome* is bone fractures requiring admission to a hospital (21) or treated in an outpatient setting, as recorded/captured in the PCBaSe. Bone fractures that did not prompt a diagnostic work-up and those diagnosed only through routine imaging techniques may not be captured in this study (detailed explanation in this limitation provided in Section 9.9).

Bone fractures are available in the PCBaSe via linkage to the National Patient Registry. Bone fractures will be defined as the first occurrence of any of the following (21):

- Fracture of the cervical vertebra or other parts of the neck (ICD-10[1]: S12)
- Fracture of rib(s), sternum, and thoracic spine (ICD-10: S22)
- Fracture of lumbar spine and pelvis (ICD-10: S32)
- Fracture of shoulder and upper arm (ICD-10: S42)
- Fracture of forearm (ICD-10: S52)

[1] ICD-10 = *International Classification of Diseases, 10th Revision.*

- Fracture at wrist and hand level (ICD-10: S62)
- Fracture of femur (ICD-10: S72)
- Fracture of lower leg, including ankle (ICD-10: S82)
- Fracture of foot and toe, except ankle (ICD-10: S92)

Fractures requiring hospitalisation identified in the National Patient Registry via ICD-10 codes have been validated via medical record review and are correct up to the third digit of the code in over 90% of the cases (22).

The *secondary outcomes* are death due to all causes and death due to prostate cancer. Date and cause of death are available in the PCBaSe via linkage to the Cause of Death Register (12). The date of death is continuously updated (i.e., no or minimal lag to obtain the information).

9.3.3 Covariate definition

The variable "line of treatment for mCRPC" will be used to define the generation of each cohort. Line of treatment for mCRPC corresponds to each of the subsequent active treatments (i.e., abiraterone, enzalutamide, docetaxel, cabazitaxel, Ra-223, others) that are administered after progression to hormonal treatment. We will consider that a patient starts a new line of treatment when the previous drug is stopped and a new mCRPC-specific drug is initiated, under the assumption that treatments are changed because of disease progression or toxicity. The PPC database records the reason for stopping a drug; therefore, allowing discrimination of line of treatment from other reasons for drug pauses, like shorter breaks due to toxicity or other reasons. Inconsistencies will be reviewed by a medical oncologist.

The following variables are considered potential confounders (23) and will be described and adjusted for to achieve conditional exchangeability among exposure groups. All are available in the PCBaSe (12).

- Baseline variables (extracted at the beginning of each cohort)
  - Age
  - Calendar year at cohort entry
  - Time from diagnosis to baseline
  - History of skeletal-related events
  - Tumour, node, metastasis staging
  - Tumour grade (Gleason/World Health Organization [WHO])
  - ECOG-PS (Eastern Cooperative Oncology Group performance status)
  - Prostate-specific antigen (PSA)
  - Haemoglobin
  - Alkaline phosphatase
  - Osteoporosis
  - Charlson comorbidity index

- Site of metastasis (visceral, bone, lymph node)
- History of spinal cord compression
- Use of bone-health agents (zoledronate, denosumab)
- Use of steroids
- Time on bone-health agents
- Time on ADT
- Prior radiation therapy
- Line of treatment for mCRPC
- Type of drugs for mCRPC used in the past (taxanes, second generation antiandrogens, others)

- Time-varying variables (updated during the follow-up within each cohort)
  - Eastern Cooperative Group Performance Status
  - Prostate-specific antigen
  - Alkaline phosphatase
  - Haemoglobin
  - Osteoporosis
  - Charlson comorbidity index
  - Site of metastasis
  - Radiation therapy
  - Spinal cord compression
  - Use of bone-health agents (zoledronate, denosumab)
  - Use of steroids
  - Line of treatment for mCRPC
  - Type of drugs for mCRPC in the past (taxanes, second generation antiandrogens, others)

9.4 Data sources

9.4.1 National Prostate Cancer Register of Sweden

Since 1998, the primary register of the NPCR of Sweden captures 98% of all men with incident prostate cancer compared with the National Cancer Registry to which registration is mandated by law. Comprehensive data on cancer characteristics, work-up, and primary treatment are registered by staff at each respective department in Sweden where men with prostate cancer are treated (12).

9.4.2 Prostate Cancer data Base Sweden (PCBaSe) and Patient-overview Prostate Cancer (PPC)

By using the unique Swedish person identity number, the NPCR has been linked with a number of other health care registers including the Swedish National Cancer Register, the National Patient Register (with hospital and outpatient hospital clinic diagnoses), the Cause of Death Register, the Prescribed Drug Register with filled prescription since July 2005, the Multi Generation Register, and the LISA database, a socioeconomic database with information on the educational level, income, and marital status of patients (12). PCBaSe 4.0 was created with patients diagnosed with prostate cancer from 01 January 1998 through 31 December 2016.

Information on bone fractures in the PCBaSe is available by using information from the Patient Registry with data from hospital admissions and outpatient visits. ICD-10 codes for all fractures and specific fractures will be used to characterise fractures (e.g., location) and to ascertain comorbidities or conditions of interest (e.g., osteoporosis).

Information on the cause of death in the PCBaSe is available through the Cause of Death Register. The validity of prostate cancer as a cause of death has been found to be high. In a comparison of the cause of death in the Cause of Death Register and cause of death as assessed by a chart review of medical records, there was an 86% overall agreement (24). In another study, an independent cause-of-death committee reviewed medical data including death certificates according to a standardised algorithm. The overall agreement between cause of death recorded in the death certificates and determined by the committee was 96% (25).

More than a hundred research manuscripts have been published based on data in the PCBaSe since its inception in 2010. Specifically, a pilot study on the use of enzalutamide and abiraterone based on data in the Prescribed Drug Registry was recently published (26). Information on the drug of interest is considered highly valid thanks to implementation of the PPC, which is a longitudinal quality registration in the NPCR.

The NPCR captures data around date of diagnosis regarding cancer characteristics, work-up, primary treatment, etc. However, treatments that are initiated at a later stage of the disease, such as mCRPC-treatments, are not captured in the NPCR. Instead, this information is captured in a subregister of the NPCR, the PPC, which is a longitudinal register that provides the treating clinician with an overview of previous treatments, laboratory values, clinical data, etc. The PPC collects data on men from initiation of ADT to death and has collected data since 2014. Data from earlier dates is made available from retrospective inclusion of data from medical charts, back to the initiation of ADT for each patient.

Currently, the PPC contains data on approximately 6,800 men from 33 health care providers including Akademiska sjukhuset (Uppsala), Sahlgrenska sjukhuset (Göteborg), Södersjukhuset (Stockholm), Norrlands universitetssjukhus (Umeå), Skånes universitetssjukhus (both Lund and Malmö), and most recently Karolinska sjukhuset (Stockholm) (see Annex 3 for the full list). Contributing centres cover almost all the sites licensed to administer Ra-223 in Sweden; therefore, the PPC has almost complete coverage for the treatment of radium-223 in Sweden today. In order to enrich the PPC with more men treated with Ra-223, PCBaSe researchers identified these men by (1) medication distribution information for each hospital from Bayer and (2) treatment records at the departments of nuclear medicine at these hospitals, where the person identity numbers of the treated men were obtained. Regardless of how patients were identified, the pattern of care and follow-up will not differ by centre because of the characteristics of the Swedish health system. All centres

connected to the PPC contribute data in a standardised way through the same platform (the Information Network for Cancer care).

The Swedish health system provides complete national coverage and therefore it is safe to assume that most, if not all, fractures requiring medical attention will be captured in the Swedish databases used in this project and there will not be losses to follow-up.

9.5 Study size

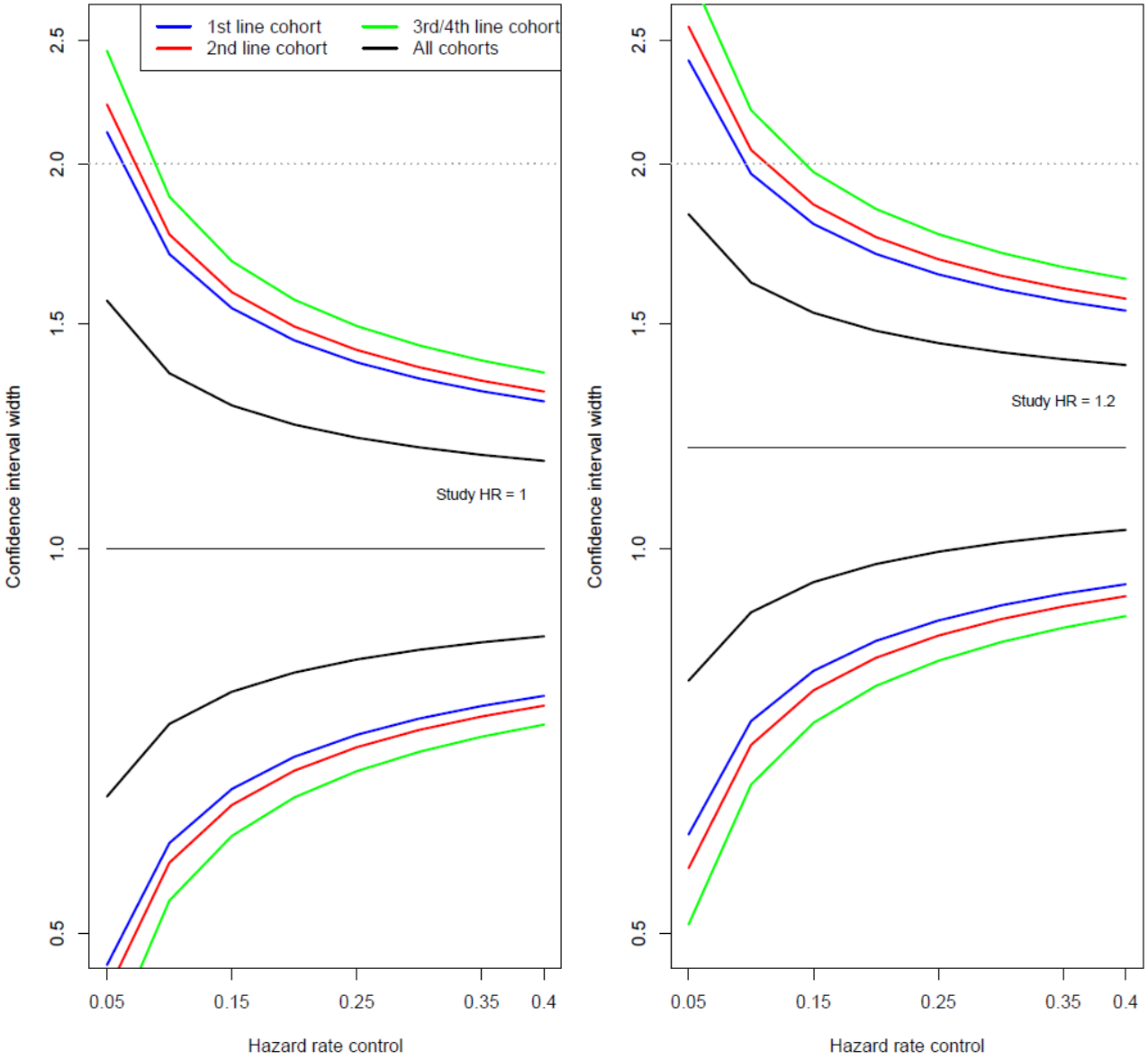
The number of patients in each of the groups is determined by the available data (27). For the analysis of the first-, second-, and third-/fourth-line treatment cohorts, the expected number of patients are shown in Table 2.

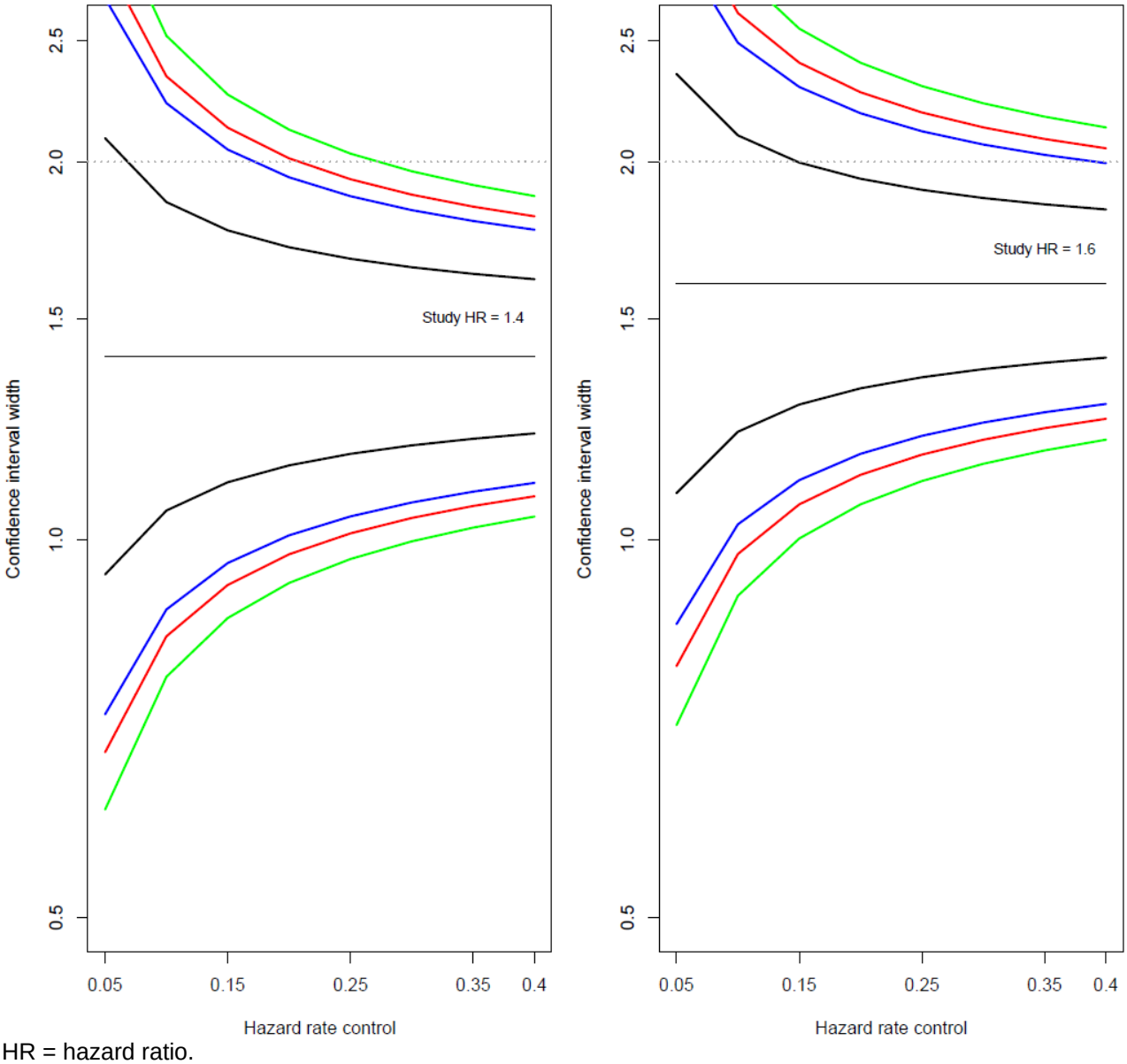
Table 2: Expected number of patients in each comparison group, by line of treatment

	First line	Second line	Third/fourth line	All
Ra-223	240	280	280	800
Comparator drug	1,800	750	450	3,000

Below we present the width of the confidence intervals (28) for different potential values of the true hazard ratio of bone fractures for the analysis of first, second, and third/fourth lines of treatment and for the pooled analysis (Figure 1). The incidence of bone fractures in patients recently diagnosed with prostate cancer in Sweden is approximately 5 per 100 person-years (21). We used this as the lower bound for the expected rate of bone fractures in this study, because eligible patients present more advanced stages of their disease. Based on personal communication with PCBaSe researchers, we assumed that 60% of the comparator group and 100% of the Ra-223 group had recorded bone metastases because it is the indication of the drug. Therefore, the figures use a range of bone fracture incidence from 5 to 40 fractures per 100 person-years. We will use inverse probability weighting to adjust for pre- and postbaseline factors. While no methods have been previously used for power calculations of inverse probability–weighted estimates, we can approximately estimate the relative power of these estimates based on published estimates that used inverse probability weighting. A review of some representative papers (29, 30) shows that, in settings with large amounts of time-varying confounding, the width of the 95% confidence interval of the inverse probability–weighted estimate is never 16% greater than that of the 95% confidence interval of the unadjusted estimates. We have increased the standard error of these calculations by 20% to account for this.

Figure 1: **Confidence interval width in relation to the rate of fractures in the control group for four potential true hazard ratios, by line of treatment**





HR = hazard ratio.
Note: Width of the confidence intervals (dashed lines) for different effect estimates of Ra-223 (solid line), for different hazard rates of fractures in the control group. Grey dotted line represents a harmful effect with a HR of 2. Y-axis is in a logarithmic scale.

9.6 Data management

Data will be managed by the registry holder and designated staff in accordance with standard operating procedures for data management and statistical programming. All data management will be performed using R, version 3.5.1 or higher on Windows. All data management will be documented and stored at the Regional Cancer Centre in Uppsala, Sweden, to ensure reproducibility. A data management plan is provided in Annex 4.

9.7 Data analysis

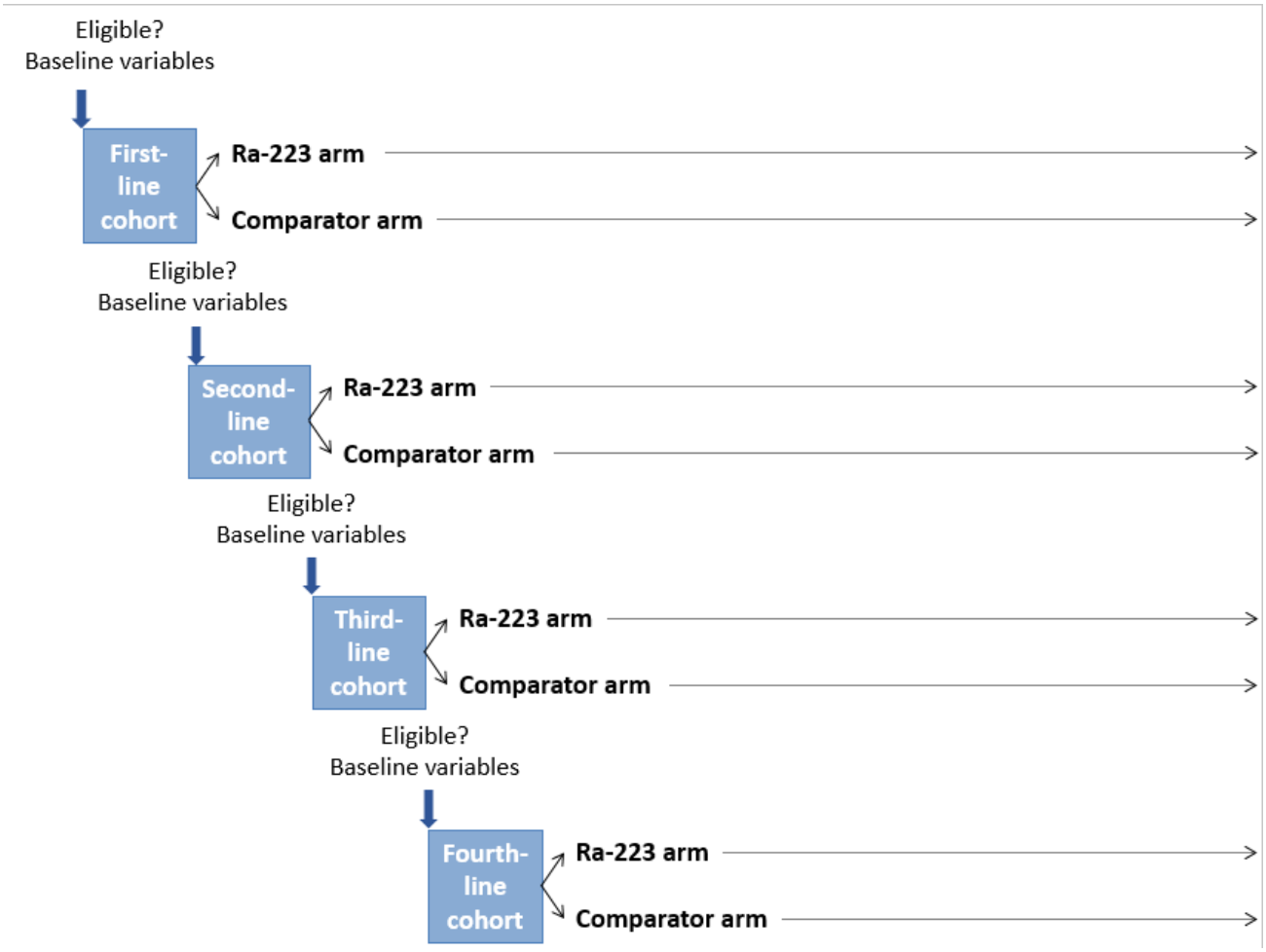
A stand-alone statistical analysis plan will be generated. The sections below are the key elements of the proposed analysis. They will be expanded in detail in the statistical analysis plan.

9.7.1 Creation of the cohorts

The cohort of first-line treatment (see definition of line of treatment in Section 9.3.3) will include patients meeting the selection criteria described in Section 9.2.3 when they start a first-line treatment for mCRPC (docetaxel, abiraterone, enzalutamide, cabazitaxel, Ra-223), which will be considered the baseline date.

The cohort of second-line treatment will include patients meeting the selection criteria described in Section 9.2.3 when they start a second line of treatment for mCRPC. Patients will be assigned to each exposure group (see Section 9.3.1) according to the drug they start taking, and the date of the start of treatment will be the baseline date. The same approach will be used for third- and fourth-line treatment cohorts (16). Figure 2 contains a summary.

Figure 2: Schematic generation of the four cohorts



Under this design, patients can contribute to several cohorts, if eligible, and to both arms in different cohorts (14). Baseline variables are updated at baseline in each cohort.

See Figure 3 for a hypothetical example of the cohort generation for the main analysis: the first table represents three patients, the treatments they receive over time (times when the line of treatment starts are arbitrary and synced for simplicity), and their eligibility status. The bottom panel represents the database created after the generation of the cohorts. Patient 1 contributes only to the first-line cohort as part of the Ra-223 group because having received Ra-223 in the past is an exclusion criterion for subsequent cohorts. The patient is followed until death or administrative end of follow-up because subsequent standard of care is allowed after Ra-223. Patient 2 contributes to the first-, second-, and third-line cohorts as part of the comparator group, and to the fourth-line cohort as part of the Ra-223 group. The patient is followed until time interval 15 in the first three cohorts, where he contributes to the comparator group and until death or administrative end of follow-up in the fourth-line cohort, where he contributes to the Ra-223 group. The patient's value of the baseline variable (e.g., performance status) changes in each cohort. Patient 3 contributes to the first- and second-line treatment cohorts and is not followed beyond time interval 10 because starting Ra-223 is a censoring event for the comparator group. A more detailed technical explanation can be found elsewhere (14, 15, 31).

Figure 3: Hypothetical example of observed treatments, cohort generation, and strategy assignment

Time interval when line of treatment starts

		(First line)	(Second line)	(Third line)	(Fourth line)
		1	**5**	**10**	**15**
Patient 1	*Treatment*	Ra-223	Docetaxel	Abiraterone	Nothing
	Eligible?	Yes	No	No	No
Patient 2	*Treatment*	Docetaxel	Abiraterone	Enzalutamide	Ra-223
	Eligible?	Yes	Yes	Yes	Yes
Patient 3	*Treatment*	Docetaxel	Abiraterone	Abi + Ra-223	Enzalutamide
	Eligible?	Yes	Yes	No	No

ID	Cohort	Arm	Start follow-up	End follow-up	Baseline variable
1	First line	Ra-223	1	Death or AEFUP	0
2	First line	Comparator	1	15	0
3	First line	Comparator	1	10	1
2	Second line	Comparator	5	15	1
3	Second line	Comparator	5	10	1
2	Third line	Comparator	10	15	2
2	Fourth line	Ra-223	15	Death or AEFUP	2

AEFUP = administrative end of follow-up.
Note: Time intervals are arbitrary and synced for simplicity.

9.7.2 Exposure assignment and follow-up

Patients will be assigned to each exposure group (see Section 9.3.1) that is consistent with their observed data at the baseline date (32):

A. Patients will be assigned to the Ra-223 arm when they start Ra-223. Patients will be artificially censored if and when they combine other treatment for mCRPC with Ra-223. Patients will be followed from Ra-223 initiation until the artificial censoring, death, or the administrative end of follow-up, whichever occurs first.

B. Patients will be assigned to the comparator group when they start a standard of care other than Ra-223 (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients will be artificially censored if and/or when they start Ra-223.
Patients will be followed from the standard of care initiation until the artificial censoring, death, or the administrative end of follow-up, whichever is first.

Baseline characteristics, as well as the number of treatment cycles received, will be described by treatment strategy.

9.7.3 Outcome measures

9.7.3.1 Bone fractures

The main outcome will be cumulative incidence of bone fractures, which will be estimated with a 1-Kaplan-Meier survival curve, as well as with adjusted parametric incidence curves (33). Time-to-bone fracture will be defined as the time from the baseline date until the occurrence of the first bone fracture event. For patients without bone fractures, the censoring date is defined as the earlier of date of death and the end of follow-up.

9.7.3.2 Overall survival

OS will be estimated with a Kaplan-Meier survival curve, as well as with adjusted parametric survival curves (33). OS will be defined as the time from the baseline date until death. For patients alive at the end of follow-up, the censoring date is defined as the last available date of follow-up.

9.7.3.3 Prostate cancer–specific survival

Prostate cancer–specific survival will be estimated with a Kaplan-Meier survival curve, as well as with adjusted parametric survival curves (33). Prostate cancer–specific survival will be defined as the time from the baseline date until death because of prostate cancer. For patients that do not die because of prostate cancer, the censoring date is defined as the earlier of date of death (for causes other than prostate cancer) and the end of follow-up.

Besides presenting adjusted time-to-event curves, effect estimates for time to bone fracture, OS, and prostate cancer–specific survival will be reported both as HR and as the absolute risk difference (34) at 6-month intervals of follow-up. All effect estimates will be bound with 95% confidence intervals.

9.7.4 Adjusted analyses

The validity of these analyses requires that the adjustment variables include all important baseline and postbaseline risk factors for fractures and mortality that also predict treatment assignment and adherence to the strategy.

Therapies to treat mCRPC must be prescribed by doctors who use clinical judgement to decide which treatment to administer and when. Specifically, doctors leverage the risk of progression of the disease (e.g., via Gleason score, PSA doubling time), tumour-related prognostic factors (e.g., metastatic burden), and patient-related prognostic factors (e.g., comorbidities, ECOG-PS) to administer treatments. We have included a panel of clinicians who have used subject-matter knowledge (23) to curate a list of baseline and time-varying covariates that are used in practice to decide on treatments and are thus needed to be adjusted for (Section 9.3.3).

We described in Section 9.7.2 how patients are assigned to the exposure strategies and how artificial censoring is implemented to select the person-time that correspond to full adherence to each strategy. Essentially, for the Ra-223 group, we will censor patients if and when they combine other treatment for mCRPC with Ra-223; for the comparator group, we will censor patients if and when they start Ra-223.

9.7.4.1 Adjustment for baseline imbalances (potential confounding by indication)

The outcome model for the three outcomes (fractures, death, prostate cancer death) will be a discrete hazards model, approximated through the following pooled logistic model (33, 35):

$$\text{logit}\,\Pr(Y_{t+1} = 1 | Y_t = 0, C_t = 0, X) = \alpha_{0t} + \alpha_1 X$$

Where $Y_t = 1$ is an indicator of the outcome at time interval t, C_t is an indicator for censoring and X is an indicator for the treatment group (initiators of Ra-223 vs. initiators of other standard of care). We will model the time-varying intercept α_{0t} using a flexible function (e.g., linear and quadratic terms) for duration of follow-up to allow for time-varying hazards (33, 36). Time will be categorised in units of 14 days.

We will also estimate parametric cumulative incidence curves and survival curves standardised to the observed distribution of the baseline variables by fitting a pooled logistic regression model as described previously, and that also includes product terms for the exposure arm and time variables to allow for time-varying HRs (15, 33). This will allow the estimation of adjusted differences in the risk of fractures and death.

To adjust for potential baseline confounding, we will weigh the outcome model using stabilised weights for the inverse probability of treatment initiation at baseline:

$$SW^X = \frac{f[X]}{f[X|L_0]}$$

Where L_0 is the vector of baseline variables in Section 9.3.3. The numerator of these SW^X weights will be estimated using the marginal probability of receiving Ra-223 or the standard of care, as appropriate. The denominator of these SW^X weights will be estimated using the following logistic model:

$$\text{logit}\,\Pr(X = 1 | L_0) = \beta_0 + \beta_1 L_0$$

9.7.4.2 Adjustment for adherence to treatment strategies

The artificial censoring described in Section 9.7.2 to select the person-time that corresponds to full adherence to the therapeutic strategies can introduce selection bias if factors (e.g., symptoms, metastatic burden, ECOG-PS) are associated with combining or initiating Ra-223 during follow-up and also with the outcome. To adjust for the potential selection bias (37) introduced by the artificial censoring, each individual's contribution to the outcome model will be inverse-probability weighted

(38), with weights depending on a priori–defined adjustment variables (baseline and time-varying) itemised in Section 9.3.3. In the context of time-varying exposures, inverse probability weighting works by estimating a sequential propensity score that is then used to reweight participants over time according to their time-varying factors. In the resulting weighted population, treatment is stochastically independent of the measured prognostic factors, which eliminates postrandomisation confounding and selection bias due to those measured factors (18). As in previous applications of this technique, we will truncate the weights at the 99th percentile to avoid undue influence of outliers (32, 39, 40). Informally, the denominator of the weights is each patient's time-varying probability of following the assigned strategy, conditional on baseline and time-varying covariates, and the numerator is the probability that a patient received his observed treatment conditional only on his past treatment history and baseline prognostic factors (15). Formally, the weights to adjust for adherence to treatment will be defined as:

$$SW_t^A = \prod_{k=0}^{t} \frac{f[A_k|\bar{A}_{k-1}, L_0, \bar{Y}_{k-1}=0]}{f[A_k|\bar{A}_{k-1}, \bar{L}_k, \bar{Y}_{k-1}=0]},$$

Where the overbar denotes the history of a variable since *k = 0*. In the above equation $\overline{A}_{-1}$, is defined to be 0 (41).

We will estimate the denominator of the SW_t^A weights by fitting the pooled logistic model:

$$\text{logit}\Pr(A_k = 1|\bar{A}_{k-1} = 0, \bar{L}_k, Y_{k-1} = 0) = \gamma_{0t} + \gamma_1 L_0 + \gamma_2 L_k$$

Where A_k is an indicator for initiating a treatment discordant with the assigned strategy at time *k* (in the Ra-223 group, patients deviate from the strategy when they combine Ra-223 with another drug for mCRPC after baseline; in the comparator group, patients deviate from the strategy if they start Ra-223 after baseline), L_k is the vector of time-varying covariates measured at time *k*, and $\bar{L}_k = \{L_0, L_1, . L_k\}$ is the history of measured covariates by time *k*. We will assume that $\bar{L}_k$ is appropriately summarised by the variables in Section 9.3.3.

We will estimate the numerator of the SW_t^A weights by fitting the pooled logistic model:

$$\text{logit}\Pr(A_k = 1|\bar{A}_{k-1} = 0, L_0, Y_{k-1} = 0) = \delta_{0t} + \delta_1 L_0$$

The weights for the outcome model adjusted for potential baseline imbalances and for adherence to treatment strategies will be defined as follows:

$$SW_t = SW^X \times SW_t^A$$

We will assess the balance of the treatment groups after weighting by describing baseline variables in the weighted cohorts and will evaluate the use of diagnostics for time-varying exposures (42).

To account for the dependencies introduced by the contribution of a single individual to multiple trial arms and for the weighting procedure, to estimate the 95% confidence intervals of the HRs, we will use the robust estimation of the variance. To estimate 95% confidence intervals of the risk differences, we will use a non-parametric bootstrap estimation of the variance based on 500 samples. Each bootstrap sample will be the same size as the study population and will be randomly selected, allowing for replacement.

Under the identifiability assumptions of exchangeability, positivity, and consistency, inverse probability weighting appropriately adjusts for the measured baseline and postbaseline covariates (33). Because of the characteristics of the Swedish health system (universal with a very high rate of

coverage), it is safe to assume that censoring due to infrequent contact with the health care system is ignorable given the measured covariates.

9.7.5 Pooling of the line-specific cohorts

The primary analysis will pool the cohorts created at each line of treatment unless evidence for a heterogeneity of the effect of Ra-223 on fractures or death across lines of treatment exists. We will evaluate, separately for the risk of fractures and the risk of death, the homogeneity of the 12-month standardised risk difference estimates across line-of-treatment strata (first and second line vs. third and fourth line) using the I^2 statistic (43). In the ERA 223 trial, the curves for symptomatic skeletal event–free survival already diverged by month 12 (11). If the percentage of heterogeneity estimated by I^2 is high (> 50%), we will report the results by line of treatment: first, second, and third/fourth lines. If the number of outcomes is too small for stable estimations of the heterogeneity, we will consider alternative approaches.

9.7.6 Missing data handling

Missing data on covariates is small in the PCBaSe database (12). Several approaches to handle missing data will be considered (i.e., inverse probability weighting of the complete case population, multiple imputation, complete case analysis), based on the amount of missing data and the most reasonable assumption on the pattern of how the data are missing (missing completely at random, missing at random). Additional details on when and which method will be used will be provided in the statistical analysis plan.

9.7.7 Sensitivity analysis for unmeasured confounding

We will perform a sensitivity analysis to evaluate how strong unmeasured confounding would have to be to explain away the association reported in the main analysis. We will use the following formula to compute the bias factor *B*: the maximum relative amount by which such unmeasured confounding could reduce the relative risk (RR) from the main analysis (44).

$$B = \frac{RR_{UD}RR_{EU}}{(RR_{UD} + RR_{EU} - 1)}$$

Where RR_{UD} is the maximum risk ratio for the outcome comparing any two categories of the unmeasured confounders within either treatment group, conditional on the observed covariates, and RR_{EU} is the maximum risk ratio for any specific level of the unmeasured confounders comparing those with and without treatment, with adjustment for the measured covariates.

If the RR of the main analysis is greater than 1, we will obtain the maximum amount this set of unmeasured confounders could alter the observed RR in the main analysis by dividing that RR by *B*. If the RR of the main analysis is lower than 1, we will obtain the maximum amount this set of unmeasured confounders could alter the observed RR in the main analysis by multiplying that RR by *B*.

We will plot the value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away the estimated RR of the main analysis, for different values of RR_{EU} (x-axis) and RR_{UD} (y-axis)

In the plot, we will identify the E-value, which will be computed as follows (44, 45):

- If the RR reported for the main analysis is > 1: E-value $= RR + sqrt\{RR \times (RR - 1)\}$
- If the RR reported for the main analysis is < 1: E-value $= +sqrt\{\frac{1}{RR} \times (\frac{1}{RR} - 1)\}$

The E-value represents the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates (44).

9.7.8 Sensitivity analysis for the effect of information on bone metastasis

The primary analysis will assume that all patients receiving Ra-223 have bone metastasis. To evaluate how strong this assumption is, a sensitivity analysis will be performed by including patients with recorded bone metastasis (both in the Ra-223 and in the comparator group). This analysis will follow the same analytical approach and will evaluate the same outcomes as the main analysis.

9.7.9 Sensitivity analysis for the effect of Ra-223 alone or in combination

The main analysis estimates the effect of Ra-223 alone versus the standard of care on the incidence of bone fractures. Therefore, the main analysis does not use the person-time when Ra-223 is combined with other anticancer drug(s) (see Section 9.7.2). To evaluate if the exclusion of this person-time impacts the results of the main analysis, we will estimate, as a sensitivity analysis, the effect of Ra-223 alone or in combination with other treatments for mCRPC compared with other standard of care on the incidence of bone fractures. To operationalise this comparison, patients in the Ra-223 group will not be censored when they combine other treatment for mCRPC with Ra-223.

9.7.10 Sensitivity analysis using a potential follow-up of at least 18 months

Patients who become eligible in the last months of 2018 will have a short follow-up because data on follow-up will be available only until 31 December 2018. The proposed time-to-event analysis appropriately considers the time when participants are at risk and therefore this cannot be a source of bias. To evaluate if a short follow-up has any impact on the effect estimates, we will run a sensitivity analysis where patients can be eligible for the analysis only up to June 2017 and thus can have a potential follow-up of at least 18 months.

9.8 Quality control

The PCBaSe investigators are required to archive documents and data sets, statistical programmes, and study-relevant documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended that documents be stored for a retention period of at least 15 years, unless local regulations define otherwise.

9.9 Limitations of the research methods

The pivotal trial ALSYMPCA (4) included patients that “had received docetaxel, were not healthy enough or declined to receive it, or it was not available.” Therefore, it is likely that in real practice, patients receiving Ra-223 as a first line of treatment for mCRPC (which is frequently docetaxel) are more frail than those who do not. The PCBaSe is rich in data and allows for a comprehensive characterisation of the patients when they start treatment (including the ECOG performance status), and the study is designed to run the analyses by line of treatment (to be pooled together if no evidence of heterogeneity is found). Nevertheless, potential differences across the exposure groups

will need to be taken into account in the interpretation of the effect estimates. Also, Ra-223 is a drug with a good safety profile, which may lead to selective prescribing to frailer patients, with the potential for residual confounding. We plan to work with an exhaustive list of potential confounders, including the use of bone-health agents (Section 9.3.3), to adjust for confounding, and a sensitivity analysis will estimate the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates (Section 9.7.7).

The ALSYMPCA and ERA 223 trials differed not only in the eligibility criteria, but also in the treatments that were administered. Whereas in the ALSYMPCA trial patients were required to have received docetaxel (or were not healthy enough, declined to receive it, or it was not available) (4), patients in the ERA 223 trial were excluded if they had previously received treatment with cytotoxic chemotherapy. A small percentage of patients in the ERA 223 trial received a prior line of therapy: docetaxel (1.9%), enzalutamide (6.6%), or sipuleucel-T (2.7%) (11). Additionally, patients in the ALSYMPCA trial were required to have symptomatic disease with regular use of analgesic medication or treatment with external beam radiation therapy for cancer-related bone pain within the previous 12 weeks (4), as opposed to patients in the ERA 223 trial, who were asymptomatic or mildly asymptomatic (11). In terms of treatment, patients in the ALSYMPCA trial were randomised to Ra-223-dichloride plus best standard of care or placebo plus best standard of care (4), and patients in the ERA 223 trial were randomised to of Ra-223 dichloride in combination with abiraterone acetate plus prednisone/prednisolone (APP) versus placebo in combination with APP (11). Thus, the factors behind the different results in the ALSYMPCA and ERA 223 trials are diverse and may be attributable to the definition of the study population, to the administered treatment, or to both.

The PRECISE study will describe baseline characteristics of the patients comprehensively, but without information on symptoms. We also expect that patients treated in a real-world setting will be different from those enrolled in randomised clinical trials. Consequently, whereas the PRECISE study will yield informative results about the safety of Ra-223 in a real-world setting, we believe that an accurate comparison with the ALSYMPCA and ERA 223 trial will not be straightforward.

The precision of the estimates for the excess risk of fractures or death will depend on the number of events in each of the exposure groups. The size of the database is relatively small, and the use of weights to adjust for postbaseline variables can increase the variance. Therefore, a limitation can be a small precision in the 95% confidence intervals for the estimates of bone fractures and OS. This has been taken into account in calculating the precision of the effect estimates in Section 9.5. The pooling of the treatment line–specific cohorts and the stabilisation of the weights are attempts to improve precision. By increasing the centres contributing to PCBaSe, (the Karolinska Institutet and others), we expect that the precision of the estimates will improve further, while preserving the external validity because the added patients should not differ appreciably from those in PCBaSe, neither in the pattern of care nor in the way data are collected and managed. Although PCBaSe does not capture all Ra-223 use in Sweden, the capture is high (60%-70%), and the database is representative of the Swedish population of prostate cancer patients (12).

The proposed analytic approach uses inverse-probability-of-treatment weighting to adjust for baseline and postbaseline variables. This method was chosen because, based on previous observational research on prostate cancer (32), it is likely that the following two conditions will be met: (1) there exists a time-dependent covariate that is both a risk factor for the outcome and also

predicts subsequent exposure and (2) past exposure history predicts the risk factor. for example, evolution of PSA fulfils these two conditions. When these conditions are met, traditional regression-based approaches (e.g., time-dependent Cox proportional hazards model) are biased, as opposed to g-methods like inverse-probability-of-treatment weighting (46). When inverse-probability-of-treatment weighting is used, the weighted outcome model must contain the baseline variables (15, 36). Therefore, if the number of outcomes is small, the number of covariates or their categories may need to be reduced to allow a proper model fitting. Other approaches based on the computation of propensity scores allow including a larger number of covariates in parsimonious outcome models (47), but under the untenable assumption of lack of time-varying confounding.

This study lacks validation of the main outcome, bone fractures, in an outpatient setting. Nevertheless, bone fractures in the inpatient setting have been validated (22), and patients with symptomatic bone fractures are expected to seek medical assistance. Given the national coverage of the Swedish health system, it is safe to assume that most, if not all, fractures requiring medical attention will be captured in the Swedish databases used in this project. However, around 20% of the fractures identified during the clinical trials were asymptomatic and diagnosed through imaging for another purpose. This study will not be able to capture any fracture that does not have a diagnosis recorded in the inpatient or outpatient hospital setting, thus it is likely that none of these asymptomatic fractures will be captured.

Cause of death is available in the PCBaSe with annual updates in October for the cause of death during the prior calendar year and a reporting lag of a few months. Therefore, the study period covers the time for which available data include also cause of death. Information on the site of progression (e.g., bone, visceral) is not available in PCBaSe and it cannot be analysed.

Results from the ERA 223 study suggested that the risk of fractures with radium-223 was increased in patients with fewer bone metastases (< 6). Unfortunately, the number of metastases is not available in PCBaSe, and we will not be able to explore these subgroups.

9.10 Other aspects

This study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Epidemiology Practices* (48), the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology* (49), and applicable regulatory requirements including the EMA *Guideline on Good Pharmacovigilance Practices: Module VIII – Post-Authorisation Safety Studies* (1). The ENCePP Checklist for Study Protocols can be found in Annex 2.

10. Protection of human subjects

This is a retrospective non-interventional study and does not pose any risks for patients. All data collected in the study will be deidentified with no breach of confidentiality with regard to personal identifiers or health information. The PCBaSe researchers have obtained an independent ethics committee approval according to local regulations. Country-specific data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

11. Management and reporting of adverse events/adverse reactions

As per the EMA *Guideline on Good Pharmacovigilance Practices: Module VI – Management and Reporting of Adverse Reactions to Medicinal Products*, individual reporting of adverse reactions is

not required for non-interventional study designs that are based on secondary use of data (50). Reports of adverse events/reactions will be summarised in the study report.

12. Plans for disseminating and communicating study results

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

The study protocol and final study report will be included in regulatory communications in line with the risk management plan, Periodic Benefit-Risk Evaluation Reports (PBRER), and other regulatory milestones and requirements. Study reports will be prepared using a template following the *Guideline on Good Pharmacovigilance Practices (GVP): Module VIII*, Section B.4.3 (1) and the template based on the *Guidance for the Format and Content of the Final Study Report of Non-interventional Post-authorisation Safety Studies* (51).

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the marketing authorisation holder (MAH). Current guidelines and recommendations on good publication practice will be followed (1, 52, 53). No individual investigator may publish on the results of this study, or their own patients, without prior knowledge and review by the MAH.

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Annex 1: List of stand-alone documents

None

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

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

Study title:

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6

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

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.3
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.3
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.2
4.2.2 Age and sex	☐	☒	☐	
4.2.3 Country of origin	☒	☐	☐	9.4
4.2.4 Disease/indication	☒	☐	☐	8
4.2.5 Duration of follow-up	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4.2
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2 and 9.7.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2 and 9.7.3

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	9.7.4
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.7.4
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.4.2 and 9.7.4

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.1

Comments:

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

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

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.4
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.4
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.4
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.6
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.7, 9.7.8, 9.7.9, 9.7.10

Comments:

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

Comments:

An independent Data Management Plan is provided. Data will be analysed by PCBaSe researchers and the results will be independently reviewed by RTI-HS

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.7.7
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

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

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: PPD

Date: 6/Sep/ PPD

Signature: _____

Annex 3: List of contributing centres

Akademiska sjukhuset
Borås
Borås urologcentrum
Capio S:t Görans sjukhus
Carlanderska
Centrallasarettet i Växjö
Falu lasarett
Gävle sjukhus
Helsingborgs lasarett
Jönköping
Kalmar
KS Solna (Karolinska)
Kungsbacka
Lasarettet Trelleborg
Lasarettet Ystad
Lidköping
Linköping US
Länssjukhuset i Halmstad
MT Urologi
Norrköping ViN
NUS Umeå
Skånes universitetssjukhus Lund
Skånes universitetssjukhus Malmö
Skövde
SU/Sahlgrenska
Sundsvalls sjukhus
Södersjukhuset
Uddevalla
Universitetssjukhuset Örebro
Varberg
Visby Lasarett
Västmanlands sjukhus Västerås
Östersunds sjukhus

Annex 4: Data management plan

PRECISE Post-Authorisation Safety Study

Data Management Plan

Version: 1.0
Date: 12 May 2019

Prepared for

Bayer AG

Medical Affairs & Pharmacovigilance, Pharmaceuticals

Epidemiology

Berlin, Germany

Prepared by

PPD **and** PPD

1. PPD

2. PPD

E-mail: PPD

APPROVAL PAGE: UPPSALA UNIVERSITY

Document Title:	PRECISE Data Management Plan
Author	PPD and PPD
Version Number:	1.0

The following people have reviewed the data management plan and give their approval:

PPD

[DM Name] [Title]	*Signature*	*Date*

APPROVAL PAGE: BAYER AG

Document Title:	PRECISE Data Management Plan
Author	PPD and PPD
Version Number:	1.0

Bayer AG

[Client Name] *Signature* [Title]	*Date*

DOCUMENT HISTORY

The initial data management plan (DMP) will be listed below with version and date. After the first version of the DMP has been approved, any subsequent changes to the content of the DMP will be documented in this section.

Version	Date	Author	Description of Change
0.1	2 April 2019	[MW PST]	Initial release of document
0.2	12 April 2019	[MW PST]	RTI revisions of document
1.0	12 May 2019	[MW PST]	Final document submitted to EMA PRAC

TABLE OF CONTENTS

ABBREVIATIONS

CRPC	castration-resistant prostate cancer
DMP	data management plan
ECOG	Eastern Cooperative Oncology Group
ICD	International Classification of Diseases
INCA	the Information Network on Cancer care
ITS	ICT Services and System Development
mCRPC	metastatic castration-resistant prostate cancer
NPCR	National Prostate Cancer Register of Sweden
PASS	post-authorisation safety study
PCBaSe	Prostate Cancer data Base Sweden
PPC	Patient-overview Prostate Cancer
PSA	prostate-specific antigen
RCC	Regional Cancer Centre
TNM	tumour node metastasis (classification system)

1 STUDY OVERVIEW

This data management plan describes and defines all data management activities for the PRECISE Post-Authorization Safety Study (PASS) using data from the Prostate Cancer data Base Sweden (PCBaSe). Radium-223 (Ra-223) is an alpha particle–emitting radioactive agent approved for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC). This observational cohort study will compare outcomes between patients starting Ra-223 versus those starting any other treatment for mCRPC.

The primary objective of this study is to estimate the effect of Ra-223 on the incidence of bone fractures compared with other standard treatments for mCRPC.

The secondary objectives are as follows:

- To estimate the effect of Ra-223 on overall survival compared with other standard treatments for mCRPC
- To estimate the effect of Ra-223 on prostate cancer–specific survival compared with other standard treatments for mCRPC

2 DATA SOURCES

Data from the National Prostate Cancer Register (NPCR) and the Patient-overview Prostate Cancer data (PPC) in the Information Network for Cancer care (INCA) platform have been merged at a secured server at the regional cancer centre (RCC) in Uppsala to form a study file, which has been transferred to the National Board of Health and Welfare. There, linkages with registers held at this authority were performed in order to create PCBaSe 4.0. In this study file, the person identity number has been replaced with a code, and the code key is held at National Board of Health and Welfare.

The following data sources we will be used in the PASS:

- Patient-overview Prostate Cancer, with longitudinally collected data from routine health care of men with advanced prostate cancer
- The primary registration in the NPCR
- The Patient Register
- The Cause of Death Register
- The Prescribed Drug Register

2.1 National Prostate Cancer Register

The NPCR is a clinical cancer register (a “quality register”), containing comprehensive data on cancer characteristics, work-up, and primary treatment. Data are registered by staff at each respective department in Sweden where men with prostate cancer are treated (Tomic, 2018). In 1998, all six health care regions in Sweden joined to register

all incident cases of prostate cancer. The completeness of NPCR is 98% in comparison to the Swedish Cancer Register, in which registration is mandated by law (Tomic et al., 2015a). Record linkages with other data sources and re-abstraction of data showed that data quality in the NPCR is high (Tomic et al., 2015b), and missing data on risk category classification are low (Tomic et al., 2016).

Data registered in the NPCR describe diagnostic work-up, tumour characteristics, and treatment. Four registration forms are currently used in the NPCR: one form for diagnostic data, one for subsequent work-up and primary cancer treatment, and separate forms for radical prostatectomy and radiotherapy. For diagnosis, examples of variables are date of diagnosis, diagnostic unit, and means of diagnosis. Tumour characteristics are described according to the tumour node metastasis (TNM) classification. Differentiation is reported using the Gleason classification, including indicators of extent of cancer, number of biopsies obtained at diagnostic biopsy and number of cores with cancer, and total extent of the cancer in millimetres. Serum level of prostate-specific antigen (PSA) at date of diagnosis is also recorded. Primary treatment delivered within 6 months of date of diagnosis is recorded.

Since 2007, all data in Swedish cancer quality registers are recorded with the INCA platform. Registration is performed by staff at each reporting unit and checked by staff at RCCs. The organisation of the reporting with six RCCs, one in each health care region, enables close contact between register and reporting units and simplifies corrections and error checking in the registered data. The INCA platform was created to enable all cancer quality registers to use a common platform and thus collaborate in a structured manner, to enable fully digital registration without the use of paper forms, and to allow real-time extraction of data from each clinic for regional and national comparisons.

2.2 Swedish Cancer Register

The nationwide Swedish Cancer Register was created in 1958, and approximately 50,000 new cases of cancer are registered in Sweden each year (Tomic, 2018). The National Board of Health and Welfare is responsible for this register. Registration is mandated by law; since the mid-1980s, registration is performed by the six RCCs, previously regional oncological centres. Data in the Swedish Cancer Register are structured according to data about the patient (age, sex, place of residence, personal identity number), medical data (date and basis of diagnosis, reporting hospital and pathology/cytology department, tumour site, histological type, and stage), and follow-up data (date and cause of death or date of migration). Overall register quality is high, with approximately 99% of cases morphologically verified. An assessment of the completeness, using a comparison to the National Patient Register, concluded that underreporting was around 4%. This underreporting, which is acceptable for most uses in research and health surveillance, was found to vary largely among clinics, increase with patient age, and be overrepresented by diagnoses without verification by histology or cytology.

2.3 National Patient Register

The National Patient Register covers all inpatient care in Sweden since 1987 (Tomic, 2018). Day surgery has been recorded since 1997, and all outpatient care delivered by non–primary health care units has been recorded since 2001, when private health care providers were also included. These groups of cases are registered in the In-Patient and Out-Patient registers, which are both part of the National Patient Registers. The register is updated on a monthly basis since 2015. Key variables include personal identity number, hospital, diagnoses (main and contributing), and procedures.

Data quality controls are enforced for key variables—if the amount of incorrect data is above a threshold, new data are requested from the reporting clinic. The validity of this register was found to be high, varying from 85% to 95% among different diseases, and these numbers were later confirmed in an independent study (Ludvigsson et al., 2011). For this PASS, the National Patient Register is used to validate NPCR data regarding radical prostatectomy and surgical castration. Importantly for this study, the validity of a diagnosis of a fracture is high (Bergström et al., 2011; Michaëlsson et al., 2005).

2.4 Prescribed Drug Register

The Prescribed Drug Register includes all filled prescriptions in Sweden since July 2005 (Tomic, 2018). Data include the prescribed drug, amount and daily dose, date of prescription, and date of filling. The register is limited to outpatient care, and thus excludes drugs administered to inpatients at hospitals and non-prescription drugs acquired by patients over the counter. The Prescribed Drug Register is extensively used for research.

2.5 Cause of Death Register

The Cause of Death Register records causes of death (ICD [International Classification of Diseases] codes) for all persons registered as residents in Sweden from 1991, with an extension since 2012 to also include non-residents (Tomic, 2018). Around 1% of all registered deaths are missing a death certificate; for slightly less than 3%, the cause of death is inconclusive.

Since 1911, cause of death determination has been mandatory in Sweden. The validity of prostate cancer as a cause of death has been found to be high. In a comparison of the cause of death in the Cause of Death Register compared with cause of death as assessed by a chart review of medical records, there was an 86% overall agreement (Fall et al., 2008). In another study, an independent cause-of-death committee reviewed medical data including death certificates according to a standardised algorithm. The overall agreement between cause of death recorded in the death certificates and determined by the committee was 96% (Godtman et al., 2011).

2.6 Patient-overview Prostate Cancer

Patient-overview Prostate Cancer, also held at the INCA platform (Cazzaniga et al., 2019), is a register of men who start hormonal treatment for prostate cancer. These men were registered in the NPCR at the date of their diagnosis. The PPC captures information on men with advanced prostate cancer from the initiation of androgen deprivation therapy to death, including date of diagnosis of castration-resistant prostate cancer (CRPC), dates for start and stop of treatments, assessment of treatment effects, and quality of life. These data are entered into the PPC by staff at each visit. In the PPC, registration is also made of imaging investigations, laboratory testing (e.g., serum levels of PSA and alkaline phosphatase), symptomatic skeletal-related events, and assessment of clinical cancer status by use of the Eastern Cooperative Oncology Group (ECOG) performance status.

In February 2019, around 6,000 men had been registered in the PPC at 30 departments in Sweden. For men who already had CRPC at the time of inclusion in the PPC, selected data from the date of initiation of androgen deprivation therapy and onwards are retrieved from medical charts and are retrospectively entered into the PPC.

Data in the PPC are used for several purposes. First, a dashboard panel in the PPC for each individual patient has a longitudinal overview of treatments, providing a user-friendly graphic representation of the disease trajectory that is used to inform decisions by the physician and the patient at each outpatient visit. Second, at each participating department, PPC users can generate online interactive reports at the INCA platform on their use of cancer drugs with dates for initiation, dose adjustment, and cessation. Third, data in the PPC can also be used for benchmarking of cancer care by comparing centres with each other and the national average. Finally, after linkage of the PPC to PCBaSe, a unique set of real-world data for research is created.

3 DATA MANAGEMENT SYSTEM TO BE USED

Data in the NPCR and PPC are held at the INCA platform, which is the platform for all clinical cancer registers in Sweden. Over 500,000 cases of around 20 cancer forms are held at this platform. The INCA server is held at Umeå University at ICT Services and System Development (ITS), which develops, manages, and operates information technology systems for universities and colleges in Sweden and has several large assignments with organisations in the public sector. Maintenance and updates of the INCA platform are shared between an INCA team employed by the Federation of Regional Cancer Registers in Sweden and Sogethi, a software company.

4 DATA SET CREATION AND TRANSFER METHODS

Data from the NPCR have been encrypted and transferred from INCA to the National Board of Health and Welfare. Data in the PPC, including enriched data for men treated with Ra-223, will now be transferred in the same way. These data will be linked by use of the person identity number to the Patient Register, the Cause of Death Register, and the Prescribed Drug Register in order to update PCBaSe 4.0. Pseudoanonymised files, one for each register, will be returned to the RCC in Uppsala in which the person identity number has been replaced by a code, and the code key will be kept at the National Board of Health and Welfare until data have been checked. The National Board of Health and Welfare receives and sends out data on encrypted DVD discs.

4.1 PCBase Linkage and PRECISE Cohort Creation

The linkage is described above. The PRECISE cohort will be created by linking the data sets generated from the NPCR, PPC, Patient Register, Cause of Death Register, and Prescribed Drug Register.

4.2 Database Lock and Unlock

See Section 4.1. Once the PRECISE cohort has been created from the source registers, no data will be added or altered.

5 DATA CLEANING AND QUALITY CONTROL

See above for quality checks of the registers that will contribute data to the PRECISE cohort. Potential inconsistencies and the guidance for resolving them are located in Table 1.

Table 1. Resolution of Potential Inconsistencies in Data

Potential Inconsistency	Guidance
Differing dates between the PPC and Patient Register	Use dates recorded in the Patient Register (for example, date of diagnosis)
Differing tumour characteristics at diagnosis, PPC and NPCR	Use characteristics recorded in the NPCR (for example, Gleason score, PSA, TNM stages)

NPCR = National Prostate Cancer Register (of Sweden); PPC = Patient-overview Prostate Cancer; PSA = prostate-specific antigen; TNM = tumour node metastasis (classification system).

6 DATA REVIEW

See Sections 2.1 through 2.6 for quality control procedures at the source registers.

7 DATA STORAGE AND ARCHIVING

Data source files are indexed by date of creation and stored on a secured, specifically designated server at RCC. When creating the study cohort from the data source files, scripts, documentation and resulting data sets will be stored in subfolders indexed by date of creation.

8 SUPPORTING DOCUMENTATION

The data manager will ensure that the following additional supporting documentation is maintained:

- Data dictionary representing the final data sets; for example, table names; name, label, type, and length of variables; coding.

9 REFERENCES

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Annex 5: Signature pages

Signature Page – Principal Investigator

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
Protocol version and date	v 2.1, 6 SEP 2019
IMPACT study number	20437
Study type/study phase	Observational, Phase IV PASS ☒ YES Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product/active substance	Xofigo®, Ra-223
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature:_____, _____

Signature Page – OS Conduct Responsible

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
Protocol version and date	v 2.1, 6 SEP 2019
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Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature:_____, _____

Signature Page – Qualified Person responsible for Pharmacovigilance (QPPV)

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
Protocol version and date	v 2.1, 6 SEP 2019
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Study initiator and funder	Bayer AG

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Print Name: PPD

Date, Signature:_____, _____

Signature Page – OS Safety Lead

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Study initiator and funder	Bayer AG

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Print Name: PPD

Date, Signature:_____, _____

Signature Page – OS Medical Expert

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
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Study initiator and funder	Bayer AG

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Print Name: PPD

Date, Signature:_____, _____

Signature Page – OS Statistician

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
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Date, Signature_____, _____

Signature Page – OS Statistician

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Print Name: PPD

Date, Signature_____, _____

Signature Page – OS Epidemiologist

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
Protocol version and date	v 2.1, 6 SEP 2019
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Study initiator and funder	Bayer AG

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Print Name: PPD

Date, Signature:_____, _____

Signature Page – OS Health Economics and Outcomes Research (HEOR) responsible

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
Protocol version and date	v 2.1, 6 SEP 2019
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Study initiator and funder	Bayer AG

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Print Name: PPD

Date, Signature:_____, _____

Signature Page – Regulatory Affairs responsible

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
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Print Name: PPD

Date, Signature:_____, _____

Signature Page – OS Medical Expert

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