Observational Study Information

Title	Incidence of Second primary MAlignancies in pRostate Cancer patients with bOne metastases – an observational retrospective cohort study in Sweden (SMARCOS)
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Research question and objectives	The primary objective is to evaluate the incidence of developing any second primary malignancy (including myelodysplastic syndrome/acute myeloid leukemia and osteosarcoma) among prostate cancer patients with bone metastases (mPC) and among a subgroup of mPC patients among whom the prostate cancer is castration-resistant (mCRPC). The secondary objectives are • To evaluate separately the incidences of site-specific second primary malignancies among mPC and mCRPC patients, • To evaluate the overall survival of mPC and mCRPC patients, and • To investigate factors affecting the incidence of second primary malignancies. Information from this study will serve as a historical comparator for an international prospective observational single-arm cohort study in which the occurrence of second primary malignancies in mCRPC patients treated with radium-223 is studied (The REASSURE study).

Country of study	Sweden
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Marketing authorization holder

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The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

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

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2. LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
ATC code	Anatomical therapeutic chemical classification system code
CI	Confidence interval
CoD	Cause of Death Register
CRPC	Castration-resistant prostate cancer
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
LHRH	Luteinizing hormone-releasing hormone
mPC	Prostate cancer with (bone) metastases
mCRPC	Castration-resistant prostate cancer with (bone) metastases
ICD-10	International classification of diseases, 10th revision
NCSP code	NOMESCO classification of surgical procedure codes
NPCR	National Prostate Cancer Register of Sweden
NPR	National Patient Register
PC	Prostate cancer
PDR	Prescribed drug register
PID	Personal identification number
PSA	Prostate-specific antigen
SAP	Statistical analysis plan
SID	Study identification number
SIR	Standardized incidence ratio

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title of study: Incidence of Second primary MAlignancies in pRostate Cancer patients with bOne metastases – an observational retrospective cohort study in Sweden (SMARCOS)

Rationale: Prostate cancer (PC) is the most common non-cutaneous malignancy in men[1]. Once it becomes metastatic, it poses a serious threat to the patients' quality of life and survival. The most common site of metastases is the skeletal system: Among castration-resistant prostate cancer patients bone metastases are involved in over 90% of metastatic cases[2,3].

The development of new treatments has led to improved quality of life and prolonged lifetime among castration-resistant prostate cancer patients with metastases (mCRPC)[4,5]. A recent randomized clinical trial indicated significant improvement in survival and quality of life among patients with bone metastases treated with alpha emitter radium-223 as compared with placebo[6]. To further evaluate the safety profile of Radium-223 in patients with castration resistant prostate cancer with bone metastases, Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation (the REASSURE study), an international prospective observational single-arm cohort study was implemented as a post-marking requirement requested by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).

In the case that new treatments improve the length and quality of life substantially, it can be challenging to obtain an appropriate comparison group in the post-authorization phase. This study is conducted to obtain information about prostate cancer patients with bone metastases before the end of 2013. The incidence of second primary malignancies and overall survival are of particular interest[7]. Information from this study will serve as a historical reference for the REASSURE study.

Objectives: The primary objective is to evaluate the incidence of developing any second primary malignancy (including myelodysplastic syndrome/acute myeloid leukemia and osteosarcoma) among prostate cancer patients with bone metastases (mPC) and among a subgroup of mPC patients among whom prostate cancer is castration-resistant (mCRPC).

The secondary objectives are

- To evaluate separately the incidences of site-specific second primary malignancies among mPC and mCRPC patients,
- To evaluate the overall survival of mPC and mCRPC patients and
- To investigate factors affecting the incidence of second primary malignancies.

Study design: This is a retrospective, non-interventional cohort study that will be conducted in Sweden using nationwide healthcare registers as data sources. Patients with prostate cancer and with metastases will be identified using The International Classification of Diseases, 10th revision (ICD-10) diagnosis codes recorded in the databases. Additional information on treatments will be used to create a proxy that prostate cancer has become castration-resistant. Information on cancer diagnoses and times of death will be used to determine the main outcome variables.

Study period: Hospital diagnoses are available from 1998 and drug purchases from mid-2005. Therefore, 1.1.1998 is the start of the study period but for all analyses that use treatment information the follow-up starts after 1.1.2006. The end of the study period is 31.12.2013.

Time period 1.1.1998 – 31.12.2011 will be used for identifying PC diagnoses and 1.1.2006 – 31.12.2011 for identifying the castration-resistant condition. Bone metastases diagnoses that define the cohort entry date will be used from 1.1.1999 onwards for the mPC population and from 1.1.2007 onwards for the mCRPC population to ensure at least a year of history before enrolment for each patient. New patients are enrolled into the study populations until 31.12.2011. No new patients are included during 1.1.2012 – 31.12.2013 to ensure a minimum of two years of potential follow-up time.

Study populations: Patients with PC diagnosis in 1.1.1998 – 31.12.2013 and with bone metastases diagnosis or bone-directed treatments (bisphosphonates or denosumab) in 1.1.1998 – 31.12.2013 will be initially included into the large study population. From this initial population, the main analyses will concentrate on the mPC and mCRPC populations described below.

Patients are included in the mPC population if they fulfill the two following criteria:

A. PC diagnosis in 1.1.1998 – 31.12.2011
B. Bone metastases diagnosis in 1.1.1999 – 31.12.2011

Patients are included in the mCRPC population if they fulfill the three following criteria:

1) PC diagnosis in 1.1.1998 – 31.12.2011
2) Bone metastases diagnosis in 1.1.2007 – 31.12.2011
3) One of the following in 1.1.2006 – 31.12.2011 and before or at the same time with bone metastases diagnosis:
    a. Discontinuation of the initial chemical castration (androgen deprivation therapy, ADT), change of the agent or modality of ADT, or start of treatment for advanced PC after the primary ADT (including chemotherapy or mitoxantrone)
    b. Surgical castration and initiation of ADT treatment, chemotherapy or mitoxantrone afterwards
    c. Treatment with medication specific to either castration-resistant PC or mCRPC

(cabazitaxel, enzalutamide or abiraterone).

(d.) In a sensitivity analysis, also those who have had at least 6 months since the initiation of castration treatment before cohort entry date (bone metastases diagnosis) are included in the mCRPC population.

Patients are excluded from the mPC and from the mCRPC populations if they fulfill any of the following:

I. First PC diagnosis later than 2 months after the diagnosis of bone metastases, or
II. Permanent residence not in Sweden or patient otherwise not contributing to the registers at least a year before the diagnosis of bone metastases (patient counted not contributing also if database existence less than a year before cohort entry), or
III. Use of any radiopharmaceuticals for bone metastases (samarium, strontium, rhenium or radium).

Follow-up time: Follow-up starts at the date of first bone metastases diagnosis. Follow-up of mPC patients can start in 1.1.1999 – 31.12.2011. Follow-up of mCRPC patients can start in 1.1.2007 – 31.12.2011. Follow-up ends at death or the end of the study period 31.12.2013. Follow-up also ends if patient moves abroad from Sweden. Also in the analyses in which the outcome is other than death, follow-up ends after first occurrence of the outcome.

The follow-up period ensures that all enrolled patients have the possibility to contribute at least two years of follow-up time before the study period ends.

Outcome variables: The primary outcome is an incidence of any second primary malignancy (including myelodysplastic syndrome/acute myeloid leukemia and osteosarcoma).

The secondary outcomes are

- Incidences of any site-specific second primary malignancies, and
- Overall survival.

Definition of exposures: This study does not have a specific exposure of interest. Drug exposure periods for general medicinal products involved will be defined based on dates and amounts of purchase, and used for defining treatment discontinuation.

Relevant covariates: Patients' demographic variables: date of birth, place of residence.

Patients' baseline characteristics: year of PC and bone metastases diagnosis, prostate-specific antigen (PSA) values at PC diagnosis, TNM staging and Gleason score at PC diagnosis, primary treatment at PC diagnosis, history of cancers other than PC, history of visceral metastases.

Past and current treatments such as endocrine treatments (including antiandrogens, luteinizing hormone-releasing hormone (LHRH) agonists and antagonists) and cytotoxic chemotherapy (taxanes, mitoxantrone and others), as well as bone-directed treatment (bisphosphonates and denosumab), corticosteroids, all surgical operations, radiation therapy.

Patients' history of comorbidities.

Statistical methods: The population will be described with respect to relevant variables at cohort entry, including but not limited to age, year of cohort entry, time from PC diagnosis to bone metastases, treatment history, PC-related information at diagnosis and history of comorbidities. Categorical variables will be described by proportion of patients in each category and continuous variables with the

relevant summary statistics (mean, median, 1st and 3rd quartiles, range and standard deviation).

Summary of the survival time in the study populations will be described with mean median, 1st and 3rd quartiles, range and standard deviation. In addition, yearly survival rates will be reported and Kaplan-Meier survival curves presented for the mPC and mCRPC populations.

For studying second primary malignancies, stratified incidence rates will be calculated and the corresponding 95% confidence intervals (CIs) derived under the Poisson assumption. Different strata will be defined by categorical or categorized variables specified in the statistical analysis plan.

Estimates of incidence of second primary malignancies from this study will be used as an external reference in a single-arm radium-223 study.

Population size: Based on the number of PC patients in Sweden and on the risk of PC developing into metastatic state, it was estimated that 1,160 mPC patients would be available per study year. During the inclusion time period 1.1.1999 – 31.12.2011 there would be approximately 15,000 mPC patients. During the inclusion time period 1.1.2007 – 31.12.2011 there would be approximately 5,800 mPC patients for whom castration-resistant proxy will be determined.

Ethics: All data for this study will be observational, based on retrospective records and therefore the study does not pose any potential harm to patients, neither will patients be contacted in any phase. All patient data will be made de-identifiable, which ensures the full data protection of patients. Approval from relevant the Ethical Review Board will be requested before conducting the study.

Results and publications: The study protocol and the key results will be published in the ENCePP E-register of studies. The results are also planned to be published in a peer-reviewed journal.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	Q1 2016
End of data collection	Q2 2016
Final report of study results	Q4 2016

7. RATIONALE AND BACKGROUND

Prostate cancer (PC) is the most common non-cutaneous malignancy in men[1]. In the Nordic countries, the number of patients living with PC diagnosis at the end of 2012 was 200,000 (1900 per 100,000 men)[8]. Of the Nordic countries, the number of PC patients was particularly high in Sweden (3700 per 100,000 men)[8]. In 2012 in the Nordic countries, 5400 men died of prostate cancer and 2400 of these were in Sweden (crude rate 50 per 100,000 person years)[9]. PC mortality in Europe is highest in the Baltic countries and in Scandinavia, with age-standardized rates being 18 – 21 per 100, 000[1].

PC is unique amongst solid tumors in that the greatest threat to a patient's survival and quality of life is posed by bone metastases rather than visceral involvement. The most common site of metastases for advanced prostate cancer is the skeletal system, which is involved in more than 90% of the patients[2,10]. Therefore, nearly all treatments are directed toward eradicating or limiting osseous metastases or palliating their side effect[11]. Once prostate cancer becomes metastatic, the survival of the patient depends on the extent of the disease and the site of metastases.

PC cells are stimulated by androgens, in particular testosterone. Androgen deprivation therapy (ADT) aims to reach sufficiently low levels of testosterone in order to stop progression of the disease. However, castration treatment commonly ceases to be effective after a period of time and the disease progresses despite low levels of testosterone. At this stage, the disease is referred to as castration-resistant prostate cancer (CRPC). Development of CRPC to bone metastatic state (mCRPC) is associated with substantial pain and risk of pathological fractures notably in the spine, pelvis and hip. The prostate-specific antigen (PSA) level after initial ADT affects prognosis: After 7 months of ADT, patients with PSA < 0.2 ng/ml (undetectable) have a better prognosis than patients with PSA $\geq$ 4 ng/ml[12].

The development of bone metastases is a serious threat to the patients' quality of life and survival. Approximately 53% of patients with bone metastases at prostate cancer diagnosis die within 12 months, and 97% within 5 years[13]. Radium-223 is a new mCRPC treatment that selectively targets bone metastases with high-energy, short-range alpha particles. In a phase III clinical trial, radium-223 significantly improved overall survival as compared to placebo: The median overall survival was 14.0 vs. 11.2 months[6]. In addition, the incidence of symptomatic skeletal events as well as other adverse events was lowered in the radium-223 arm.

To further evaluate the safety profile of Radium-223 in patients with castration resistant prostate cancer with bone metastases, Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation (the REASSURE study), an international prospective observational single-arm cohort study was implemented as a post-marking requirement requested by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).

However, as in the case of radium-223, it can be unethical not to give new treatments to patients in the case that their efficacy on patients' life has been shown in a phase III trial. Therefore, it may be challenging to form a comparison group in the post-authorization setting for highly efficacious medicines. An alternative strategy for the formation of a comparison group is historical reference. The Nordic nationwide population registers containing treatment information, hospital diagnoses, times and causes of death among other relevant information that are collected as part of the daily administrative routines, provide an excellent data source for this purpose.

Following feasibility assessment on appropriate external secondary data sources, an epidemiology program is established which consists of three observational studies using population-based databases in Europe (Germany and Sweden/Nordic country) and US. The study in Germany will be performed using the German Pharmacoepidemiological Research Database via the Leibniz Institute for Prevention Research and Epidemiology. The study in Sweden will be conducted using the Swedish register databases. The US study is planned to be conducted using the US Surveillance, Epidemiology and End Results and Medicare linked database. The current study protocol is the Swedish part of this epidemiology program. Age-standardized results from this study will be compared independently of the two other studies (US, GER) to the results from the REASSURE study. When necessary, pooled comparisons can be considered using results from the three studies (SWE, GER, US) together against the REASSURE with geographical area as an additional stratifying variable, and also by meta-analysis methods[14,15].

8. RESEARCH QUESTIONS AND OBJECTIVES

8.1 Primary objective

- To evaluate among prostate cancer patients with bone metastases (mPC) and among a subgroup of mPC patients for whom the prostate cancer can be considered to be castration-resistant (mCRPC):
    - The incidence of developing any second primary malignancy (including myelodysplastic syndrome/acute myeloid leukemia and osteosarcoma).

8.2 Secondary objectives

- To evaluate the incidences of site-specific second primary malignancies among mPC and mCRPC patients.

- To evaluate the overall survival of mPC and mCRPC patients.
- To investigate factors affecting the incidence of second primary malignancies.

This study does not aim to test a priori hypothesis. Information from this study will serve as a historical reference for the international prospective observational single-arm cohort study in which the occurrence of second primary malignancies in mCRPC patients treated with radium-223 is studied (The REASSURE study).

9. RESEARCH METHODS

9.1 Study design

This is an observational retrospective cohort study that uses existing nationwide register data from Sweden.

9.2 Setting

This non-interventional study will be conducted in Sweden using nationwide registers as data sources. Patients with prostate cancer and with metastases will be identified using diagnosis codes (The International Classification of Diseases, 10th revision (ICD-10)) recorded in the healthcare registers. Additional information on treatments (based on The Anatomical Therapeutic Chemical classification system (ATC) codes) will be used to create a proxy for a prostate cancer that has become castration-resistant. Information on cancer diagnoses and time of death will be used to determine the main outcome variables.

9.2.1 Study period

The data collection period is 1.1.1998 – 31.12.2013 but information on drug purchases is available only from 1.1.2006 onwards. Therefore, different enrolment and follow-up periods are defined for the mPC (formation based on diagnoses) and mCRPC (formation requires also information on treatments) populations. Time period 1.1.1998 – 31.12.2011 will be used for identifying PC diagnoses and 1.1.2006 – 31.12.2011 for identifying the castration-resistant condition. Bone metastases diagnoses that define the cohort entry date will be used from 1.1.1999 onwards for the mPC population and from 1.1.2007 onwards for the mCRPC population to ensure at least a year of history before enrolment for each patient. New patients are enrolled into the study populations until 31.12.2011. No new patients are included during 1.1.2012 – 31.12.2013 to ensure a minimum of two years of potential follow-up time.

9.2.2 Study population

Patients with PC diagnosis in 1.1.1998 – 31.12.2013 and with bone metastases diagnosis or bone-directed treatments (see Section 9.3) in 1.1.1998 – 31.12.2013 will be initially included into the large study population. From this initial population, the main analyses will concentrate on the following two populations:

- Prostate cancer patients with bone metastases (mPC), and
- Castration-resistant prostate cancer patients with bone metastases (mCRPC).

Identification of the mPC population is based on diagnoses but identification of mCRPC population requires information on treatments as well. Schematic presentation of the formation of the two study populations is given in Figure 1 and detailed inclusion and exclusion criteria below.

Inclusion criteria

Patients are included in the mPC population if they fulfill the two following criteria:

A. PC diagnosis in 1.1.1998 – 31.12.2011.

B. Bone metastases diagnosis in 1.1.1999 – 31.12.2011.

Cohort entry date for mPC patients is the date of first bone metastases diagnosis in 1.1.1999 – 31.12.2011 (no previous bone metastases).

Patients are included in the mCRPC population if they fulfill the three following criteria:

1) PC diagnosis in 1.1.1998 – 31.12.2011
2) Bone metastases diagnosis in 1.1.2007 – 31.12.2011
3) One of the following in 1.1.2006 – 31.12.2011 and before or at the same time with bone metastases diagnosis:
    a. Discontinuation of the initial chemical castration (ADT), change of the agent or modality of ADT, or start of treatment for advanced PC after the primary ADT (including chemotherapy or mitoxantrone)
    b. Surgical castration and initiation of ADT treatment, chemotherapy or mitoxantrone afterwards
    c. Treatment with medication specific to either CRPC or mCRPC (cabazitaxel, enzalutamide or abiraterone).

    (d.) In a sensitivity analysis, also those who have had at least 6 months since the initiation of castration treatment before cohort entry date (bone metastases diagnosis) are included in the mCRPC population.

Cohort entry date for mCRPC patients is the date of first bone metastases diagnosis in 1.1.2007 – 31.12.2011 (no previous bone metastases).

For the classification of treatments into chemical castration, treatment against advanced PC and mCRPC treatment, please see Section 9.3.

Discontinuation of treatment such as chemical castration is defined as the absence of any new exposure (e.g. new purchase or new treatment in a hospital) for the same treatment (or class of treatments) within

the duration of the previous exposure plus an additional grace period. Duration of exposure will be based on dates and amounts of drugs purchased or received in a hospital, and will be defined in more detail in the statistical analysis plan (SAP).

Patients are excluded from the mPC and from the mCRPC populations if they fulfill any of the following:

I) First PC diagnosis later than 2 months after the diagnosis of bone metastases, or

II) Permanent residence not in Sweden or patient not otherwise contributing to the registers at least a year before the diagnosis of bone metastases (patient counted not contributing also if database existence less than a year before cohort entry), or

III) Use of any radiopharmaceuticals for bone metastases (ATC code)

   a. Samarium (V10BX02), strontium (V10BX01), rhenium (V10BX03) or radium (V10XX03).

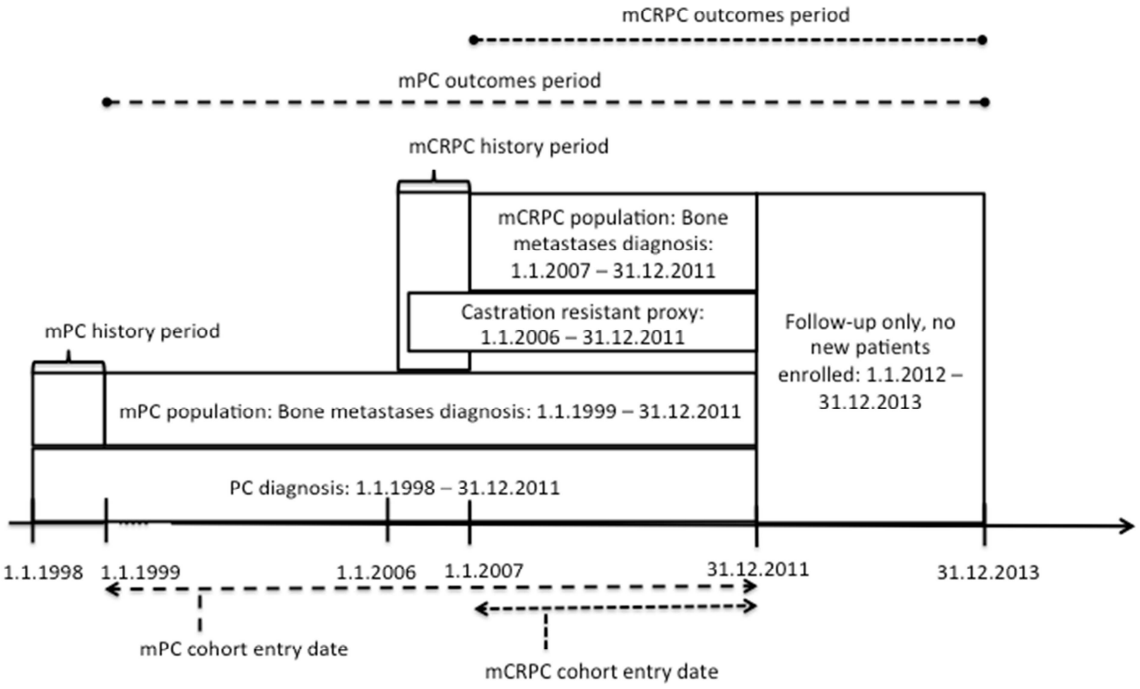

Figure 1. Schematic presentation of the formation of the two study populations.

Follow-up time

Follow-up starts at the date of first bone metastases diagnosis. Follow-up of mPC patients can start in

1.1.1999 – 31.12.2011 and follow-up of mCRPC patients in 1.1.2007 – 31.12.2011. Follow-up ends at death or at the end of the study period 31.12.2013. Follow-up also ends if patient moves abroad from Sweden. Also in the analyses in which the outcome is other than death, follow-up ends after the first occurrence of the outcome.

The late follow-up period 1.1.2012 – 31.12 2013, when no new patients are included, ensures that all enrolled patients have the possibility to contribute at least two years of follow-up time before the study period ends.

9.3 Variables

9.3.1 Diagnoses for inclusion criteria

- PC diagnosis (ICD-10 code: C61)
- Bone metastases diagnosis (ICD-10 code: C79.5)

9.3.2 Exposures for inclusion criteria

- **Chemical castration (ADT)**, class of treatments including:
    - First-generation antiandrogens (ATC code)
        - Flutamide (L02BB01), nilutamide (L02BB02), bicalutamide (L02BB03)
    - Luteinizing hormone-releasing hormone (LHRH) agonists/antagonists (ATC code)
        - Buserelin (L02AE01), leuporelin (L02AE02), goserelin (L02AE03), triptorelin (L02AE04), histrelin (L02AE05)
        - Abarelix (L02BX01), degarelix (L02BX02)
        - Gonandorelin (H01CA01), nafarelin (H01CA02)
    - Other (ATC code)
        - Cyproterone acetate (G03HA01)
        - Medroxyprogesterone acetate (L02AB02), polyestradiol phosphate (L02AA02), megestrol (L02AB01)
        - Diethylstilbestrole (G03CB02, L02AA01)
        - Estramustine (L01XX11)
        - Ketoconazole (J02AB02)
- **Surgical castration**

- Bilateral orchiectomy (NOMESCO classification of surgical procedure codes (NCSP) code: KFC10)

- **Treatment for advanced prostate cancer**, class of treatments including:
  - Chemotherapy (ATC code)
    - Docetaxel (L01CD02), cabazitaxel (L01CD04)
  - Mitoxantrone (L01DB07)

- **Treatment for mCRPC**, class of treatments including (ATC code):
  - Enzalutamide (L02BB04), abiraterone (L02BX03)

- **Bone-directed treatments**, class of treatments including (ATC code):
  - Bisphosphonates
    - Clodronate (M05BA02), pamidronate (M05BA03), aldendronic acid (M05BA04), ibandronic acid (M05BA06), risendronic acid (M05BA07), zoledronic acid (M05BA08)
  - Denosumab (M05BX04)

9.3.3 Outcome measures

The primary outcomes are

- Any second primary malignancy (ICD-10 codes: C00 – C76, C81 – C96, D00 – D09, D37 – D48)

The secondary outcomes are

- Site-specific second primary malignancies
  - Site-specific ICD-10 code groups from the range of all neoplasm codes C00 – D48
- Overall survival
- Skeletal-related events
  - Pathologic fracture (ICD-10 codes: M49.5, M84.4, M90.7)
  - Spinal cord compression (ICD-10 codes: M43.9, M48.5, G95.2, G95.8)
  - Surgery to bone (based on NCSP codes)
  - Radiation to bone (based NCSP codes)

9.3.4 Other variables

- Patients' demographic variables

  - Date of birth, place of residence, year of PC diagnosis, year of bone metastases diagnosis

- History of comorbidities
- Patient characteristics at PC diagnosis:
  - PSA value, TNM staging, Gleason score, primary treatment
- Visceral metastases (ICD-10 code)
  - Secondary malignant neoplasm of respiratory and digestive organs (C78)
  - Secondary malignant neoplasm of kidney and renal pelvis (C79.0)
  - Secondary malignant neoplasm of bladder and other unspecified urinary organs (C79.1)
  - Secondary malignant neoplasm of brain and cerebral meninges (C79.3)
  - Secondary malignant neoplasm of other and unspecified part of nervous system (C79.4)
  - Secondary malignant neoplasm of adrenal gland (C79.7)
- Other current and past treatments
  - Other cancer-related treatments
    - Radiopharmaceuticals including samarium-153 (ATC class: V10), estramustine (ATC: L01XX11), radiation therapy (based on NCSP codes), other cytotoxic chemotherapy (ATC-class: L01)
  - Addition treatments
    - Dexamethasone (ATC: H02AB02), prednisolone (ATC: H02AB06), prednisone (ATC: H02AB07)
    - Non-steroidal anti-inflammatory drugs (ATC class: M01A), other analgesics and antipyretics (ATC class: N02B), opioids (ATC class: N02A)
- All operations and medications in inpatient care, including but not limited to
  - Radical prostatectomy (NCSP class: KEC) and other operations for prostate (including NCSP classes: KEC, KEW)
  - Operations related to cytostatic treatments and radiation therapy (based on NCSP codes)

9.4 Data sources

In Sweden, all citizens have a personal identification number (PID) that allows individual-level data to be linked between registries. Registry data in Sweden have been collected for a long period of time and the standards of maintaining the registries have been developed over time.

The National Prostate Cancer Register of Sweden (NPCR)

NPCR is a quality register for prostate cancer. In 2008 NPCR was linked with other registers via PID to form Prostate Cancer data Base Sweden[16]. The NPCR covers >96% of all incident PC cases registered by the Swedish Cancer Register, which has an underreporting of <3.7%. Prostate adenocarcinomas are registered in NPCR, but no other forms of prostate neoplasia.

NPCR information	
Register holder	Regional Cancer Registers
Year Started	1996
Population coverage	>96% of all incident PC cases registered by the Swedish Cancer Register
Lag-time	1 year
Variables	PID, age at diagnosis, reporting hospital, date of referral and date of diagnosis, morphological confirmation of diagnosis, PSA value at diagnosis, prostate volume at diagnosis, TNM staging at diagnosis, Gleason score at diagnosis, primary treatment at diagnosis (completed or decided within 6 months after diagnosis)

Swedish Cancer registry

The total number of patients in the register is more than 2 million. A quality study of the cancer register was published in 2009[17] in which the coverage rate was evaluated in comparison to the inpatient registry. In this study, an average underreporting of 4 percent was estimated, but considerable variation exists depending on the cancer site.

NPCR information	
Register holder	The National Board of Health and Welfare
Year Started	1958
Population coverage	Whole Sweden with underreporting approximately 4 %
Variables	PID, age, sex, place of residence, tumor site, tumor histological type, tumor stage, tumor identification number for tissue specimen, basis of diagnosis, date of diagnosis, reporting hospital, reporting pathology department, treating doctors, clinical inpatient data, date of migration, date of death, cause of death

The National Patient Register (NPR)

NPR includes all inpatient care in Sweden and outpatient visits from 2001 onwards but does not cover primary care yet. Diagnoses recorded in the NPR have been externally reviewed and are considered highly valid[18].

NPR information	
Register holder	The National Board of Health and Welfare
Year Started	1987
Population coverage	~100%
Variables	PID, age, sex, place of residence, place of treatment, date of admission and discharge, length of stay, acute/planned admission, admitted from/discharged to, discharge diagnosis, secondary diagnoses, external cause of injury and poisoning, treatments and procedures

The Prescribed Drug Register (PDR)

PDR contains information on prescribed drugs dispensed by community pharmacies from 2006 onwards. According to a quality review of the register, PDR accounts for approximately 80% of total drug utilization and expenditure in Sweden[19].

PDR information	
Register holder	The National Board of Health and Welfare
Year Started	Mid-2005
Population coverage	~100%
Variables	PID, age, sex, place of residence, prescriber and dispensing pharmacy, trade name, substance, ATC code, date of purchase, defined daily dose, package size, strength, number of purchased packages, The Nordic Article Number, reimbursement type, exchange to generic drug

The Cause of Death Register (CoD)

The register includes all deaths of persons registered in Sweden at the time of death. Deaths occurring outside of Sweden are recorded for persons registered in Sweden, but stillbirths, persons who died during temporary stay in Sweden or persons without a residence permit are not included. ICD code is used for classification of causes of death. In 1994, the non-reporting rate was 0.45% of all deaths. The register has published a study on the methods used and quality of the cause of death data[20].

CoD information	
Register holder	The National Board of Health and Welfare
Year Started	1953

Population coverage	~100%
Variables	PID, age, sex, place of residence, cause of death, nature of injury, intent in case of injury or poisoning, multiple causes of death, surgery within four weeks from death, date of death

Population register

The population register contains information about the people living in Sweden and about where in the country they reside. The Swedish Tax Agency is responsible for the population register. The origins of the register date back to 17th century when it was maintained by the Church of Sweden.

Population register information	
Register holder	Swedish Tax Agency (Statistics Sweden)
Year Started	
Population coverage	~100%
Variables	Name, PID, place of birth, citizenship, civil status, spouse, children, parents, legal guardians and adoption, address, immigration and emigration dates, addresses abroad, death and burial site

9.5 Study Size

Based on the number of PC patients in Sweden and on the risk of PC developing into metastatic state, it was estimated that 1,160 mPC patients would be available per study year. With inclusion time period 1.1.1999 – 31.12.2011 there would be approximately 15,000 mPC patients. With inclusion time period 1.1.2007 – 31.12.2011 there would be approximately 5,800 mPC patients for whom castration-resistant proxy will be determined. It is expected that each enrolled patient contributes 14 months of follow-up time[6].

Expected number of second primary malignancies

Based on the number of PC and metastases diagnoses in 2007 in Sweden (Socialstyrelsen data), the expected age distribution of mPC patients is presented in Table 1 below. The table also presents the incidences of PC and all cancers per 100,000 person years in each age group, based on NORDCAN data from 2007 in Sweden.

Table 1. Hypothesized PC patient age distribution and cancer incidences per 100,000 person years by age, based on NORDCAN 2007 data from Sweden.

Age	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Proportion of patients (%)	0.9	2.4	3.9	5.5	14.2	16.7	16.1	16.6	13.0	10.9
Overall cancer incidence	101	160	363	694	1233	1894	2382	2772	3033	2817
PC incidence	3	19	99	273	527	850	932	948	972	741
Cancer incidence excluding PC*	98	141	264	421	706	1044	1450	1824	2061	2076
Expected number of second cancers; 15,000 patients	0	1	2	4	18	30	41	53	47	40
Expected number of second cancers; 4,060 patients	0	0	0	1	5	8	11	14	13	11
Expected number of second cancers; 25,000 patients	0	1	3	7	29	51	68	88	78	66

*Overall incidence - PC incidence

With 15,000 mPC patients and 17,500 person years of follow-up, the expected number of second primary malignancies would be in the range 215 – 254 with 80% probability. With 4,060 (= 70%*5,800) mCRPC patients and 4,737 person years of follow-up, the expected number of second primary malignancies will be in the range 53 – 74 with 80% probability.

Validity of using estimates from this study as an external reference

Estimates of incidence of second primary malignancies from this study will be used as an external reference in a single-arm radium-223 study (REASSURE). The method of comparison will be indirect, i.e., standardized incidence ratios (SIR) will be calculated. Validity of estimates from this study for this purpose is explored in the following. In the radium-223 treated arm, 1,200 mCRPC patients and 1,400 person years are expected to be available, in which case the expected reference incidence based on Table 1 would be 19. If the true reference would be available, the minimum detectable SIR in the radium-223

study would be 1.78: With 80% certainty the lower 95% confidence interval (CI) of the SIR will be above 1 if true SIR is 1.78 or higher. By sampling variation in the reference group with 15,000 patients, the reference 19 would be estimated with 80% probability in the range 17.2 – 20.3 and with 4,060 patients in the range 15.7 – 21.9. When taking into account sampling variation in the calculation of confidence intervals for SIR, the minimum detectable SIR would become 1.93, 1.81 and 1.79, with 4,060, 15,000 and 25,000 patients in the reference population, respectively.

If the number of mCRPC patients in this study remains below 2,600, the minimum detectable SIR in the REASSURE study, when using the incidence of second primary malignancies from this study as a reference, will be 2 or higher (with the expected incidence rate given in Table 1, and taking into account sampling variation from this study). In this case, the study could be extended to another Nordic country, to ensure that the provided reference group is sufficient in size. Due to similarities in the register data sources in the Nordic countries, it is expected that only small adjustments to this protocol need to be made when applied to another Nordic country.

9.6 Data management

R language (http://www.r-project.org) will be used for data management, for creating the analysis database and in statistical analysis for creating tabulations and graphics as well as in all statistical modeling. R language is described in a detailed report "R: Regulatory Compliance and Validation Issues: A Guidance Document for the Use of R in Regulated Clinical Trial Environments" (www.r-project.org/doc/R-FDA.pdf). Full audit trail, starting from raw data obtained from register holders and ending with the creation of statistical tables and graphs in reports, will be maintained. Source code of data management and data analyses is kept for inspection for ten years after publication of results. The study may be inspected by the sponsor's independent representative(s) or by competent authorities.

According to the Swedish Personal Data Act, individual-level data cannot be preserved for a longer time period than necessary[21]. Since the results from this study will be used as a reference in the REASSURE study, which is scheduled to be finished in 2024, all study data and supporting documents will be retained for ten years (ultimately subject to data holder permit) after the completion of the study report. EPID Research shall not destroy any relevant material related to the study without prior approval from the Sponsor. As the register holder of the study register EPID Research is in charge of archiving and deleting the data. Secure archives will be maintained for the orderly storage and retrieval of all study-related material. An index shall be prepared to identify the archived contents and their location. Access to the archives will be controlled and limited to authorized EPID Research personnel only. Access to the study data cannot be given to any third parties, and the study data cannot be used for other purposes than prescribed in this protocol. All requests to use the study data for other purposes than mentioned in this study protocol must be subjected to appropriate data permit processes.

9.7 Data analysis

EPID Research will perform the statistical analyses by using the R programming language (http://www.r-

project.org). A separate detailed statistical analysis plan will be written after approval of the study protocol.

9.7.1 Characteristics of the study population

The population will be described with respect to relevant variables at cohort entry including but not limited to age, year of PC diagnosis, place of residence, year of bone metastases diagnosis, treatment history: never/ever use of each treatment (treatment class if such is defined), PC-related information at diagnosis: PSA value, TNM staging, Gleason score, history of other cancers, visceral metastases and other comorbidities. Treatment patterns (initiations, discontinuations and changes) for treatments in Section 9.3 will be described separately during the time period from PC diagnosis to cohort entry and during the follow-up. Categorical variables will be described by proportion of patients in each category and continuous variables with the relevant summary statistics (mean, median, 1st and 3rd quartiles, range and standard deviation).

9.7.2 Analysis of primary objectives

Incidence of any second primary malignancies

For studying the incidence of any second primary malignancies (including myelodysplastic syndrome /acute myeloid leukemia and osteosarcoma), the number of incident cases, total follow-up time and the ratio of these two (i.e. the incidence rate) and the 95% CI of the incidence rate, derived under the Poisson assumption, will be presented separately for the mPC and mCPRC study populations. In the primary analyses of second primary malignancies, follow-up time will be censored at death and also at the first occurrence of the event.

To investigate the effect of different factors on the incidence of second primary malignancies (secondary objective), the incidence rates will also be presented in different strata of mPC and mCRPC patients. The stratifying variables include but are not limited to demographic variables, comorbidities, patient characteristics at PC diagnosis, exposures for inclusion criteria, other current and past treatments and operations in inpatient care (see Section 9.3). The strata will be defined in detail in the SAP.

Age-stratified estimates of incidence of second primary malignancies from this study will be used as an external reference in the single-arm radium-223 study (REASSURE). By employing the incidences estimates from this study and the observed person years in each age category in the REASSURE study, the expected number of cases for the REASSURE study will be calculated. The total number of expected cases in all age categories will be compared to the observed one, i.e., the age-standardized incidence ratio will be calculated. The 95% CI of SIR will be calculated assuming both the observed and expected incidences follow the Poisson distribution.

9.7.3 Analysis of secondary objectives

Site-specific second primary malignancies and skeletal-related events

For all site-specific second primary malignancies and for skeletal related events, the number of incident

cases, total follow-up time and the ratio of these two (i.e. the incidence rate) and the 95% CI of the incidence rate, derived under the Poisson assumption, will be presented separately for the mPC and mCPRC study populations. In the primary analyses of second primary malignancies and skeletal-related events, follow-up time will be censored at death and also at the first occurrence of the event.

Overall survival

Overall survival will be studied as time from cohort entry (determined by the date of first bone metastases diagnosis) to death due to any cause. Summary of the survival time in the population will be described with mean, median, 1st and 3rd quartiles, range and standard deviation. Furthermore, yearly survival rates will be reported for the mPC and mCRPC populations and Kaplan-Meier survival curves presented. The age-standardized mortality rates will be provided to investigate the effect of death as a competing risk in the SIR comparisons against the REASSURE study.

The analyses of secondary objectives will also be performed in different strata of mPC and mCRPC patients. The stratifying variables and strata (from those presented in Section 9.3) such as age will be defined in the SAP.

9.7.4 Sensitivity analyses

The analyses of second primary malignancies and overall survival will be re-performed as listed below.

1. To verify that diagnoses are recorded completely in the patient register, the following proxies will be used:
    a. Initiation of prostate cancer treatment as a proxy for the date of PC diagnosis.
    b. Bone-directed treatments as a proxy for bone metastases diagnosis.
2. To test the sensitivity of results for the definition of mCRPC proxy: In addition to the other inclusion criteria, those who have had at least 6 months since the initiation of ADT treatment before the diagnosis of bone metastases are included in the mCRPC population.

All proxies in 1. and 2. will be used together in one sensitivity analysis and, if the results differ substantially from the original analyses, the effect of each proxy will be subsequently determined by re-performing the analyses using one proxy at a time.

3. To further investigate the sensitivity of results for the definition of mCRPC proxy: castration-resistant PC will be defined solely through medication specific to either CRPC or mCRPC.
4. To investigate the temporal relation of mCRPC proxy and bone metastases diagnosis, the mPC population who fulfill the mCRPC proxy criterion only after entering the cohort will be described.
5. To verify that the results from this study concern population with bone metastases from PC and not from other cancers: patients who have ever been diagnosed with cancer other than PC before bone metastases diagnosis will be excluded.

6. To provide general information on the possible effect of visceral metastases on the study results (overall survival in particular): patients with visceral metastases will not be excluded.

7. To completely exclude the possibility that the results could be affected by exposure to radium-223, the two last months (1.11.2013 – 31.12.2013) will be removed from the follow-up time.

8. When studying the incidence of second primary malignancies and skeletal-related events, follow-up will not be censored after the first occurrence of second primary malignancy.

9. Patients receiving radiopharmaceuticals samarium, strontium or rhenium will not be excluded.

9.7.5 Missing data

For study variables, if a variable is totally missing from a database, it will be excluded from the analysis. If a variable is missing for only some of the patients a missing data category will be added and used in the analysis.

9.8 Quality control

The study will be conducted as specified in this protocol. The principal investigator, the co-investigators and the sponsors of the study must approve all revisions to the protocol. All changes to the protocol shall be properly documented as protocol amendments and when necessary such protocol amendments are delivered to relevant ethics committees and register holders.

The study protocol has been written following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The protocol also follows the key elements of the Guideline for Good Pharmacoepidemiology Practices by International Society for Pharmacoepidemiology (www.pharmacoepi.org/resources/guidelines_08027.cfm).

EPID Research, the principal investigator, co-investigators, the sponsor and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety. The study protocol will be registered in the ENCePP E-register of Studies (www.encepp.eu/encepp/studiesDatabase.jsp). Study results will also be published in the ENCePP E-register.

This is a register-based study and the quality of the data sources has been described in Section 9.4. Quality check will be performed for the collected data and update requests will be sent to the data holders if required. All programs used for statistical analyses will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement. Due to the study type (register study using administrative databases) on-site monitoring will not be performed.

9.9 Limitations of the research methods

It is expected that prostate cancer diagnoses have been recorded thoroughly but that some of the bone metastases diagnoses could be left unreported, due to the use of non-specific metastases diagnosis code.

However, the missingness of bone metastases diagnoses can be expected to occur completely at random, i.e., that neither the patient's current medical condition nor the potential occurrence of outcomes in the future would affect whether the diagnosed metastases were recorded to the study registers or not.

With regard to the subgroup analysis (mCRPC), only treatment information will be available to define the castration-resistant state of prostate cancer. This will likely leave out some patients that would be diagnosed as mCRPC patients based on laboratory measurements such as PSA values. The method might also include some patients into the mCRPC group that would not have this indication based on PSA values. However, treatment failure, i.e., disease progression during or after treatment should always lead to change of treatment so all disease progressions should be traceable, even if new treatments are not always specific to mCRPC.

Detailed information on prescribed medications that are dispensed by community pharmacies is available, but the level of details on medications given in a hospital may be limited. In the NPR, the use of ATC code pertaining to operation or medication given in a hospital is not mandatory. Availability of ATC code in inpatient treatments therefore likely depends on the severity of disease the treatment is for, as well as on treating hospital and doctor. This can cause under-reporting leading to misclassification that has the potential to dilute a possible difference in second cancer incidence between mCRPC and mPC patients.

Certain factors that may affect the incidence of developing cancer are not available for this study, including race, ethnicity, smoking status and other lifestyle factors. This can cause residual confounding.

Novel treatments specific to mCRPC have been introduced relatively recently and ability to identify them is likely to increase with calendar time.

The survival time after mCRPC is relatively short, typically in the range of 10 – 20 months. The expected lifetime also likely depends on the treatment, which is why death should be treated as a competing risk when investigating the incidence of second primary malignancies in mCRPC patients. In addition, it is possible that radiation-induced cancer risk manifests only after a certain latency period. Due to these reasons, the number of second cancers is likely to remain low, which reduces the precision of the estimates for incidence of second cancer. It is to be noted that all study size calculations, in particular those pertaining to the validity of using estimates from this study as an external reference, concern all second primary malignancies combined, not site-specific ones. Furthermore, when using results from this study as an external reference, uncertainty in the provided estimates should be taken into account (e.g. in the calculation of 95% CI of SIR).

The European Commission granted a marketing authorization valid throughout the European Union for Xofigo® on 13 November 2013. Therefore, it is in principle possible that patients in this study were exposed to Xofigo® during the two last months of the study. The assumption in this study that all patients are unexposed to Xofigo® is most likely justified with no impact on the study results. This will be ensured in a sensitivity analysis (see Section 9.7.4). When used as a historical comparison group for

Xofigo® REASSURE study, there is potential time bias since the REASSURE study starts in 2014.

9.10 Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

This is a fully register-based study and patients will not be contacted in any phase of the study. The study does not affect the treatment of the patients.

EPID Research will receive unidentifiable data including study identification numbers (SID) only. Patient data handled by the researchers do not include PIDs or other identification numbers, which ensures the data protection of the patients. EPID Research employees have undertaken professional secrecy agreements. The study databases will further be constructed and data will be handled according to the national data protection requirements.

The protocol will be subjected to relevant ethical committees in each country for review and approval. Register notification of the forming of study register will be sent to the relevant data protection office in Sweden.

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), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. If applicable, adverse reactions will be reported in aggregated form in the final report.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The principal investigator together with the co-investigators will write a study report. This report will be delivered to the sponsor (Bayer). The study protocol and the key results will be published in the ENCePP E-register of studies. In addition, study results will be communicated in appropriate scientific venues. The results are also planned to be published in a peer-reviewed journal following guidelines of the selected journal and STROBE checklist[22].

13. LIST OF REFERENCES

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009	20 January 2016	**ENCePP Checklist for Study Protocols** (Revision 2, amended)

Annex 2. Signature pages

Signature Page - EPID Research

Title	Incidence of second primary malignancies in prostate cancer patients with bone metastases – an observational retrospective cohort study in Sweden.
Protocol version identifier	1.0
Date of last version of protocol	20 January 2016
IMPACT study number	18105
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Research Director
Name	Pasi Korhonen
Title	Research Director
Address	EPID Research Oy, Metsänneidonkuja 12, FI-02130 Espoo.

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page – Global Pharmacovigilance and Risk Management

Title	Incidence of second primary malignancies in prostate cancer patients with bone metastases – an observational retrospective cohort study in Sweden.
Protocol version identifier	1.0
Date of last version of protocol	20 January 2016
IMPACT study number	18105
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Global Pharmacovigilance and Risk Management
Name	Cinara McCarthy
Title	Global Safety Leader
Address	Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page – Global Medical Affairs

Title	Incidence of second primary malignancies in prostate cancer patients with bone metastases – an observational retrospective cohort study in Sweden.
Protocol version identifier	1.0
Date of last version of protocol	20 January 2016
IMPACT study number	18105
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Global Medical Affairs
Name	Monica Seger-Van Tol
Title	Global Medical Expert, Oncology
Address	Global Medical Affairs Oncology, Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ, USA

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page – Global Regulatory Affairs

Title	Incidence of second primary malignancies in prostate cancer patients with bone metastases – an observational retrospective cohort study in Sweden.
Protocol version identifier	1.0
Date of last version of protocol	20 January 2016
IMPACT study number	18105
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Global Regulatory Affairs
Name	Jens Leopold
Title	Global Regulatory Strategist
Address	Bayer Pharma AG, Muellerstrasse 178, 13352 Berlin, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page – Global Epidemiology

Title	Incidence of second primary malignancies in prostate cancer patients with bone metastases – an observational retrospective cohort study in Sweden.
Protocol version identifier	1.0
Date of last version of protocol	20 January 2016
IMPACT study number	18105
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Global Epidemiology
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Title	Study Epidemiologist
Address	Bayer AB Pharmaceuticals, Solna, Sweden

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page – Global Integrated Analysis

Title	Incidence of second primary malignancies in prostate cancer patients with bone metastases – an observational retrospective cohort study in Sweden.
Protocol version identifier	1.0
Date of last version of protocol	20 January 2016
IMPACT study number	18105
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Global Integrated Analysis
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page – Global Epidemiology

Title	Incidence of second primary malignancies in prostate cancer patients with bone metastases – an observational retrospective cohort study in Sweden.
Protocol version identifier	1.0
Date of last version of protocol	20 January 2016
IMPACT study number	18105
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Bayer HealthCare

Signature Page - Global Health Economics and Outcomes Research

Title	Incidence of second primary malignancies in prostate cancer patients with bone metastases – an observational retrospective cohort study in Sweden.
Protocol version identifier	1.0
Date of last version of protocol	20 January 2016
IMPACT study number	18105
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page - Global Project Manager Non-Interventional Studies

Title	Incidence of second primary malignancies in prostate cancer patients with bone metastases – an observational retrospective cohort study in Sweden.
Protocol version identifier	1.0
Date of last version of protocol	20 January 2016
IMPACT study number	18105
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Global Project Manager Non-Interventional Studies
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____