Observational Study information

Acronym / Title	A Drug Utilization Study of Xofigo Use in Sweden
Protocol version identifier	Version 2.0
Date of last version of protocol	10- Oct-2014
IMPACT study number	17399
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	TBC
Active substance	Radium-223 dichloride
Medicinal product	Xofigo®
Product reference	BAY88-8223
Procedure number	NA
Marketing authorization holder(s)	Bayer Pharma AG, Berlin, Germany
Research question and objectives	The aim of this study is to assess the use of Xofigo including patients with a diagnosis of castration-resistant prostate cancer with bone metastasis (mCRPC) and patients in whom Xofigo may be potentially used off-label.
Country(-ies) of study	Sweden
Author	Anders Kjellman, Department of Urology, Karolinska University Hospital, Stockholm, Cell phone: +46 73 620 43 26

Marketing authorization holder

Marketing authorization holder(s)	Bayer Pharma AG, Muellerstrasse 178, 13353 Berlin, Germany
MAH contact person	Jihong Zong, MD, MS, PhD Bayer HealthCare Pharmaceuticals Inc Whippany, New Jersey 07981 USA

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

AE	Adverse Event
ADR	Adverse Drug Reaction
AR	Adverse Reaction
CRF	Case Report Form
CRPC	Castration Resistant Prostate Cancer
DMP	Data Management Plan
EC	European Commission
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
GMA	Global Medical Affairs
GPP	Good Pharmacoepidemiology Practice
GPP	Good Publication Practice
GSL	Global Safety Lead
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board

LHRH	luteinizing hormone releasing hormone
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
OS	Overall Survival
PASS	Post-Authorization Safety Study
PBRER	Periodic benefit-risk evaluation report
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible For Pharmacovigilance
SAE	Serious Adverse Event
SSE	Symptomatic skeletal events

3 Responsible parties

3.1 Sponsor / MAH

Function: Global Medical Affairs & Pharmacovigilance

Name: Michael Kayser

Title: Qualified person responsible for pharmacovigilance (QPPV)

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Function: Global Pharmacovigilance

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Title: Global Safety Leader

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Name: Jihong Zong

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Name: Gunnar Brobert

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Function: Study epidemiologist

Name: Montse Soriano-Gabarró

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Function: Global Regulatory Affairs

Name: Jens Leopold

Title: Global Regulatory Strategist

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3.2 Collaborators / Committees

This study will be conducted in collaboration with Karolinska University Hospital in Stockholm. Dr. Anders Kjellman from the Department of Urology at Karolinska University Hospital will be the project leader of this study.

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	A Drug Utilization Study of Xofigo use in Sweden
Protocol version identifier	V 2.0
Date of last version of protocol	10-Oct-2014
IMPACT study number	17399
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
Author	Anders Kjellman, Department of Clinical Science, Intervention and Technology, Karolinska Institutet
Rationale and background	▪ Prostate cancer is the second most common cancer and the sixth leading cause of cancer mortality among men worldwide. A large number of men has disseminated disease at diagnosis or has a relapse after treatment with curative intent. Bone metastases and their clinical sequelae are among the most frequent and debilitating complications in patients with castration resistant prostate cancer (CRPC). Xofigo , a well-tolerated alpha-emitter with a half-life of 11.4 days, is a calcium mimetic that naturally self-targets to areas of increased bone turnover in bone metastases. It emits high-energy alpha particles of short range (less than 100 um) that produce a potent and highly localized cytotoxic effect in the target areas. Xofigo was approved in the European Union on November 13, 2013 for the following indication: Xofigo is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases. Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman. Xofigo has not been tested on children. The purpose of this study is to evaluate use of Xofigo including potential off-label use in the post marketing setting.

Research question and objectives	The objective of this study is to evaluate the extent of potential off-label use of Xofigo in Sweden. This study will include all patients for whom a medical decision has been made to treat with Xofigo. In particular, this study is designed to evaluate the use of Xofigo in • Men with mCRPC • women. • children. • Patients with bone metastasis but having a diagnosis of other cancer than CRPC. • Patients with repeated courses of treatment or in excess of those recommended in the label.
Study design	This is a single arm descriptive observational drug utilization study of patients treated with Xofigo in Sweden.
Population	The study population are the persons receiveing treatment of Xofigo at nuclear medicine centers across Sweden during a two year period. It will consist of patients for whom a medical decision has been made to treat with Xofigo. . This study will be based on data extracted from two pre-established secondary data sources: 15 Nuclear medicine centers across Sweden and the Swedish national cancer registry.
Variables	• Gender • Age • Cancer diagnosis/Indication for treatment • Dosage level (kBq/kg), number of doses
Data sources	Two data sources will be used for the conduct of this study: 15 Nuclear medicine centers in Sweden and the Swedish National Cancer Registry The investigator will manually record the Personal Identification Numbers (PINs) for all patients treated with Xofigo at the Nuclear Medicine Centers in Sweden. The PIN is an unique identification number for all inhabitants in Sweden including information on gender and birth year. Through a record-linkage between the Nuclear Medicine Centers and the National Swedish Cancer Registry based on the individuals' PINs, information on individuals' cancer diagnosis will be confirmed. Information on

	indication for treatment, dosage level (kBq/kg) and number of doses will be obtained from the Nuclear medicine centers.
Study size	All patients receiving treatment of Xofigo at participating nuclear medicine centers in Sweden during the two year period will be included in this study. It is estimated that about 200 patients will be treated with Xofigo during this period of time.
Data analysis	This is a single arm descriptive observational drug utilization study based on secondary data collection. This study is not aimed to confirm or reject pre-defined hypotheses. Statistical analyses will be descriptive in nature. All variables will be analyzed descriptively with appropriate statistical methods.
Milestones	Start of data collection: 15 November 2014 End of data collection: 30 June 2016 Final report of study results: 01 December 2017.

5 Amendments

None.

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 and enrolment do not require amendments to the protocol. The final report will be provided 17 months after study end since there is a lag time in reporting to the Swedish cancer registry.

Table 1: Milestones

Milestone	**Planned date**
Start of data collection	15 November 2014
End of data collection	30 June 2016
Registration in the EU PAS register	01 March 2014
Update in PSUR/ PBRER	Status will be provided in corresponding with PSUR/ PBRER submission schedule

Final report of study results	01 December 2017

7 Introduction: Background and Rationale

Prostate cancer is the second most common cancer and the sixth leading cause of cancer mortality among men worldwide. A majority of cancers (approx. 70 %) are curable or do only need surveillance. Even so a large number of men has disseminated disease at diagnosis or has a relapse after treatment with curative intent.

Prostate cancer spreads predominantly to the skeleton and to local lymph nodes. Treatment with luteinizing hormone releasing hormone (LHRH) analogue is the cornerstone of treatment for advanced prostate cancer. LHRH analouges lowers the testosterone level in the body and most tumours thrive on testosterone. The effect of lowering testosterone eventually weans off and the tumour starts growing again. This is called castration-resistant prostate cancer (CRPC).

In the last few years, several new treatments for patients with CRPC has evolved. Bone metastases and their clinical sequelae are among the most frequent and debilitating complications in patients with CRPC. Bone metastases are characterized by increased osteoclast activity and are associated with significant skeletal morbidity (ie, skeletal-related events(SREs), including fractures, radiation to bone, spinal cord compression, and surgery to bone). The underlying pathophysiology of bone metastases is an increased pathological rate of bone remodeling, including increased osteoclast activity. Several drugs have been approved to prevent pain and SREs in patients with CRPC, but none of these drugs improves survival.

In the phase III trial Alpharadin in Symtomatic Prostate Cancer Patients (ALSYMPCA), 921 patients with CRPC and bone metastases were enrolled and randomized between Xofigo and placebo treatment. Xofigo, a well-tolerated alpha-emitter with a half-life of 11.4 days, is a calcium mimetic that naturally self-targets to areas of increased bone turnover in bone metastases. It emits high-energy alpha particles of short range (less than 100 um) that produce a potent and highly localized cytotoxic effect in the target areas. The trial's primary endpoint was overall survival. Secondary endpoints included time to first symptomatic skeletal events (SSE) and quality of life measures. The term SSE was used because it more precisely describes the endpoint and discriminates between an endpoint composed of only symptomatically driven components and that including asymptomatic events.

Xofigo was approved in the European Union on November 13, 2013 for the following indication: Xofigo is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases. Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman. Xofigo has not been tested on childrenThe licensed dosage of Xofigo is 50kBq (1.35 microcurie) per kg body weight given at 4 weeks interval for six injections

8 Research questions and objectives

This study will include patients for whom a medical decision has been made to treat with Xofigo.

The primary objectives in this study are:

- To estimate the use of Xofigo for men with mCRPC
- To estimate the use of Xofigo in women.
- To estimate the use of Xofigo in children.
- To estimate the use of Xofigo in patients with bone metastasis but having a diagnosis of other cancer than castration resistant prostate cancer.
- To estimate the use of Xofigo in dosage level (kBq/kg) and number of doses outside recommendations.

8.1 Secondary objective(s

Not applicable.

9 Research methods

9.1 Study design

This is a single-arm descriptive observational drug utilization study based on secondary data collection of patients treated with Xofigo in Sweden.

This study will include patients receiving treatment of Xofigo at certified nuclear medicine centers across Sweden during a two year period. It will consist of mCRPC patients and potentially some other patient groups in whom Xofigo may be used off-label including women, children, cancer patients having bone metastasis with a diagnosis other than CRPC, and patients with repeated courses of treatment or in excess of those recommended in the label. This study will be based on data extracted from two pre-established data sources: 15 nuclear medicine centers across Sweden and the Swedish National Cancer Registry.

The Personal Identification Numbers (PINs) for all patients treated with Xofigo at the 15 Nuclear Medicine Centers in Sweden will be extracted and recorded manually by the investigator. The PIN is an unique identification number for all inhabitants in Sweden including information on gender and birth year. Information on treatment indication, dosage level (kBq/kg) and number of doses will be obtained from the nuclear medicine centers. Information on if the patient is included in a clinical trial will also be obtained.

Through a record-linkage between the information provided from the Nuclear Medicine Centers and the Swedish National Cancer Registry based on the individuals' PINs, the cancer diagnosis will be confirmed.

9.1.1 Primary endpoint(s)

The primary endpoints are:

- The use of Xofigo in mCRPC
- The use of Xofigo in women.
- The use of Xofigo in children.
- The use of Xofigo in patients with bone metastasis but having a diagnosis of other cancer than mCRPC.
- The use of Xofigo in dosage level (kBq/kg) and number of doses outside recommendations.

9.1.2 Secondary endpoint(s)

Not applicable.

9.1.3 Strengths of study design

The proposed study will capture information on Xofigo utilization and potential off label use among patients receiving Xofigo in Sweden during a 2 year study period. The proposed data sources will be extracted from two pre-existing data systems, the certified nuclear medicine centers across Sweden and the Swedish National Cancer registry. This study employs a simple approach to obtain relevant data through record linkage of two secondary data sources to address the request from Health Authority. This design eliminates the potential recall bias since all data collection will be done through registers.

9.2 Setting

The study population are the persons receiveing treatment with Xofigo at nuclear medicine centers in Sweden during a two year period.

9.2.1 Inclusion criterion/criteria

Patients receiving Xofigo with data recorded at nuclear medicine centers in Sweden between 01 July 2014 and 30 June 2016 will be included in the study.

9.2.2 Exclusion criterion/criteria

Patients receiving Xofigo in a clinical trial.

9.2.3 Withdrawal

Not applicable.

9.2.4 Replacement

Not applicable

9.2.5 Representativeness

Currenly there are in total 15 nuclear medicine centers that will provide Xofigo treatment in Sweden. All these 15 nuclear medicine centers are commercially licensed and they have a close collaboration with the Oncology Department in the same hospital. This study will cover all patients receiving treatment of Xofigo at these 15 nuclear medicine centers. Therefore it is expected that this study will cover all potential Xofigo users in Sweden (highly representative) at least in the beginning of the study period. There is a chance that more centers will start treatment with Xofigo in the later part of the study period. We will add later certified centers to the study.

9.2.6 Visits

Not applicable

9.3 Variables

- Study variables will be collected from two pre-existing secondary data sources: 15 Nuclear medicine centers in Sweden and the Swedish National Cancer Registry. Study variables include patients' age, gender, cancer diagnosis/treatment indication, dosage level (kBq/kg) and number of doses.

9.3.1 Variables to determine the primary endpoint(s)

The variables for primary objectives are:

- Gender
- Age
- Indication for treatment (cancer diagnosis)
- Dosage level (kBq/kg) and number of doses

9.3.2 Variables to determine the secondary endpoint(s)

Not applicable.

9.3.3 Demography

For demographic / socio-demographic assessment, the following data will be recorded:

- Year of birth
- Gender

9.3.4 Co-morbidities (medical history, concomitant diseases)

Not applicable

9.3.5 Prior and concomitant medication

Not applicable

9.3.6 Exposure / treatment

The dosage level and the number of doses..

9.3.7 Assessment of therapy

Not applicable.

9.4 Data sources

Two pre-existing secondary data sources will be used for the conduct of this study: 15 nuclear medicine centers in Sweden and the Swedish National Cancer Registry

Investigators will collects data of exposed patients from 15 nuclear medicine centers. Information extracted from the nuclear medicine centers will be linked with Swedish National Cancer Registry via the PINs. Each patient will be identified by a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the investigator is able to identify the patients based on the patient identification code. It has been shown that the prostate cancer diagnosis in The Swedish National Cancer Registry has a completeness of 98% .

9.5 Study Size

The study size is depending on the market penetration of the product. It's expected that approximately 200 CRPC patients will receive Xofigo in Sweden in a two year period. The study is population based and should cover all patients who will receive Xofigo from all nuclear centers that are commercially licensed in Sweden (15 nuclear centers so far). Under the circumstances that the number of study sites or subjects are limited, the current study can be considered for an extension of another year (conditioning on that the market penetration is favorable). If additional nuclear centers become commercially licensed at a later time, they can be considered to be added to this study when it's necessary. The estimated sample size will be updated and communicated to the Agency in relation to PSUR/PBRER reporting schedule. Alternatively, a similar study in another European country is under evaluation. Whether such a study is feasible would depend on results from the feasibility assessment.

9.6 Data management

STATA 13.1 will be used as software for statistical analysis (this is the standard stastistical package used at the Karolinska Institutet, Sweden). Paper-based CRF will be used to record PINs. Data will be entered into the database twice by different persons to identify potential human errors. Data will be matched with information from the Swedish National Cancer Registry. In case of non-match, the CRF will be reviewed manually. Information on the database is available upon request.

Information on quality control are referred to section 9.8.

9.7 Data analysis

9.7.1 Statistical considerations

Statistical analyses will be of descriptive nature. The study is not aimed to confirm or reject pre-defined hypotheses.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Patients receiving at least one dose of Xofigo will be included in the analysis. Whenever possible, Data will be stratified by subgroups (e.g. age, gender).

Sample size and disposition information by analysis time point will be displayed in a frequency table.

9.8 Quality control

9.8.1 Data quality

All variables will be recorded in a standardized CRF. Data will be entered twice by different persons in the EDC to identify errors of typing. After data entry, missing or implausible data will be queried and the data will be validated. A check for multiple documented patients will be done. Data will be matched with information from the Swedish National Cancer Registry. In case of non-match investigators will review the CRF manually.

National and international data protection laws as well as regulations on observational studies will be followed.

9.8.2 Quality review

Source data verification will be conducted among a subset of patients randomly selected (at least 10 % of all sites/patients). The purpose of this validation process is to review the documented data for completeness and plausibility, adherence to the study protocol, and verification with source documents. It will be carried out by research staff at our institution with education in study monitoring.

9.8.3 Storage of records and archiving

The data will be stored inside firewalls on campus of Karolinska Institutet, in locked rooms, as established in the legal agreement between the Karolinska Institutet and Bayer Healthcare.

9.8.4 Certification/qualification of external parties

Not applicable

9.9 Limitations of the research methods

There is a risk of missing data if the nuclear medicine centers does not register every patient receiving Xofigo treatment. This risk can be reduced by site visits and a good communication plan during the

research project. There is a risk that communication with the nuclear medicine centers could influence prescribers' decisions or behavior. Diagnosis of the treated patients will be confirmed by information from the Swedish National Cancer Registry. The Swedish National Cancer Registry is of good quality but has a lag time period to include the necessary information. Therefore, the investigators have extended the time for completing the final report to 17 month after the study ends.

9.10 Other aspects

10 Protection of human subjects

10.1 Ethical conduct of the study

This study is an observational study where Xofigo is prescribed and administered in routine clinical practice setting. There is no assignment of a patient to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used to analyze the collected data. This study has no ethical concern.

10.2 Regulatory authority approvals/authorizations

ICH-GCP guidelines will be followed whenever possible. Good Pharmacoepidemiology Practices[4] will be followed for the conduct of this study. Recommendations given by other organizations will be followed as well (e.g. EFPIA[2], ENCePP[3]).

In addition, the guidelines on good pharmacovigilance practices (GVP[5, 6]) will be followed.

10.3 Independent ethics committee (IEC) or institutional review board (IRB)

Documented approval from appropriate IECs/IRBs will be obtained for all participating centers prior to study start.

10.4 Patient information and consent

An approval from IEC is in accordance with regulations and investigators will seek ethical permit without patient consent given that the study is based on secondary data collection and the IEC usually approve waiver from informed consent in this type of study. The patients will remain anonymous to the sponsor.

10.5 Patient insurance

In this study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study

related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the investigators and, respectively, the institutions involved provide sufficient protection for both patient and investigator. No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10.6 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names will not be supplied to the sponsor. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the investigator.

11 Management and reporting of adverse events/adverse reactions

According to the new European Pharmacovigilance Legislation and Guidelines on Good Pharmacovigilance Practices (GVP), individual reporting of adverse reactions is not required for observational studies based on secondary data collection*. Reports of adverse events / reactions should only be summarised in the observational study report, where applicable.

Based on this, aggregated data on adverse events/adverse reactions which have been identified during the conduct of this study will be reported in the final study report.

*Observational studies based on secondary data collection are those involving review of narrative documents from medical charts or electronic medical records, or administration of questionnaires to health care professionals to be completed based on review of medical charts or electronic medical records.

11.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or

disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.[7]

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- An effect of the comparator product
- An effect related to off-label use or occupational exposure
- Medication error, overdose, product abuse, product misuse or product dependency itself, as well as any resulting event
- Product exposure via mother/ father (exposure during conception, pregnancy, childbirth and breastfeeding)
- An effect related to lack of product effect
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)

As mentioned above no causal relationship with a product is implied by the use of the term “adverse event”.

Hospitalizations will not be regarded as adverse events, if they:

- were planned before inclusion in the study,
- are ambulant (shorter than 12 hours),
- are part of the normal treatment or monitoring of the studied disease, i.e. they were not due to a worsening of the disease.

An Adverse Reaction (AR) is defined as a response to a medicinal product which is noxious and unintended. An Adverse Drug Reaction (ADR) is any AE judged as having a reasonable suspected causal relationship to Xofigo.

A drug related adverse event is any adverse event judged either by the investigator or by the company as having a reasonable suspected causal relationship to [treatment]. It is defined as a response to a drug, which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

An Adverse Event is serious if it:

- Results in death
- Is life-threatening

- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an other important medically important serious event.

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the Serious Adverse Event. The one exception to this rule is 'sudden death' where no cause has been established. In this instance, 'sudden death' should be regarded as the Adverse Event and 'fatal' as its reason for being 'serious'.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be automatically considered as Serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours, OR
- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), OR
- The admission is not associated with an adverse event (i.e. social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a 'serious Adverse Event' when: i)The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery; or ii) The father was exposed to a medicinal product prior to conception.

Other medically important serious event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition.

Important medical events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

11.2 Management and reporting

In this study, based on secondary data collection, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation.

Agregated data on adverse events/adverse reactions which have been identified during the conduct of this study will be reported in the final study report.

11.3 Evaluation

Evaluation of individual adverse event reports is not applicable for this study, based on secondary data collection.

12 Plans for disseminating and communicating study results

This study will be registered at “www.clinicaltrials.gov". Results will be disclosed in a publicly available database within the standard timelines.

The study will be registered on the EU PAS register (currently the ENCePP reg) and other registers or databases, as appropriate.

Progress reports will be provided together with each PBRER/PSUR to the competent authorities on yearly basis.

The results of this study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the sponsor. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines[8], STROBE[9]). No individual investigator may publish on the results of this study, or their own patients, without prior approval from the sponsor.

13 List of references

[1] Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council. Official Journal of the European Union. 20.06.2012.

[2] EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals, EFPIA, October 2007.

[3] ENCePP guide on methodological standards in pharmacoepidemiology. European Medicines Agency. EMA/95098/2010. Revison 2, 18 June 2013.

[4] Guidelines for good pharmacoepidemiology practices (GPP). Andrews EB, et al. Pharmacoepidemiol Drug Saf. 2008 Feb;17(2):200-8.

[5] Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products; EMA/873138/2011, 22 June 2012; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf

[6] Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies; EMA/330405/2012, 9 July 2012; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf

[7] ICH Harmonized Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2D), November 2003.

[8] Graf C, Battisti WP, Bridges D, Bruce-Winkler V, Conaty JM, Ellison JM, Field EA, Gurr JA, Marx ME, Patel M, Sanes-Miller C, Yarker YE; International Society for Medical Publication Professionals. Research Methods & Reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines. BMJ. 2009; 339: b4330..

[9] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE-Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies. J Clin Epidemiol. 2008; 61(4): 344-9.

Annex 1. List of stand-alone documents

None.

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009

Study title: A Drug utilization Study of Xofigo use in Sweden

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	x	☐	☐	
1.1.2 End of data collection[2]	x	☐	☐	
1.1.3 Study progress report(s)	☐	☐	x	
1.1.4 Interim progress report(s)	☐	☐	x	
1.1.5 Registration in the EU PAS register	x	☐	☐	
1.1.6 Final report of study results.	x	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	x	☐	☐	
2.1.2 The objective(s) of the study?	x	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	x	☐	☐	

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☐	☐	x	
2.1.5 If applicable, that there is no *a priori* hypothesis?	x	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	x	☐	☐	
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	x	☐	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	x	

Comments:

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

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	x	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	x	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	x	☐	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the product?	☐	☐	x	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	x	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	x	☐	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	x	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	x	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	x	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	x	☐	☐	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	x	☐	☐	
8.1.3 Covariates?	x	☐	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, product quantity, dose, number of days of supply prescription, daily dosage, prescriber)	x	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	x	☐	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	x	☐	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	x	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	x	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	x	☐	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	x	☐	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☐	x	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	x	
10.2 Is the choice of statistical techniques described?	x	☐	☐	
10.3 Are descriptive analyses included?	x	☐	☐	
10.4 Are stratified analyses included?	☐	☐	x	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	x	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	x	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	x	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	x	☐	☐	
11.3 Are methods of quality assurance described?	x	☐	☐	
11.4 Does the protocol describe possible quality issues related to the data source(s)?	x	☐	☐	
11.5 Is there a system in place for independent review of study results?	☐	x	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☐	x	
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	x	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	x	
12.3 Does the protocol address other limitations?	x	☐	☐	

Comments:

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

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	x	☐	☐	

Comments:

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

Comments:

Name of the main author of the protocol: Anders Kjellman

Date:10-Oct-2014

Signature: _____

Annex 3. Additional information.

None.

Annex 4. Signature pages

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Title	A Drug Utilization Study of Xofigo use in Sweden
Protocol version identifier	Version 2.0
Date of last version of protocol	10-Oct-2014
IMPACT study number	17399
Study type	☒ PASS ☐ non PASS
EU PAS register number	TBC
Active substance (medicinal product)	Radium-223 dichloride
Marketing authorization holder(s)	Bayer Phmarma AG, Berlin, Germany

Function	Global Medical Affairs & Pharmacovigilance
Name	Michael Kayser
Title	Qualified person responsible for pharmacovigilance (QPPV)
Address	Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany

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

Date, Signature: _____,
_____

Bayer HealthCare

Signature Page - Study Medical Expert

Title	A Drug Utilization Study of Xofigo use in Sweden
Protocol version identifier	Version 2.0
Date of last version of protocol	10-Oct-2014
IMPACT study number	17399
Study type	☒ PASS ☐ non PASS
EU PAS register number	TBC
Active substance (medicinal product)	Radium-223 dichloride
Marketing authorization holder(s)	Bayer Pharma AG, Berlin, Germany

Function	Global Pharmacovigilance
Name	Nils Opitz
Title	Global Safety Leader (GSL)
Address	Bayer Pharma AG, Muellerstrasse 178, 13353 Berlin, Germany

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

Date, Signature: _____,
_____

Bayer HealthCare

Signature Page - Study Conduct Responsible

Title	A Drug Utilization Study of Xofigo use in Sweden
Protocol version identifier	Version 2.0
Date of last version of protocol	10-Oct-2014
IMPACT study number	17399
Study type	☒ PASS ☐ non PASS
EU PAS register number	TBC
Active substance (medicinal product)	Radium-223 dichloride
Marketing authorization holder(s)	Bayer Pharma AG, Berlin, Germany

Function	Study conduct responsible
Name	Jihong Zong
Title	Director, Global Epidemiology
Address	Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981, USA

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

Date, Signature: _____,
_____

Bayer HealthCare

Signature Page - Study Epidemiologist

Title	A Drug Utilization Study of Xofigo use in Sweden
Protocol version identifier	Version 2.0
Date of last version of protocol	10-Oct-2014
IMPACT study number	17399
Study type	☒ PASS ☐ non PASS
EU PAS register number	TBC
Active substance (medicinal product)	Radium Ra 223 dichloride
Marketing authorization holder(s)	Bayer Pharma AG, Berlin, Germany

Function	Study Epidemiologist
Name	Gunnar Brobert
Title	Director, Global Epidemiology
Address	Bayer AB Pharmaceuticals, Solna, Sweden

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

Date, Signature: _____,

_____

Bayer HealthCare

Signature Page - Study Epidemiologist

Title	A Drug Utilization Study of Xofigo use in Sweden
Protocol version identifier	Version 2.0
Date of last version of protocol	10-Oct- 2014
IMPACT study number	17399
Study type	☒ PASS ☐ non PASS
EU PAS register number	TBC
Active substance (medicinal product)	Radium-223 dichloride
Marketing authorization holder(s)	Bayer Pharma AG

Function	Study Epidemiologist
Name	Montse Soriano-Gabarró
Title	Head, Global Epidemiology
Address	Bayer Pharma AG, Muellerstrasse 178, 13353 Berlin, Germany

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

Date, Signature: _____,
_____

Signature Page – Regulatory Responsible

Title	A Drug Utilization Study of Xofigo Use in Sweden
Protocol version identifier	Version 2.0
Date of last version of protocol	10-Oct-2014
IMPACT study number	17399
Study type	☒ PASS ☐ non PASS
EU PAS register number	TBC
Active substance (medicinal product)	Radium-223 dichloride
Marketing authorization holder(s)	Bayer Healthcare AG, Berlin, Germany

Function	Global Regulatory Affairs
Name	Jens Leopold
Title	Global Regulatory Strategist
Address	Bayer Pharma AG, Muellerstrasse 178, 13353 Berlin, Germany

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

Date, Signature: _____,
_____