Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	A Drug Utilization Study of Xofigo Use in Sweden
Report version and date	V 2.0 21 NOV 2018
Study type / Study phase	Phase IV PASS ☒ YES Joint PASS: ☐ YES ☒NO
EU PAS register number	EUPAS 8494
Active substance	Radium-223 dichloride
Medicinal product	Xofigo®
Product reference	BAY88-8223
Procedure number	*NA*
Study Initiator and Funder	Bayer AG, Germany Muellerstr. 178 D-13353, Berlin, Germany
Research question and objectives	The aim of this study was to assess the use of Xofigo including patients with a diagnosis of castration-resistant prostate cancer with bone metastasis (mCRPC) and patients for whom Xofigo may be potentially used off-label.
Country of study	Sweden
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, Germany
MAH contact person	[redacted]

Confidentiality statement:

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1. Abstract

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Acronym/Title	A Drug Utilization Study of Xofigo Use in Sweden
Report version and date **Author**	V 2.0 21 NOV 2018 [redacted]
Keywords	Xofigo, off-label use, prostate cancer
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 have disseminated disease at diagnosis or have 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, an alpha-emitter is a calcium mimetic that self-targets areas of increased bone turnover in bone metastases. It emits high-energy alpha particles of short range that produce a highly localized cytotoxic effect in the target areas. Xofigo was approved in the European Union on November 13, 2013 for the treatment of adults with CRPC, symptomatic bone metastases and no known visceral metastases. Xofigo is contraindicated in women who are or may become pregnant. Xofigo has not been tested on children. The purpose of this study was to evaluate use of Xofigo including potential off-label use in a post marketing setting.
Research question and objectives	The objective of this study was to evaluate the extent of potential off-label use of Xofigo, in Sweden. The study included patients for whom a medical decision had previously been made to treat with Xofigo in Sweden. The study objectives were: • To estimate the use of Xofigo in 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.
Study design	This was a single-arm descriptive observational drug utilization study based on secondary data collection of patients treated with Xofigo in Sweden.
Setting	The study population were patients receiving treatment with Xofigo at nuclear medicine centers in Sweden during a two-year period.
Subjects and study size, including dropouts	Patients receiving Xofigo with data recorded at nuclear medicine centers in Sweden between 01 July 2014 and 30 June 2016 were included in the study. Patients participating in clinical trials were excluded. Data from 12 out of 17 centers treating patients in Sweden during the time period was obtained.
Variables and data sources	Study variables included patients' age, gender, cancer diagnosis/treatment indication, dosage level (kBq/kg) and number of doses.
Results	A total of 310 patients were included in the study. Of these, 306 (98,7%) had mCRPC. Four (1,29%) patients were treated for an indication other than mCRPC, 2 with breast cancer, 1 with lung cancer, and 1 with osteosarcoma. All these patients had bone metastasis. One patient in the mCRPC group had both skeletal and visceral metastasis at time of treatment. Two (0,64%) women were treated with Xofigo, both with breast cancer. No children (under 18 years) were treated with Xofigo. No patient was treated with more than 6 doses. 1.7 % of evaluable doses were given either with less than 90% of planned dose or more than 110% of planned dose.
Discussion	In this study of contemporary Xofigo use in Sweden, a low rate of off-label use and no use of children (<18 yrs) were observed
Marketing Authorization Holder(s)	Bayer AG, Germany

Names and affiliations of principal investigators	[redacted]

2. List of abbreviations

AD	Associated Document
AE	Adverse Event
AG	Aktiengesellschaft
ATC	Anatomical Therapeutic Chemical (Classification System)
CFR	Code of Federal Regulations
CMD	Country Medical Director
CRF	Case Report Form
CRO	Contract Research Organization
DMP	Data Management Plan
EC	European Commission
EDC	Electronic Data Capture
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food & Drug Administration Amendments Act
GCP	Good Clinical Practice
GPP	Good Publication Practice
GPV	Global Pharmacovigilance
GSL	Global Safety Leader
GVP	Good Pharmacovigilance Practice
HEOR	Health Economics and Outcomes Research
ICD	International Classification of Diseases
ICH	International Conference of Harmonization
ID	Identifier
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
IRB	Institutional Review Board
IT	Information Technology
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
N/A	Not Applicable
NNH	Number Needed to Harm
OM	Operational Manual

OS	Observational Study
OSP	Observational Study Protocol
OSR	Observational Study Report
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PBRER	Periodic benefit-risk evaluation report
PMCF Study	Post Market Clinical Follow-up Study
PPS	Per Protocol Set
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEAE	Treatment-Emergent Adverse Events
WHO DD	World Health Organization Drug Dictionary

3. Investigators

This study was conducted in collaboration with Karolinska University Hospital and Karolinska Institutet in Stockholm. [redacted]

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5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual Date	Comments
Start of data collection	01 JUL 2014	01 JUL 2014	
End of data collection	30 JUN 2016	30 JUN 2016	
Registration in the EU PAS register	01 MAR 2014	01 MAR 2014	
Final report of study results	01 DEC 2017	01 DEC 2017	
Amended Final report incorporating validation of cancer diagnosis	01 DEC 2017	21 NOV 2018	Validation of cancer diagnosis could not be completed as initially planned due to a delay in availability of Swedish National Cancer Registry data. Study report amendment incorporating validation of cancer diagnosis, following availability of Cancer Registry data.

6. Rationale and background

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 analogues lowers the testosterone level in the body and most tumors thrive on testosterone. The effect of lowering testosterone eventually weans off and the tumors starts progressing again. This is called castration-resistant prostate cancer (CRPC).

In the last few years, several new treatments for patients with mCRPC have been developed. Bone metastases and their clinical sequelae are among the most frequent and debilitating complications in patients with CRPC. Bone metastases in prostate cancer are characterized by increased osteoblast and osteoclast activity, leading to an increased pathological rate of bone remodeling. Bone metastases are associated with significant skeletal morbidity (i.e., skeletal-related events (SREs), including fractures, radiation to bone, spinal cord compression, and surgery to bone). Several drugs have been approved to prevent pain and SREs in patients with CRPC, but none of these drugs improve 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, 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 children. The licensed dosage of Xofigo is 55kBq (1.35 microcurie) per kg body weight given at 4 weeks interval for six injections

7. Research question and objectives

This study included patients for whom a medical decision had been made to treat with Xofigo.

The primary objectives in this study were:

- 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.

Note: It had been anticipated, as part of this study, to confirm the cancer diagnosis leading to Xofigo treatment through the validation of cancer outcomes using information from the Swedish National Cancer Registry. Given delays by health authorities in releasing cancer register data, such confirmation of events has not been possible for inclusion in the study report V 1.0 dated 1 DEC 2017. An amendment has been incorporated 21 NOV 2018 (study report V 2.0) following access to Swedish National Cancer Registry in 2018.

8. Amendments and updates

This final report has been amended following confirmatory information on cancer diagnosis from the Swedish National Cancer Registry in 2018. Validation of cancer diagnosis is now incorporated in the final study report. Other updates are also incorporated in the report as shown below:

Nr.	Date	Section of Final Report	Amendment or Update	Reason
1	21 NOV 2018	Document version	V 2.0 21 NOV 2018	Study report version change due to Amendment
2	21 NOV 2018	Page 11, QPPV name	Justin Daniels	Update: Change in QPPV name and contact address
3	21 NOV 2018	Page 11, Pharmacovigilance (PV) study team member	Gustavo Borghesi	Update: Change in PV representative and contact address
	21 NOV 2018	Page 12, Regulatory Affairs (RA) study team member	Joerg Frauenschuh	Update: Change in RA representative and contact address
	21 NOV 2018	Page 12, Medical Expert (ME) study team member	Per Sandstrom	Update: Change in ME title and contact address
	21 NOV 2018	Page 12, Milestones table	Milestones table updated	Milestones table updated incorporating validation of cancer diagnosis
	21 NOV 2018	Page 14. Rephrasing of “note”	Paragraph updated describing plans for validation of cancer diagnosis as part of this amendment	Note updated incorporating validation of cancer diagnosis

	21 NOV 2018	Page 14: Section 8. Amendments and Updates	Section updated. Table incorporated including amendments and updates	Section updated incorporating reference to validation of cancer diagnosis
	21 NOV 2018	Page 17. Section 9 Bias	Section updated	Section updated incorporating reference to validation of cancer diagnosis
	21 NOV 2018	Page 22, Addition of section 10.5: Validation of Cancer diagnosis	Section updated incorporating results from validation of cancer diagnosis following availability of Swedish National Cancer Registry data	Section updated incorporating validation of cancer diagnosis
	21 NOV 2018	Page 24: Section Limitations	Section updated incorporating results from validation of cancer diagnosis following availability of Swedish National Cancer Registry data	Section updated incorporating reference to validation of cancer diagnosis

9. Research methods

9.1 Study design

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

The study included patients receiving treatment of Xofigo at certified nuclear medicine centers across Sweden during a two-year period. It consisted of mCRPC patients and other patient groups in whom Xofigo had been used off-label. This study was based on data extracted from 12 nuclear medicine centers across Sweden.

The Personal Identification Numbers (PINs) for all patients treated with Xofigo at the 12 participating Nuclear Medicine Centers in Sweden were extracted and recorded manually by the investigator. The PIN is an unique identification number for all inhabitants in Sweden that is linked to basic patient information such as gender and birth year. Information on treatment indication, dosage level (kBq/kg) and number of doses were obtained from the nuclear medicine centers. Information on if the patient was included in a clinical trial was also obtained and these patients excluded from the database.

The study captured information on Xofigo utilization and potential off label use among patients receiving Xofigo in Sweden during a 2-year study period. This design eliminates the potential recall bias since all data collection will be done through registries.

9.2 Setting

The study population was patients receiving Xofigo treatment at nuclear medicine centers in Sweden during a two year period. For the purposes of this study, we were able to gain access to 12 out of 17 potential nuclear medicine treating centers in Sweden. Patients receiving Xofigo treatment at the 12 nuclear medicine centers in Sweden between 01 July 2014 and 30 June 2016 were included in the study. The data collection process started on May 2015 and ended 05 Oct 2017.

9.3 Subjects

All patients included in this study received Xofigo treatment at the nuclear medicine centers between 01 July 2014 and 30 June 2016. We excluded patients participating in clinical trials. In most centers, these patient's data were excluded before we received the data, which made it hard for us to estimate the original number of patients, prior to exclusion. One center gave us all the initial data, with 7 out of 54 patients participating in a clinical trial. Other than this center, no exclusion criteria was used. We scrutinized medical charts and treatment protocols at the centers to get full inclusion of patients. Since 5 nuclear medicine centers did not share their data, we did not get full coverage of all treatment in Sweden during the period. We estimate that we missed approximately 30 % of all treated patients in Sweden during this time period.

9.4 Variables

The variables for primary objectives was:

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

9.5 Data sources and measurement

After receiving approval by the ethical board for the conduct of this study, we contacted each nuclear medicine center treating patients with Xofigo in Sweden. In most locations in Sweden, there is an oncology or urology department prescribing the treatment for the patient and the treatment is then administered at the nuclear medicine center. The information on gender, age, weight and indication for treatment was usually provided by the department prescribing the drug and the information also came from the electronic health records. Information on dosage level and number of doses was obtained from the nuclear medicine centers either from treatment cards or from electronic health records.

The information was entered in the database twice by a research nurse. Since we visited most centers on multiple occasions the earlier recorded data was also double-checked by another research nurse and the data reentered in the database. In this way, we validated the data. We had planned to

do this validation for at least 10% of the patients but since we changed the research nurse during the project it was done for approximately 80% of the patients.

9.6 Bias

To reduce the risk of missing data, we stood in close contact with the participating nuclear medicine centers and made several site visits. We do not believe this influenced their treatment decisions. We had planned to confirm the cancer diagnosis leading to treatment by information from the Swedish National Cancer Registry but due to delays by health authorities in releasing cancer register data we had not time to do this for the initial study report (V 1.0 1 DEC 2017). An amendment has been created (V2.0 21 NOV 2018) incorporating validation of cancer diagnosis

9.7 Study size

We projected that the study size would be dependent on the market penetration of the product. We noticed that there were only 8 patients registered during the first 6 months of the study period (of note, Bayer experienced a stock out of Xofigo from October 2014 to early 2015). Prescription of Xofigo became more and more common during the study period. We had projected to include 200 patients in the study plan but were able to find 310 patients. We did not get access to all centers but added new centers as they became licensed to treat patients with Xofigo.

9.8 Data transformation

Gender was recorded as male or female and age was recorded by birth date. Indication for treatment was recorded in full text and we also added a variable of mCRPC (YES/NO). Number of doses were recorded continuously for each patient starting at 1. We entered treatment data on dose for each separate treatment.

9.9 Statistical methods

Statistical analyses are of descriptive nature. The study was not aimed to confirm or reject pre-defined hypotheses.

All variables were analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by sample statistics.

Patients receiving at least one dose of Xofigo were included in the analysis. Patients receiving Xofigo in clinical studies were excluded from the study.

9.9.1 Main summary measures

Frequency table for different variables with percentage.

9.9.2 Main statistical methods

Descriptive statistics

9.9.3 Missing values

No imputing of missing values was done

9.9.4 Sensitivity analyses

Not applicable

9.9.5 Amendments to the statistical analysis plan

Not applicable

9.10 Quality control

All variables were recorded in a standardized Case Report Form (CRF). Data was entered twice in the electronic data capture (EDC) to identify clerical errors from typing. After data entry, missing or implausible data was queried. A check for multiple documented patients was done.

To validate the data we had different research persons collect the data at different time points. Since we visited the treatment centers at several occasions we had new research persons recollect earlier collected data. This procedure was done for approx. 80% of the data.

National and international data protection laws as well as regulations on observational studies was followed. All data for the study was stored in secure location at Karolinska Institutet.

10. Results

10.1 Participants

At the beginning of the study period, there were 15 nuclear medicine centers administering Xofigo treatment in Sweden. During the study period, three more centers were opened and licensed. One of these centers did not treat any patient during the study period. Of the 17 possible treatment centers, we got access to 12 (**Figure 1**).

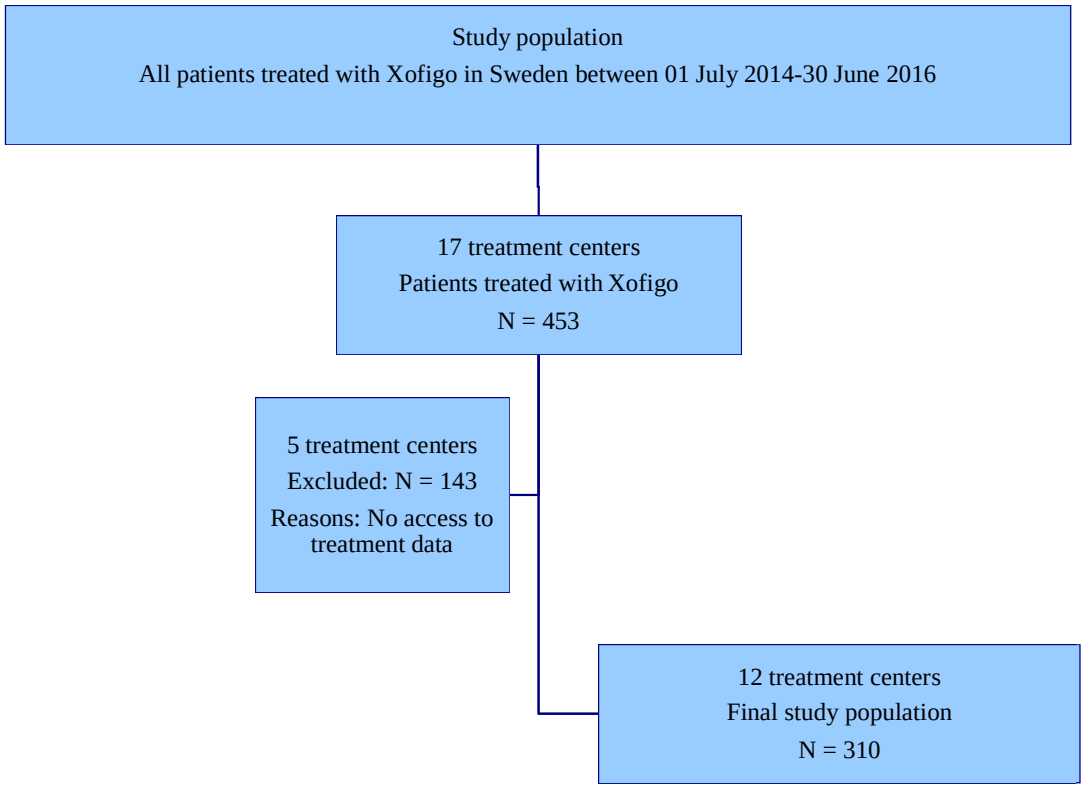

Figure 1: Patient recruitment by treatment sites

10.2 Descriptive data

The inclusion from each nuclear medicine center is shown in **table 1**

Nuclear Medicine Center	**Number of patients**
Skånes Universitetssjukhus, Lund-Malmö	**57**
Sahlgrenska Universitetssjukhuset, Göteborg	**51**
Norrlands Universitetssjukhus, Umeå	**47**
Södersjukhuset, Stockholm	**41**
Västmanlandssjukhus, Västerås	**21**

Södra Älvsborgssjukhus	**21**
Karolinska Universitetssjukhuset, Stockholm	**20**
Mälarsjukhuset, Eskilstuna	**16**
Centralsjukhuset, Växjö	**13**
Länssjukhuset Sundsvall-Härnösand, Sundsvall	**11**
Länssjukhuset Kalmar, Kalmar	**7**
Universitetssjukhuset Örebro, Örebro	**5**

Table 1: List of participating centers with number of patients

10.3 Outcome data

See 10.4

10.4 Main results

Of the 310 patients, 306 had diagnosis of metastatic Castration Resistance Prostate Cancer. 4 patients had other diagnosis (**Table 2**).

Indication	**n (%)**
mCRPC	**306 (98.7)**
Other	**4 (1.29)**

Table 2: Use of Xofigo in men with metastasized Castration Resistant Prostate Cancer (mCRPC)

Of the 310 patients, 308 were male and 2 female (**Table 3**).

Gender	**n (%)**
Male	**308 (99.4)**
Female	**2 (0.65)**

Table 3: Use of Xofigo by gender

We could not find any treatment of patients < 18 years old (**Table 4**). The youngest patient was 32 years old at start of treatment and he had an osteosarcoma. The median age in the cohort was 73.4 years (range 32.5-94.8).

Age	**n (%)**
>18 years old	**310 (100)**
< 18 years old	**0**

Table 4: Use of Xofigo in children (<18 years old)

As mentioned earlier 4 patients with another diagnosis than mCRPC was treated. Their diagnosis is shown in **Table 5**.

Indication	**n (%)**
mCRPC	**306 (98.7)**
Breast cancer	**2 (0.65)**
Lung cancer	**1 (0.32)**
Osteosarcoma	**1 (0.32)**

Table 5: Use of Xofigo in other indication than mCRPC

We could not find any treatment with excess of 6 doses (**Table 6**).

Number of treatment doses	**n (%)**
> 6 doses	**0**
≤ 6 doses	**310 (100)**

Table 6: Use of Xofigo in excess of 6 doses

We defined a too low or too high dose as a dose less than 90% or more than 110% of the expected, respectively. This data must be interpreted with some caution, however, because different nuclear

medicine centers had different routines of recording the weight of the patient. Some had a new weight registered before each treatment and others just registered weight at the beginning of the treatment period. Of the given doses 1.7 % were given with a too low or high dose from our definition (**Table 7**).

Dose	< 90 % or > 110 % (%)	< 90 % (%)	>110 % (%)	Total number patients
1	**3 (1.0)**	**0**	**3 (1.0)**	**310**
2	**7 (2.5)**	**6 (2.1)**	**1 (0.4)**	**281**
3	**4 (1.6)**	**1 (0.4)**	**3 (1.2)**	**244**
4	**5 (2.6)**	**1 (0.5)**	**4 (2.1)**	**190**
5	**2 (1.3)**	**0**	**2 (1.3)**	**154**
6	**1 (0.9)**	**0**	**1 (0.9)**	**112**
All	**22 (1.7)**	**8 (0.6)**	**14 (1.1)**	**1291***

- **Total of 310 unique patients were given 1 to 6 doses**

Table 7: Use of Xofigo in doses outside recommendations

10.5 Validation of cancer diagnosis

By linking the treated patients to the national cancer registry, we got information on all cancer diagnosis for the patients from 1990 onwards. Of the 306 patients with mCRPC, three patients did not have a prostate cancer diagnosis in the registry. When looking in the medical charts for the patients we could however see that they did have a mCRPC-diagnosis. The first patient was diagnosed 1988 before our extract from the cancer registry, the second had his diagnosis from a lymph node metastasis and the third from bone biopsy of a bone metastasis thus preventing them from being entered in the prostate cancer registry.

For the four patients with other diagnosis, one, the patient with osteosarcoma was not found in the Swedish cancer registry. In the charts we could see that he was diagnosed in Norway and later moved to Sweden.

Overall, in this study we observed a concordance of 98.7 % between the cancer registry and our cancer registration

10.6 Safety data (Adverse events/adverse reactions)

This is an observational study based on secondary data collected by reviewing electronic medical records and individual reporting of adverse reactions were not collected as part of the study. To assess safety data in this cohort would require a study protocol with other objectives and variables and also a new ethical application.

11. Discussion

11.1 Key results

The key results were that we found a very low off-label use of Xofigo in other diagnosis than mCRPC. The use in women was also low and no use in patients < 18 years old was found. No patient received an excess number of doses and a low percentage of doses was given in abnormal dosage.

11.2 Limitations

We could not get access to all treatment centers in Sweden. The centers not participating were from different parts of Sweden and we do not see any reason that the drug use pattern would be different in these sites.

We stood in close contact with the centers and made several site visits to most of them to be sure to not miss any patients. There is a risk that communicating so thoroughly that the study was ongoing could have changed the decisions or the behavior of the treating physicians. However no such signals have been given to us.

We had planned to validate diagnosis leading to treatment by information from the Swedish National Cancer Registry but since access to the cancer registry data took more time than anticipated we did not have time to do this for the initial study report (V 1.0 1 DEC 2017). An amendment has been created (V2.0 21 NOV 2018) incorporating validation of cancer diagnosis Following validation of cancer diagnosis we were able to validate 98.7 % of the cancer diagnoses.

11.3 Interpretation

Our interpretation is that Xofigo has a low off-label use in this contemporary study. We could not get access to data from all centers and this limits the study. However, since treatment traditions and implementation of new treatments follow a well-known pattern in Sweden, we do not think that this hampers our conclusion.

11.4 Generalizability

The study has a high generalizability for Sweden and other countries with a similar health care system organized in a similar way. In Sweden Oncology physicians have the possibility to prescribe Xofigo in off label situations under their own responsibility. All costs of prescribed oncology drugs are financed by the obligatory tax based common National health insurance, but the costs have to be financed by the clinical budget where the prescribing physician works.

12. Other information

13. Conclusion

The study gives evidence for a very low percentage of off-label use of Xofigo in Sweden. The treatment of children was non-existing. The treatment was not shown to be given in excessive number of dose and in the right dosage for a high percentage of treatments.

14. References

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Appendices

Annex 1: List of stand-alone documents

Table 2: List of stand-alone documents

Document Name	**Final version and date (if available)***
Investigator list	24 OCT 2017
CRF	24 OCT 2017
Detailed list of variables	24 OCT 2017

Annex 2 Additional information

Not applicable

Annex 3 Signature Pages

Signature Page – Principal Investigator

Title	A Drug Utilization Study of Xofigo Use in Sweden
Report version and date	V2.0 21 Nov 2018
IMPACT study number	17399
Study type / Study phase	Phase IV PASS ☒ YES Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS1549
Medicinal product / Active substance	Xofigo®/ Radium-223 dichloride
Study Initiator and Funder	Bayer AG, Germany Muellerstrasse, 178 D-13353, Berlin Germany
Function	[redacted]
Name	[redacted]
Title	Department of Urology, Karolinska University Hospital, CLINTEC
Address	K55, Karolinska Institutet, 141 86 Stockholm

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

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – Qualified Person Responsible for Pharmacovigilance

Title	A Drug Utilization Study of Xofigo Use in Sweden
Report version and date	V2.0 21 Nov 2018
IMPACT study number	17399
Study type / Study phase	Phase IV PASS ☒ YES Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS1549
Medicinal product / Active substance	Xofigo®/ Radium-223 dichloride
Study Initiator and Funder	Bayer AG, Germany Muellerstrasse, 178 D-13353, Berlin Germany
Function	Medical Affairs & Pharmacovigilance
Name	[redacted]
Title	Qualified Person responsible for Pharmacovigilance (QPPV)
Address	Bayer AG, Muellerstrasse 178 D-13353 Berlin, Germany

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

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – Pharmacovigilance

Title	A drug Utilization Study of Xofigo use in Sweden
Report version and date	V2.0 21 Nov 2018
IMPACT study number	17399
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EU PAS register number	EUPAS 1549
Medicinal product / Active substance	Xofigo®/Radium-223 dichloride
Study Initiator and Funder	Bayer AG, Germany Muellerstrasse, 178 D-13353, Berlin Germany
Function	Pharmacovigilance and Benefit Risk Management
Name	[redacted]
Title	[redacted]
Address	Bayer AG, Berlin, Germany

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

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – Study Epidemiologist

Title	A Drug Utilization Study of Xofigo Use in Sweden
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EU PAS register number	EUPAS1549
Medicinal product / Active substance	Xofigo®/ Radium-223 dichloride
Study Initiator and Funder	Bayer AG, Germany Muellerstrasse, 178 D-13353, Berlin Germany
Function	Study Epidemigologist
Name	[redacted]
Title	[redacted]
Address	Bayer AB Pharmaceuticals, Solna, Sweden

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

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – Study Epidemiologist

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EU PAS register number	EUPAS1549
Medicinal product / Active substance	Xofigo®/ Radium-223 dichloride
Study Initiator and Funder	Bayer AG, Germany Muellerstrasse, 178 D-13353, Berlin Germany
Function	[redacted]
Name	[redacted]
Title	[redacted]
Address	Bayer AG, Germany Muellerstrasse, 178 D-13353, Berlin Germany

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

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – Global Regulatory Affairs

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Report version and date	V2.0 21 Nov 2018
IMPACT study number	17399
Study type / Study phase	Phase IV PASS ☒ YES Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS1549
Medicinal product / Active substance	Xofigo®/ Radium-223 dichloride
Study Initiator and Funder	Bayer AG, Germany Muellerstrasse, 178 D-13353, Berlin Germany
Function	[redacted]
Name	[redacted]
Title	[redacted]
Address	Bayer AG, Germany Muellerstrasse, 178 D-13353, Berlin Germany

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

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – Medical Expert

Title	A Drug Utilization Study of Xofigo Use in Sweden
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IMPACT study number	17399
Study type / Study phase	Phase IV PASS ☒ YES Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS1549
Medicinal product / Active substance	Xofigo®/ Radium-223 dichloride
Study Initiator and Funder	Bayer AG, Germany Muellerstrasse, 178 D-13353, Berlin Germany
Function	[redacted]
Name	[redacted]
Title	[redacted]
Address	Bayer US, 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ

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

Print Name: [redacted]

Date, Signature: _____, _____