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Official Title:	REASSURE - Radium-223 alpha Emitter Agent in nonintervention Safety Study in mCRPC popUlation for long-teRm Evaluation
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Statistical analysis plan (prim. data collection)

Study Title REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation			
Bayer Study Drug	BAY 88-8223 / Radium-223 dichloride / Xofigo®		
Study Purpose:	Evaluate the short and long term safety profile of Radium-223 and assess the incidence of developing second primary malignancies among prostate cancer patients receiving Radium-223 in the routine clinical practice setting		
IMPACT No.:	16913	**Protocol Version/Date:**	Version 5 / 20 Aug 2018
SAP Version, Date:	V3.0, 23 OCT 2024	**SAP includes TLF specification:**	☐no ☒yes
Author:	PPD, PPD, Bayer AG		

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

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Abbreviations

AE	Adverse event
AML	Acute myeloid leukemia
ATC code	Anatomical Therapeutic Chemical code
BPI-SF	Brief pain inventory short form
BPP	Biostatistical Project Plan
CI	Confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DRECNO	Drug record number
EAIR	Exposure-adjusted incidence rate
EOD	Extend of disease
EOO	End of observation
HLGT	High level group term
IA	Interim Analysis
IBW	Ideal body weight
ID	Identifier
KM	Kaplan-Meier
LKAD	Last known alive date
mCRPC	Metastatic Castration Resistant Prostate Cancer
MDS	Myelodysplatic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLG	MedDRA Labelling Grouping
OS	Observational Study
OS	Overall Survival
PT	Preferred Term
R-223	Radium-223
ROW	Rest Of the World
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDG	Standardized drug grouping
SMQ	Standardized MedDRA Queries
SPM	Second primary malignancy
TLF	Tables, Listings and Figures
USA	United States of America
WBC	White blood cell
WHO-DD	World Health Organization – Drug Dictionary

1. Introduction

REASSURE is a non-interventional study, conducted to evaluate the short and long term safety profile of Radium-223 and assess the incidence of developing second primary malignancies among prostate cancer patients receiving Radium-223 in the routine clinical practice setting.

Background

Refer to protocol.

Protocol Version and Amendments

Observational study protocol (EUPAS7187, Impact No. 16913), Version 5.0, 20 Aug 2018

2. Study Objectives

The primary objectives of this study are:

- To assess the incidence of all second primary malignancies (including myelodysplatic syndrome (MDS)/ acute myeloid leukemia (AML) and osteosarcoma) in metastatic Castration Resistant Prostate Cancer (mCRPC) patients treated with Radium-223 in the routine clinical practice setting.
- To assess the incidence of treatment-emergent serious adverse events (SAEs) (collected up to 30 days after last administration), drug-related adverse events (AEs) (collected up to 30 days after last administration), drug-related SAEs (up to 7 years after the last administration of Radium-223).
- To assess bone marrow suppression.

The secondary objectives of this study are:

- To determine the Overall Survival (OS) in patients treated with Radium-223
- To evaluate pain over time using the “Brief pain inventory short form” (BPI-SF) questionnaire
- To assess the incidence of bone fractures and bone associated events (e.g. osteoporosis)

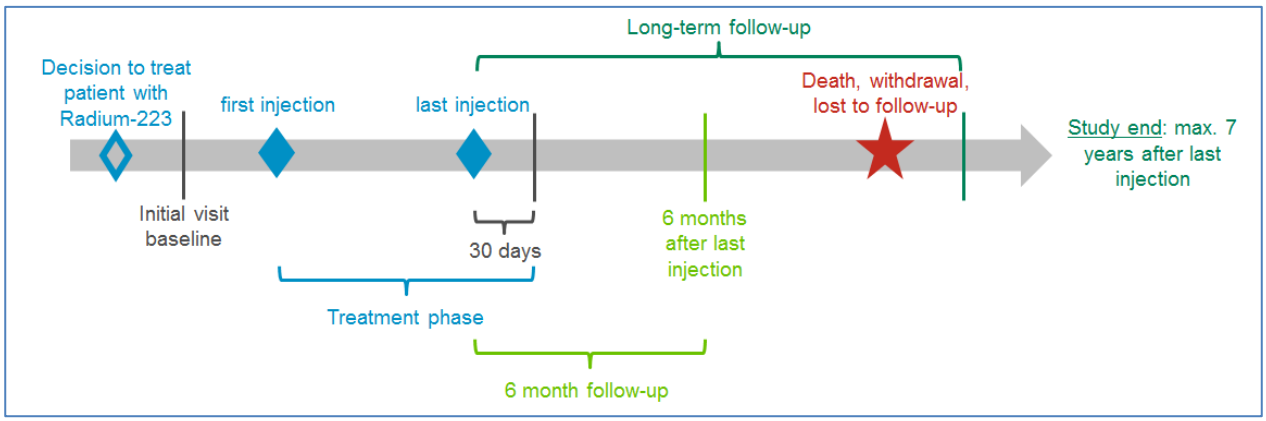
3. Study Design

This is a global, prospective, observational, multi-center, single arm cohort study. The study will be conducted in routine clinical practice settings. All patients who fulfill the inclusion and exclusion criteria are eligible for enrollment into the study.

The observation period for each patient enrolled in this study is the time from the start of therapy with Radium-223 to death, withdrawal of consent, lost to follow-up or end of this study (maximum of 7 years after last administration of Radium-223), whichever comes first in time. Study entry is indicated by date of informed consent.

The study is divided into four study phases: the initial visit (baseline), the treatment phase (from the first injection of Radium-223, to 30 days after last injection), the 6 month follow-up (from the last injection of Radium-223) and the long-term follow-up. The study phases are illustrated in Figure 3-1

Figure 3-1: Study design



4. General Statistical Considerations

All issues concerning patient eligibility, data consistency checks, permissible data modifications, and coding of medical terms and concomitant medication are to be described in detail in the Data Management Plan. All statistical issues including calculated variables are to be detailed in this Statistical Analysis Plan. Determination of sample size was detailed in the study protocol.

Sample size calculation: According to Phase III study ALSYMPCA and SEER data, the incidence proportion of second primary malignancy was estimated to be in the range of 1.1% to 6.9%. With this assumption and 1,200 patients, the width of a 95% CI (exact binomial distribution) for the rate of second primary malignancy will be approximately 1.3% to 3.0%. Therefore, it was planned to enroll approximately 1,334 patients, which accounts for 10% loss to follow-up for 1200 patients.

General Principles

The statistical evaluation will be performed by the third party organization Kantar Health, using the software package SAS version 9.2 or higher (SAS Institute Inc., Cary, NC, USA), except when noted otherwise.

All variables will be analyzed by descriptive statistical methods.

Descriptive analysis of the data will be performed using summary statistics for categorical and quantitative (continuous) data. Continuous data will be described by the number of non-missing values, median, mean, standard deviation, minimum, and maximum as well as lower and upper quartiles. Frequency tables will be generated for categorical data. Selected continuous variables will be categorized in a clinically meaningful way.

The data for this study will be collected using an electronic case report form (CRF).

Handling of Lost to Follow Up and Premature Discontinuation

Unless otherwise specified under a derivation of a relevant endpoint, no specific rules for handling loss to follow up and premature discontinuation.

Patients withdrawn from study will not be replaced. Refer to section 9.2.4 in the study protocol for withdrawal of patients from study.

Handling of Missing Data

Missing values will not be imputed or carried forward unless otherwise specified in the relevant section.

Imputation rules for incomplete dates of medication administration, blood transfusions and radiotherapies can be found in the Xofigo BPP-CM, version 1.0.

In addition, all end dates imputed after date of death will be set to date of death.

For partially documented death dates (i.e. day), the missing day will be imputed by day 15. In case imputed date is after EOO date, date of EOO will be used.

When the AE (including primary malignancy) start date is completely or partially missing, it is assumed that the start date occurs at the earliest possible time point (Day 1 if day of the month is missing, January if month is missing). If this date is prior to Radium-223 treatment start, the date of first Radium-223 treatment will be taken instead.

In case of missing dates, the respective AE will be considered as 'treatment emergent' as a worst case assumption.

Interim Analyses and Data Monitoring

A first interim analysis was conducted and reported in May 2017 (based on a database cut-off on 22 SEP 2016). An amendment of the first interim analysis results were reported on 20 APR 2018. Details can be found in corresponding CSR.

A second interim analysis was reported in September 2019 (based on a database cut-off on 20 MAR 2019). Details can be found in corresponding CSR.

An updated analysis with the same cut-off for the second interim analysis was reported in September 2020 following a quality review for underreported adverse events.

Analyses required for a final analysis are specified in Table 9-1 to 9-3 (appendix).

Data Rules

All documented therapies will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any disease and AEs will be coded using the MedDRA and CTCAE coding system. CTCAE version 4.03 and the most recent MedDRA and WHO-DD version of the dictionaries at the time of data-cut will be used.

Unless otherwise specified, baseline value is defined as last non-missing value on or prior to date of first injection of Radium-223. In case of more than one value is reported at the same date prior to first Radium-223 injection, baseline value is derived as the worst of these values.

Radium-223 dosage is converted to standard units (KBq/kg).

Calculation of durations: days = Day of last dose – day of first dose + 1.

Calculation of months is derived according to Bayer Xofigo standard: months = (days/365)*12.

Ideal body weight normalized doses = 50+[0.89 x (height(cm)-152.4)].

Definition of Derived Variables and Subgroups

All Subgroups of interest are described in Table 4-1. All derived variables required for analyses are specified within Table 4-2 or in the corresponding analysis section.

For each patient, last known alive date (LKAD) in the study is calculated based on documented dates indicating that the patient is alive. In case of partial documented dates, only for this derivation the date is imputed as earliest possible date.

Prior, Concomitant and Post Anti-Cancer Medication

Systemic anti-cancer therapies will be identified by the medical expert, as specified in the referenced document of identification of medications of interest (refer to section 8).

Based on the timing of the medications are taken, there are different types of medications:

- **Any Prior Medication**: All medications taken before first Radium-223 injection.

- **Prior completed Medication**: all prior medication with stop date prior to first Radium-223 injection

- **Concomitant Medication**: All medications taken in addition to Radium-223
- **Post Radium-223 medication**: All medications after the last Radium-223 injection.
  - **Subsequent medication:** post treatment starting after last injection of Radium-223

Medications, including systemic anti-cancer medications, need to be re-classified based on medication administration dates in case they are reported on different CRF pages during the study (pre-treatment, during treatment, and post-treatment).

The handling of prior, concomitant, post treatment blood transfusions and radiotherapies is analogues to the handling prior, concomitant, and post medication as described above.

Prior, concomitant and subsequent opioid use (identified by ATC groups 'N02A', 'N01AH', N02AG, R05DA, R05FA, A07DA) will be summarized by ATC levels 3 and 4 as described above.

Other medications than for anticancer or opioids will be summarized by ATC levels 2 and 4, separately as described above.

For further details (medication classification, programming algorithm, imputation rules), refer to the Xofigo BPP - med, version 1.0. To follow conservative approach in this non-interventional setting, step 3 of the spec – consolidation with category – will not be applied.

A patient can have multiple therapies and/or fall into multiple medication categories.

Subgroups of interest

Table 4-1: Subgroups of interest

Subgroup Label		Definition
Region	Europe	Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom
	North America	USA, Canada
	ROW[a]	Argentina, Brazil, Columbia, Mexico
Chemo[b] subgroups	Prior chemo[b]	Patients with chemotherapy[b] start date prior to first Radium-223 injection, regardless of the chemotherapy[b] stop date
	Subsequent chemo[b]	Patients with chemotherapy[b] starting after last Radium-223 injection

[a]ROW: Rest of the world
[b]Chemo: Chemo therapies will be identified by the medical expert according to the identification of medication of interest (refer to section 8).

5. Analysis Sets

Assignment of Analysis Sets

Safety Analysis Set: A patient will be included in the safety analysis set if he has received at least one injection of Radium-223.

Full Analysis Set: not applicable, since this is a safety study.

6. Statistical Methodology

All statistical analyses will be descriptive.

Subgroup analyses are described in the corresponding section, if applicable.

Frequency tables for categorical data will include the number of missing values as additional categories. Percentages will be calculated as proportion of each category including the category of missing values.

Population Characteristics

Descriptive summaries of patient disposition, demographic and baseline characteristics will be generated.

All systemic anti-cancer medications will be summarized according to the specified types of medication (refer to section 4.6). Systemic anti-cancer therapies will be identified by medical expert.

In addition, bone scan assessment methods, extent of disease (EOD), as well as extent of exposure summaries will be generated. For further details, refer to Table 9-1 (appendix).

Analysis of Primary Variable(s)

Second primary malignancies (reported as SAE)

Second primary malignancies (SPMs) are defined as new malignancies unrelated to prostate cancer or progression of prostate cancer. All types of SPMs will be collected irrespectively of their relationship to Radium-223. All reported SPMs will be summarized as assessed by the physician.

Depending on the observed number of events, second primary malignancies (SPM) will be summarized using incidence proportion and exposure adjusted incidence rate (EAIR). For both, the incidence proportion and the EAIR, the corresponding exact 95% CI (1) will be provided.

The EAIR is defined as the number of patients with the specific event divided by the total follow-up time from first study drug dose. For patients who undergo an event, the follow-up time will be truncated at the time when the first event is reported. For patients without an event, LKAD will be used to derive follow-up time.

The incidence rate per year, defined as number of SPM events within the x^{th} year divided by the number of patients at risk at beginning of year x, will be generated. In addition, the median time to follow-up will be presented.

The Cumulative incidence rate will be derived taking into account the competing risk of death (2). Tables, including cumulative incidence rates at 6-months intervals and plots will be generated. Patients who do not die or experience an event will be censored at the LKAD. The number of patients at risk will be calculated at start of corresponding interval using the LKAD for derivation. The number of patients with SPM and number of deaths will be counted according to SPM/death occurrence within the corresponding interval. The cumulative incidence rate can be calculated using SAS procedure LIFETEST.

In addition, descriptive summaries of KM estimates (including number of failed, number censored, 25^{th} and 75^{th} percentiles with respective 95% CI, using loglog-transformation and median with 95% CI, using loglog-transformation) and KM curves will be presented for time from first Radium-223 injection to development of SPM, when sufficient data is available. Patients who start other radiopharmaceuticals or enroll into other trials will be censored when the respective radiopharmaceuticals are initiated. Patients without a SPM until data cut off will be censored at the

LKAD. Other radiopharmaceuticals will be identified as specified in the identification of medications of interest (refer section 8).

In case of a low incidence of SPM, incidences of patients with SPMs and patient listings will be provided for patients who developed SPM. Time to SPM can be estimated using descriptive statistics (e.g. median, mean, standard deviation, minimum, and maximum as well as lower and upper quartiles). Refer to Table 9-2 (appendix) for further details.

Comparison with external reference secondary data sources

Site specific incidences on cancer diagnosis will be analyzed by comparing the observed number of cases for second primary malignancies in the REASSURE cohort with corresponding expected number based on cancer incidence rated derived from the external reference secondary data source(s) (Surveillance, Epidemiology, and End Results (SEER) database results per documents 0304255_FinalReport_5Jul2017 [3], CSR 18044 PH-40151 [4]). Age (by 5-year age groups) will be accounted for in the analysis. The ratio of the observed and expected number of cases by means of Standardized Morbidity Ratio (SMR) will be used as the measure of the increased or decreased incidence rates, accompanied by an exact 95% CI assuming the observed number of second primary malignancy cases.

SMR = number of observed SPMs / number of expected SPMs. Incidence rate will be calculated per x years (e.g. 1000 years).

95% CI = 1.96 x (square root (observed SPMs) / expected SPMs) x 100.

Summarization of SPMs will be provided by site specific categories and age groups. Alignment between REASSURE and external reference data will be performed via medical review. External data did not include all sites in the reference analysis. Analysis by age group may be performed if alignment by site is not possible.

AEs / SAE

Incidence proportion and EAIR for the following adverse events (AEs) will be summarized, along with the exact 95% confidence intervals:

- Treatment-emergent SAEs (up to 30 days after last administration)
- Drug-related treatment-emergent AEs (up to 30 days after last administration)
- Drug-related SAEs (up to 7 years after last administration)
    - Drug-related treatment-emergent SAEs (up to 30 days after last administration)
    - Drug-related SAEs after treatment-emergent period (>30 days after last administration)
- Post treatment grade 3/4 hematological toxicities will be summarized up to 6 months after the last administration of Radium-223.
- For patients receiving subsequent chemotherapy, all AEs/SAEs of febrile neutropenia and hemorrhage will be summarized up to 6 months after the last administration of chemotherapy.

AEs will be summarized using the MedDRA coding system. They will be categorized and summarized according to relation, seriousness, CTCAE grade, discontinuation of therapy, action

taken (permanent discontinuation, interruption or dose modification) and outcome (patient hospitalization or prolongation of hospitalization, death). The incidence proportion and EAIR (section 6.2) will be summarized, along with the exact 95% CI.

AEs during treatment with radium-223, i.e. 'treatment-emergent (TE)' AEs are defined as any event arising or worsening on the day of start or after the start of radium-223 treatment until 30 days after last radium-223 injection.

AE tables will be summarized according to protocol reporting definitions (e.g. treatment-emergence for SAEs and related AEs, 6 months after last dose for grade 3 / 4 hematological AEs). Summaries will be provided for all entered grade 3 / 4 hematological AEs and separately for these AEs within 6 months (183 days) after last dose of radium. Summaries will be provided for all entered AEs of febrile neutropenia and hemorrhage and separately for these AEs within 6 months (183 days) after last dose of chemotherapy.

All AEs will be listed.

For further details on tables and listings, refer to Table 9-2 (appendix).

Narratives will include reportable adverse events as follows:

- Second primary malignancies
- Drug-related SAEs
- Treatment-emergent SAEs resulting in death

Bone marrow suppression

Bone marrow suppression is summarized according to Table 9-2 (appendix).

Incidence of post treatment grade 3/4 hematological toxicities will be provided by worst grade, along with the exact 95% CI. Bone marrow suppression risk search criteria are covered by the following most recent MedDRA Labelling Groupings (MLGs) and Standardized MedDRA Queries (SMQ):

- MLG Thrombocytopenia
- MLG: Neutropenia
- MLG: Leukopenia not further specified
- MLG: Pancytopenia
- SMQ: Haematopoietic erythropenia

Information for therapeutic or prevention measures, treatment modalities will also be summarized as follows:

- Erythropoietin is defined by the SDG (Standardized drug grouping): 'Erythropoiesis stimulating drugs' according to the most recent WHO-DD version.
- Colony stimulating factors (e.g. Granulocyte-macrophage colony-stimulating factor [GM-CSF]) are defined based on ATC code L03AA
- Incidences of abnormal platelet count or WBC will be summarized by period (initiation of radium-223 to 30 days after last administration, and after 30 days after last administration to 6 months after last administration) and the worst grade

- For patients who received subsequent chemotherapy, incidences of febrile neutropenia and hemorrhage after start of first subsequent chemotherapy will be summarized
- Febrile neutropenia is defined by PT: 'Febrile neutropenia'
- Hemorrhage is defined based on the most recent SMQ: 'Haemorrhage terms (excluding laboratory terms)'
- Blood transfusions

Summaries will be provided for treatments as specified above and separately for these treatments within 6 months (183 days) after last dose of radium.

Listings including all search terms and corresponding version numbers will be generated.

Analysis of Secondary Variable(s)

Overall survival

OS is defined as time from the first injection date to death due to any cause, in months and derived as Time = {[(death date)-(first R-223 injection date)+1]/365}*12

Patients alive (or patients whose death is not confirmed) at the time data cut off will be censored at the last date known alive date (LKAD, see section 4.6).

Descriptive summaries of Kaplan-Meier (KM) estimates and KM curves will be presented for OS (see Table 9-3).

When the death date is partially missing (i.e. day), the missing day will be imputed by the 15th of the month except if the 15th of the month is after the end of observation date of the same month, in which case the missing day will be imputed by the end of observation date. When the LKAD is after imputed death date, the LKAD will be used for imputation. If month and/or year are missing, the patient will be censored at LKAD.

Patient listings will be provided for deceased patients as specified in Table 9-3 (appendix)

Brief Pain Inventory Short Form (BPI-SF) Questionnaire

The BPI-SF questionnaire is requested prior to each injection of Radium-223 and also used at each follow-up visit until 6 months after the last injection of Radium-223.

The pain severity score and the pain interference score will be calculated per visit, as described in the BPI User Guide and summarized.

Baseline will be defined as last observation prior to first administration of Radium-223. If a questionnaire was filled out on the same day as first treatment, the times of completion of the questionnaire and first treatment administration will be compared to determine whether the observation matches the baseline criteria. The closest observation to the visit date will be summarized when there is more than one post-baseline observation at a visit,

Refer to Table 9-3 (appendix) for further information.

Bone Fractures and Bone Associated Events

Bone fractures and bone associated events (reported as AEs) will be summarized via incidence proportion and EAIR, regardless of investigator assessment of causality.

Bone fractures and bone associated events will be identified by MedDRA (most recent version at time of analysis) HLGTs:

- Fractures: HLGT = “Fractures”.
- Bone associated events: HLGT = “Bone disorders (excl congenital and fractures)”

In addition, the number and proportion of patients with bone fractures and bone associated events, identified by HLGT and preferred term (PT), will be summarized by bone health agents;

Bone health agents are identified as follows:

- Denosumab: ATC code: M05BX
- Bisphosphonates: ATC code: M05BA or M05BB or MB05BC

Safety Analysis

All safety variables are indicated as primary and secondary outcomes. Refer to Sections 6.2 and 6.3.

Laboratory

Laboratory will be summarized at baseline. Post-baseline measurements will be summarized as the closest measurement date to the treatment or follow-up date. In case of ties the earlier measurement will be summarized.

Analysis of Other Data

Descriptive summaries of KM estimates and KM curves will be presented for time to progression (TTP). The 25th and 75th percentiles with respective 95% CI, using loglog-transformation and median with 95% CI, using loglog-transformation) and KM curves will be presented. Progression is defined as first progression after initial treatment with Radium-223. The type of progression (as assessed by the physician) can include any of the following:

- Symptomatic Skeletal Events (SSEs). Progression defined as SSE includes any of the following: the use of EBRT to relieve skeletal symptoms, new pathological bone fractures (vertebral or non-vertebral), occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention.
- Prostate Specific Antigen Level (PSA). Progression defined as increase of PSA level and/or radiological progression is solely based on physician’s assessment.
- Radiological imaging.
- Unequivocal clinical progression.

Progression does not include second primary malignancies, tumor-related death, or death from any cause.

Patients who do not have a progression at the end of the study will be censored at the LKAD.

Confounder or Bias Adjusted Analyses

Not applicable

Analysis of Representativeness

Not applicable

Additional Analyses Planned to be Reported Outside the Study Report

Not applicable

7. Document History and Changes in the Planned Statistical Analysis

SAP version IA1 3.0, 07 Dec 2016

SAP version IA2 2.0, 10 Apr 2019

SAP version Reanalysis of IA2 1.0, 17 July 2020

8. References

[1] Clopper CJ, Pearson ES (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika, 26; 404–413.

[2] Kalbfleisch JD, and Prentice RL. The Statistical Analysis of Failure Time Data. New York: John Wiley, 1980

[3] Incidence of Second Primary Malignancies in Patients With Castration-Resistant Prostate Cancer: An Observational Retrospective Cohort Study in the US. Final report. Bayer AG, 5 Jul 2017.

[4] Second primary cancers in patients with castration resistant prostate cancer (BOCARP1), Clinical study report (CSR). Bayer AG, 20 October 2017.

Document	Version	Date
16913_REASSURE_Identification_Medication_of_Interest_3.0	3.0	04 Oct 2024
Xofigo Biostisticial Project Plan_CM_v1.0	1.0	05 SEP 2018
Briefpain_short		
BPI_UserGuide		
PREF_BASE_TRANSP_LST_2024-09-17_med_rev		17 Sep 2024
16913_REASSURE_osp_coding_final_import_20241014		14 Oct 2024
0304255_FinalReport_5Jul2017		05 Jul 2017
CSR 18044 PH-40151		12 Jan 2018

9. Appendix

Table 9-1: Population Characteristics

Section		Title	Subgroups

Enrollment	T	Patient enrollment -SCR	---
	T	Non-Eligibility - SCR	---
Demographic and baseline characteristics	T	Disposition of patients	Region
	T	Duration of observation	Region
	T	Demographics	Region
	T	Vital signs at baseline	Region
	T	Risk factors for cancer	Region
	L	Other risk factors for cancer at study entry	Region
	T	Baseline characteristics of prostate cancer	Region
	T	Reported Metastases at study entry	Region
	L	Other Metastases at study entry	Region
	T	Laboratory at baseline	Region
	T	Number of patients with medical history findings (MedDRA yx.x)	Region
	T	Medical History: ongoing conditions grouped by MedDRA yx.x	Region
<Prior /prior completed / conocomitant / post / subsequent> therapy	T	Prior diagnostic and therapeutic procedures for prostate cancer	---
	T	Details of prior diagnostic and therapeutic procedures for prostate cancer	---
	T	Prior anti-cancer therapies – other than systemic therapies - summary	---
	T	Any prior systemic anti-cancer therapy	---
	T	Any prior use of opioids	
	T	Prior completed systemic anti-cancer therapy	---
	T	Any prior completed use of opioids	
	T	Concomitant anti-cancer therapies – other than systemic therapies - summary	---
	T	Concomitant systemic anti-cancer therapy	---
	T	Any concomitant use of opioids	---
	T	Post anti-cancer therapies – other than systemic therapies - summary	---
	T	Post systemic anti-cancer therapy	---
	T	Any post radium use of opioids	---
	T	Subsequent systemic anti-cancer therapy	---
	T	Any subsequent use of opioids	---
	T	Any other subsequent therapy	---
Bone scan	T	Tumor assessment and EOD	---
Laboratory	T	Laboratory assessments during study	
Extent of Exposure	T	Extent of exposure	---

Table 9-2: Analysis of Primary Variables

Section		Title	Subgroups
Second primary malignancies (SPM)	T	Incidences of patients with second primary malignancies (SPM)	---
	L	Patients with second primary malignancies (SPM)	---
	L	Adverse events classified as second primary malignancy (SPM)	---
	L	<Any prior/ Prior completed/ Concomitant> systemic anti-cancer therapy for patients with second primary malignancies	---
	L	<Any prior/Prior completed/Concomitant> radiotherapy for patients with second primary malignancies	---
	T	Incidences proportion of patients with second primary malignancies (SPM)	---

	T	Interval specific and cumulative event rates for second primary malignancies (SPM)	---
	F	Cumulative incidence function for second primary malignancies - Kaplan-Meier Curve	---
	T	Time to second primary malignancies (SPM) from first Radium-223 injection – descriptive statistics	---
	F	Time to second primary malignancies (SPM) from first Radium-223 injection - Kaplan-Meier curve	---
	L	Listing of patients with second primary malignancies (SPM)	---
Adverse events	T	Overview of Adverse Events	---
	T	Overview of additional safety data	---
	T	<TE SAEs / drug-related TE AEs / drug-related SAEs / drug-related TE SAEs / drug related Post-TE SAEs > by worst grade (MedDRA vx.x)	---
	T	<TE SAEs / drug-related TE AEs / drug-related SAEs / drug-related TE SAEs / drug related Post-TE SAEs > resulting in permanent discontinuation of Radium-223 by worst grade (MedDRA vx.x)	---
	T	<TE SAEs / drug-related SAEs / drug-related TE SAEs / drug related Post-TE SAEs > resulting in inpatient hospitalization or prolongation of existing hospitalization by worst grade (MedDRAyx.x)	---
	T	<TE SAEs / drug-related SAEs / drug-related TE SAEs / drug related Post-TE SAEs > resulting in death by worst grade (MedDRA vx.x)	---
Bone marrow suppression (BMS)	L	Definition list of bone marrow suppression, febrile neutropenia and hemorrhage (MedDRA version yx.x)	Chemo
	L	Definition of SDG: Erythropoiesis stimulating drugs according to WHO Drug version x.x	Chemo
	T	Patients with therapeutic or preventive treatments for to bone marrow suppression after start of Radium-223	Chemo
	T	Incidences of post treatment grade 3/4 hematological AEs based on BMS (MedDRA vx.x)	Chemo
	T	Incidences of post treatment grade 3/4 hematological AEs within 6 months based on BMS (MedDRA vx.x)	Chemo
	T	Incidences of lab values relevant for BMS from radium-223 initiation to 30 days after last dose	Chemo
	T	Incidences of lab values relevant for BMS 30 days to 6 months after last radium-223	Chemo
	T	Patients with febrile neutropenia or haemorrhage events as of start of subsequent chemotherapy	
	T	Patients with febrile neutropenia or haemorrhage events up to 6 months following subsequent chemotherapy	

Table 9-3: Analysis of Secondary Variables

Section		Title	Subgroups
Overall survival	T	Summary of deaths	---
	T	Cause of death	---
	L	Cause of death	---
	T	Overall survival (OS) – descriptive statistics	---
	F	Overall survival - Kaplan-Meier curve	---
	L	Details of deaths	---

BPI-SF Questionnaire	T	Brief Pain Inventory Short Form - Pain severity score – means and change from baseline	---
	T	Brief Pain Inventory Short Form - Pain interference score – means and change from baseline	---
	T	Number of patients with a pain response in worst pain item	---
Bone fractures and bone associated events	L	Definition list of bone fractures and bone associated events coded by MedDRA yx.x	---
	L	Adverse events considered as fracture or bone associated event (MedDRA yx.x)	---
	T	Incidence of patients with bone fractures and bone associated events	---
	T	Bone health agents (BHA)	---
	T	Patients with bone fractures and bone associated events by bone health agents (BHA)	---
Time to progression	T	Summary of first progression post first dose of Radium-223 - SAF	---
	T	Time to progression (TTP) - descriptive statistics	---
	F	Time to progression (TTP) - Kaplan-Meier curve	---
Standard Morbidity Ratio	T	Incidence of second primary malignancies compared to external data source	

Statistical Analysis Plan – Signature Page

Electronic Signature

OS statistical analysis plan approval form (prim. data collection)

SAP version	3.0
SAP version date	23 OCT 2024
Study title	*REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation*
IMPACT No.	16913

The signatories agree that the study will be analyzed under the conditions described in this Statistical Analysis Plan.

Signatories

- PPD (PPD), Bayer
- PPD (PPD), Bayer
- PPD (PPD), Bayer
- PPD (PPD), Oracle
- PPD (PPD), Bayer