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Title page

A Phase 4 long-term follow-up study to define the safety profile of radium-223 dichloride

Radium-223 dichloride long-term follow-up program

Bayer study drug	BAY 88-8223 / Radium-223 dichloride / Xofigo		
Study purpose:	Safety		
Clinical study phase:	IV	**Date:**	15 FEB 2024
Study No.:	16996	**Version:**	2.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

Table of Contents

Version History

This Statistical Analysis Plan (SAP), version 2, dated 15 FEB 2024, for study 16996 is based on the Integrated Protocol Amendment 2, Version 3.0, dated 11 APR 2018. It supersedes:

- SAP, version 1.0, dated 25 MAY 2017
- SAP, version 1.1, dated 01 APR 2019, incorporating changes from Protocol Amendment 2 dated 11 APR 2018

A detailed history of the changes to the SAP can be found in Section 7.

List of Abbreviations

AE	Adverse event
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer
ATC	Anatomical Therapeutic Chemical classification system
CRPC	Castration-Resistant Prostate Cancer
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
GMS	Global Medical Standards
ID	Identifier
IDMC	Independent Data Monitoring Committee
Max	Maximum
mBC	Metastatic Breast Cancer
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
Nmiss	Number of missing data
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TAS	Therapeutic Area Standards
US/USA	United States of America
WHO-DD	World Health Organization-Drug Dictionary

1. Introduction

Radium-223 dichloride is approved in more than 50 countries (including the United States (US) and countries in the European Union) for the treatment of castration-resistant prostate cancer (CRPC) participants with symptomatic bone metastases and no known visceral metastases. Approval was based on results of the randomized Phase 3 trial Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA), in which radium-223 dichloride prolonged overall survival and time to first symptomatic skeletal event, when compared to placebo among CRPC participants with symptomatic bone metastases. Radium-223 dichloride was generally well tolerated with low myelosuppression rates and manageable gastrointestinal adverse events (AEs).

This study is conducted to define the long-term safety profile of radium-223 dichloride to meet Health Authority requirements/requests.

The key attribute of radium-223 dichloride is its specific targeting of bone with limited radiation exposure beyond the intended target. However, the proximity of the bone marrow space to site of action of radium-223 dichloride means that there is potential for radiation-induced bone marrow abnormalities. These abnormalities, including bone marrow dysplasia or new primary malignancies, may not become evident until years after the initial exposure to radium-223 dichloride; therefore, longterm follow-up is required to detect them. The ERA 223 study, a phase III randomized trial in prostate cancer participants examining radium-223 dichloride versus placebo in combination with abiraterone and prednisone (study number 15396, NCT02043678) was unblinded based on the Independent Data Monitoring Committee (IDMC) recommendation following an ad hoc independent analysis where more treatment-emergent fractures and total deaths were observed in the active treatment arm compared with the placebo arm. The IDMC also recommended that all bone fractures and bone-associated events (e.g., osteoporosis) occurring in follow-up period are to be documented regardless of investigator's causality assessment. In order to collect comprehensive safety information across all clinical trials with radium-223 dichloride, documentation of fractures (pathological and non-pathological) regardless of relationship, is also implemented in the present trial. In addition, any bone health agent taken during the study period is being collected.

The follow-up period in this study extends to up to 7 years after the last dose of radium-223 dichloride or placebo.

The study originally was intended to collect long-term follow-up data from prostate cancer studies only; however, radium-223 dichloride is also being studied for other indications. In order to collect comprehensive safety information across all clinical trials with radium-223 dichloride and to allow collection of long-term safety data across indications, participants with different tumor types (e.g., breast cancer and multiple myeloma) are also allowed to enter the long-term follow-up study. The follow-up period in breast cancer studies extends to 5 years after the last dose of radium-223 dichloride or placebo, and in prostate cancer studies to 7 years. Although Protocol Amendment 2 also provided for participants with multiple myeloma to enter this study for long-term follow-up, no multiple myeloma participants have entered or are expected to enter as of SAP Version 2.

The study protocol provided for analyses including a combined analysis of 16996 and feeder study data and pooled analyses across feeder studies. This SAP implements a Sponsor decision to perform a reduced and simplified analysis focusing primarily on data from this study, with analysis separately by feeder study and only an overall total summary pooled across studies (where applicable). Limited data from the applicable feeder studies will be

combined for specific analyses as specifed. Deviations from the per-protocol planned analysis are reported in Section 7.2.

Protocol Version and Amendments

This analysis plan is based on an integration of the following protocol versions and amendments:

- Original protocol, Version 1.0, dated 03 SEP 2014
- Integrated protocol, Version 2.0, dated 13 SEP 2016, which incorporates Amendment 1
- Integrated protocol, Version 3.0. dated 11 APR 2018, which incorporates Amendment 2

2. Study Objectives

The primary objectives are to define the long-term safety profile of radium-223 dichloride (for up to 7 years after the last dose of radium-223 dichloride); to assess the incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy; to assess the incidence of bone fractures and bone associated events (e.g., osteoporosis); and, in subjects who receive cytotoxic chemotherapy, to assess the incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice.

3. Study Design

Participants enrolled into the study will be transferred from the selected company-sponsored feeder trials with radium-223 dichloride. Following informed consent and determination of eligibility, participants, their treating health care professional, or caregiver will be contacted by telephone (face-to-face data collection is possible and will replace the telephone contact if the participant is onsite within the time window of the planned telephone contact) every 6 months (± 28 days) for 7 years (or as defined in the feeder trial protocols) following the last dose of radium-223 dichloride or placebo in the feeder trial, or until death.

3.1 Primary and secondary variables

The primary variables are all safety-related and include:

- Incidence of and severity of radium-223 dichloride/placebo related AEs
- Incidence of radium-223 dichloride /placebo related SAEs
- Incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy
- Incidence of bone fractures and bone-associated events (e.g., osteoporosis) regardless of investigator assessment of causality
- In participants who receive cytotoxic chemotherapy: incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice

4. Analysis Sets

4.1 Per-Protocol Analysis Sets

The following analysis set is defined per Protocol Amendment 2:

- **Safety:** All subjects who have received at least 1 dose of radium-223 dichloride or placebo in the feeder trials. This safety population will be used in the analysis of all safety endpoints. Subjects will be included in the analyses according to the treatment they received.

Per the Sponsor decision, a reduced and simplified analysis focusing on long-term safety data collected in study 16996 will be performed. Feeder trial data from patients not enrolled in 16996 will not be combined, therefore, the Safety analysis set defined per-protocol will not be implemented in the analyses described in this SAP. Instead, the Safety analysis set during long-term follow-up (SAF-LTF), as described in the table below (Section 4.2), will be used for safety analyses.

4.2 Per-SAP Analysis Sets

The following analysis sets will be used for the analyses described in this SAP:

Analysis Set	Description
Enrolled analysis set (ENR)	All participants who signed an informed consent to study 16996 will be included in the Enrolled analysis set. The Enrolled analysis set will be used for reports on 16996 study disposition and study conduct.
Safety analysis set during long-term follow-up (SAF-LTF)	All participants who have received at least 1 dose of radium-223 dichloride or placebo in an eligible feeder trial and who have signed informed consent to 16996. The Safety During Long-term Follow-Up analysis set will be used for analyses of long-term safety in study 16996.

Additional assignment details

For summaries based on the ENR analysis set by treatment group, participants who were assigned to treatment but not treated in the feeder trial will be classified based on assigned treatment group.

Unless otherwise specified, participants who enrolled in study 16996 but did not previously participate in an eligible feeder trial will be included in the overall totals in summaries based on the ENR analysis set, but will not be included in groupings by feeder trial or treatment group.

5. General Statistical Considerations

5.1 General Principles

Long-term follow-up data may have been collected within the feeder study, within study 16996, or both. However, only follow-up data (e.g. adverse event data and anti-cancer medication/therapy data) that are collected during study 16996 will be included in the analyses described in this SAP. Limited information from feeder studies will be integrated with study 16996 (Section 5.2.1) to provide summaries of treatment exposure, overall follow-up duration and baseline characteristics at entry into feeder study. As noted in Section 7.2 below, this reduced analysis represents a deviation from the protocol-planned analysis.

Except if otherwise specified, participants will be included in the analyses according to the treatment they received in their feeder trial. Summaries will be presented by indication, feeder study and treatment arm within the feeder study. Listings will be produced by feeder trial arm containing participant data from study 16996, based on the ENR or SAF-LTF set, as applicable.

No formal statistical testing is planned for the overall analysis. The statistical evaluation will be performed by using the software package SAS release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Data will be analyzed using descriptive statistical methods.

Unless otherwise specified, the following descriptive statistics will be presented in data summaries:

- For continuous or ordinal data, the number of participants with data available (n), arithmetic mean, standard deviation (SD), minimum (min), quartile, median, maximum (max) will be presented.
- For categorical variables, the number of participants and percentage in each category will be presented.

The structure of analysis datasets and layout of analyses and data displays will follow Bayer AG standards, including Therapeutic Area Oncology Standards (TAS) and the Global Medical Standards (GMS), as applicable.

5.2 Data rules

5.2.1 Integrating Feeder Study Data

Information to be integrated from feeder studies will include (if available): unique participant identifiers (ID), demographic and baseline characteristics (age, height, and weight), intervention randomized to, intervention received, and treatment exposure data, including date of first administration of study drug, date of last radium-223 dichloride or placebo and number of injections received. Only data from eligible feeder studies will be integrated. Data will be merged by feeder study unique subject ID as documented in the 16996 CRF.

5.2.2 Other Data Rules

Participants will be identified in listings by feeder study ID number/16996 participant ID number (concatenated).

5.3 Handling of Dropouts

A participant who discontinues study participation prematurely for any reason is defined as a "drop-out".

Premature discontinuation from study 16996 is defined as discontinuation from study 16996 prior to the end of the applicable long-term-follow-up period from the last date of radium-223 dichloride or placebo treatment in the feeder study (5 years for mBC, 7 years for mCRPC).

The reason for discontinuation for participants who withdraw from study 16996 will be recorded in the electronic case report form (eCRF) and summarized in the analysis. Summaries of premature discontinuation will be provided for SAF-LTF participants.

5.4 Handling of Missing Data

All missing or partial data will be presented in participant data listings as they are recorded in the eCRF.

Missing data will not be imputed for statistical analysis, with the exception of imputation for determining start dates of AEs. See Appendix 8.1 for details.

5.5 Interim Analyses and Data Monitoring

A series of safety analyses will be performed separately for each applicable feeder study, after the last participant from the feeder study completes the applicable long-term follow-up period (7 years after the last dose of radium-223 dichloride or placebo in the feeder study for mCRPC, 5 years for mBC), or prematurely discontinues from 16996 follow-up. These safety analyses are intended to meet Health Authority requirements to evaluate and report the long-term safety of radium-223 dichloride. For all feeder studies but the last, the relevant analysis will occur prior to the overall end of 16966 and hence will constitute an interim analysis. These safety analyses are described in a separate supplemental SAP for Health Authority Reports.

5.6 Validity Review

Validity Review meeting(s) will be conducted prior to final database lock to review participant validity (inclusion of participants in analysis sets), protocol deviations, and data issues of note. The results of validity review meeting(s) will be documented in Validity Review Reports.

6. Statistical Methodology

6.1 Population Characteristics

6.1.1 Participant Disposition

The number and percentage of ENR participants valid for SAF-LTF will be presented by treatment group, for the overall total of the treatment groups per feeder study, and pooled for the total of Study 16996.

The number of participants enrolled in 16996 (ENR) will be displayed by geographic region, country/region and center for each feeder trial.

Study disposition including the number and percent of participants who enrolled in 16996, who did not complete screening, who entered 16996 long-term follow-up, who discontinued long-term follow-up, and who completed long-term follow-up will be summarized for ENR participants. Reasons for premature withdrawal from long-term follow-up will be provided. Summaries will be provided overall (pooled across feeder studies), by feeder study, and by treatment group within each feeder study.

In addition, summary statistics for the duration of follow-up in SAF-LTF participants, period from 31 days (inclusive) after the last administration of radium-223 dichloride or placebo in the feeder study until the last known alive date, will be presented, and the numbers of participants with at least 6, 12, 18, 24, 36, 48, 60, 72, and 84 months of follow-up will be summarized. This summary of long-term follow-up analysis will combine feeder study and 16996 data.

Summary statistics for the duration of follow-up in study 16996 from the time of signing of the informed consent until the last known alive date in SAF-LTF participants will also be presented. The numbers of participants with at least 6, 12, 18, 24, 36, 48, 60, 72, and 84 months of follow-up will be summarized.

6.1.2 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be integrated from the corresponding feeder study and summarized for the SAF-LTF participants (in a per-feeder study summary table for the SAF-LTF analysis set):

- Height (cm)
- Weight (kg)

In addition, the baseline characteristics collected within study 16996 for the SAF-LTF paticipants will also be summarized in per-feeder study:

- Age (years at informed consent), continuous and categorical (<18, 18-64, 65-84, 85 years and over)
- Sex
- Race
- Ethnicity

6.1.3 Protocol Deviations

The number and percent of participants with any protocol deviations and with important protocol deviations in study 16996 will be provided along with a listing of protocol deviations for all participants enrolled in study 16996 (ENR).

Protocol deviations will be identified and specified, and assignment of importance specified, in a separate Protocol Deviations document. Protocol deviations will be reviewed, and importance finalized, at the Validity Review meeting(s).

6.1.4 All Reported Therapies

All therapies collected within the long-term follow-up in study 16996 until the date of death (or date of last visit/contact, if the participant has not died) will be summarized in SAF-LTF participants regardless of concomitant or post-treatment status: bone health agent use, systemic anti-cancer therapies, and diagnostic and therapeutic procedures (including radiotherapy) during follow-up. The number of participants with radiotherapy will be

presented by location of irradiation, intent of procedure and the number of regimens. Systemic anti-cancer therapy will be summarized by the subcategory for medication and number of regimens.

Anti-cancer therapy will be coded using the World Health Organization Drug Dictionary (WHO-DD 2005/Q3) and the Anatomical Therapeutic Chemical (ATC) classification system.

A participant data listing of all therapies including bone health agent use, systemic anti-cancer therapy for prostate cancer, and diagnostic and therapeutic procedures during follow-up will be presented for SAF-LFT participants. Radiotherapy will be listed along with: locations, intent, type of radiotherapy, given to relieve bone pain (Y/N), date of first/last fraction, total cumulative dose, best response.

6.2 Efficacy Evaluations

Survival status assessments collected in Study 16996 will be listed.

6.3 Pharmacokinetics/Pharmacodynamics

Not applicable.

6.4 Safety

6.4.1 Extent of Exposure

The number of subjects who received all planned injections of radium-223 dichloride or placebo will be tabulated. This summary will use feeder study exposure data for participants enrolled in the long-term follow-up study 16996. A listing of extent of exposure to radium-223 dichloride/placebo in subjects from feeder study, including date of first and last radium-223 dichloride or placebo dose and number of radium-223 dichloride or placebo injections received, will be provided. Extent of exposure evaluations combine 16996 and feeder study data.

6.4.2 Adverse Events

Only select categories of post-treatment AEs are to be collected in the long-term follow-up study 16996, including radium-223 dichloride/placebo related AEs and SAEs. The following AE categories identified by the protocol will be evaluated separately:

- New primary malignancies, defined as leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer, and any new primary malignancies, regardless of relationship to study drug;
- Bone fractures and bone-associated events;
- Febrile neutropenia and hemorrhage during chemotherapytreatment and for up to 6 months thereafter. A simplified analysis will be performed as specified below
- Pregnancy AEs.

In addition to the above listed select categories of post-treatment AEs collected in study 16996, events related to radium-223 dichloride/placebo by the investigator and ongoing at or occurring from the time of signing of the informed consent and the end of the study were also to be collected by the investigator.

For purposes of the safety analysis of this study, AEs first arising or worsening after signing the 16996 informed consent are defined as 16996-emergent AEs.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 or higher. When integrating feeder study and 16996 study data, a MedDRA version re-fresh will be performed. The MedDRA version used will be the version in effect per Bayer Standard Operating Procedures (SOPs) at the time of database lock, and will be documented in the study CSR. Differences in MedDRA versions in effect at the time of applicable lock may result in AEs being coded differently between the interim Health Authority reports and the final CSR.

The grade severity of an AE will be documented using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03).

The set of MedDRA preferred terms (PTs) constituting each category of AEs for analysis purposes will be documented in an appendix to this SAP. The appendix will be approved separately from, and may be approved later than, this SAP.

Per protocol, febrile neutropenia and hemorrhage AEs are to be collected during and within 6 months of cytotoxic chemotherapy treatment. For the protocol-specified analysis of the incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter, a simplified analysis will be performed, of febrile neutropenia and hemorrhage AEs without regard to cytotoxic chemotherapy association. All 16996-emergent febrile neutropenia and hemorrhage AEs documented in the study CRF will be reported, without regard to chemotherapy treatment.

For the analysis of fractures and bone associated events, separate analyses of patients with bone fractures, patients with bone associated events, and patients with bone fractures and/or bone associated events will be performed. The applicable MedDRA appendix will identify the MedDRA preferred terms applicable to each sub-category.

Unless otherwise specified, the analysis for each AE category will include a summary of the total number and percent of SAF-LTF participants with an AE of the applicable category. Participants with an applicable AE will be summarized by MedDRA preferred term (PT), overall within each applicable MedDRA system organ class (SOC), and overall (any applicable AE), both by worst CTCAE grade and for any grade. For summaries by worst grade, the AE with the worst grade in the applicable summary category will be used. AEs with missing grade will be included in any-grade summaries but not in summaries by worst grade. In addition, listings will be provided.

6.4.2.1 16996-Collected Adverse Events

All AEs collected in study 16996, whether or not collection was required per study 16996 protocol, will be listed for SAF-LTF including AE PT, 16996-emergent (Y/N), start and stop dates, grade, treatment-related (Y/N), serious (Y/N), reason for seriousness, outcome of AE, and time (days) since last dose of study drug. The listing will include all 16996-collected AEs, whether or not emerging within study 16996.

6.4.2.2 16996-Emergent Adverse Events

Summaries of the total number and percent of SAF-LTF participants with an AE of the following categories of 16996-emergent AEs will be presented :

- All 16996-emergent adverse events

- Radium-223 dichloride- or placebo-related 16996-emergent AEs;
- Radium-223 dichloride- or placebo-related serious 16996-emergent AEs;
- 16996-emergent new primary malignancies;
- 16996-emergent bone fractures;
- 16996-emergent serious bone fractures;
- 16996-emergent bone-associated events;
- 16996-emergent serious bone-associated events;
- 16996-emergent pregnancy AEs;
- 16996-emergent febrile neutropenia and hemorrhage without regard to cytotoxic chemotherapy status.

6.4.2.3 Deaths

The number and percent of participants with deaths, and the primary cause of death (as reported by the investigator), will be tabulated and listed for SAF-LTFU participants.

7. Document History and Changes in the Planned Statistical Analysis

7.1 Document History

SAP Version	Date	Change	Rationale
1	25 May 2017	Not Applicable	Original version
1.1	01 Apr 2019	• Collection and analysis of bone fractures and bone-associated events included • Imputation rules for missing AE start dates specified • Presentation of systemic anti-cancer medications updated • Provision to provide listings in lieu of any tables added, in the event of few reported AEs during 16996 • Definition of SAF-LTF analysis set	Changes to align the SAP with Amendment 2 of the protocol. Additional analysis set for the analysis of 16996-enrolled participants
2	15 FEB 2024	1. Introduction • Specification of duration of follow-up period for breast cancer and prostate cancer studies. • Notion no multiple myeloma participants are expected to enter study 16996. 4. Analysis sets • Definiton of ENR analysis sets • Removal of SAF analysis set • Description of additional assignment details for participants enrolled in 16996 from non-eligible feeder trials • Updated document history table for SAP v1.1 to include SAF-LTF addition 5. General statistical considerations • Removal of safety and post-treatment therapy data integration from feeder studies with study 16996 into a longitudinal database • Description of limited data (including baseline characteristics and exposure) integration • Update and further description of listings presentation	Additional changes align the SAP with the protocol (Amendment 2), reporting and webposting requirements.

		• Definition of premature discontinuation • Description of interim safety analyses to meet Health Authority requirements. 6. Statistical methodology • Listing of survival assessments • Definition of 16996-emergent AEs • Description of analyses of safety endpoints and corresponding analysis sets; • Additional evaluation of fracture events and incidence of bone-associated events separately • Inclusion of demographic and baseline characteristics as well as protocol deviation summaries tables; • Specification of categories of AEs for analysis per protocol; • Definition of a SAP appendix to include the MedDRA preferred term constituting each category of AE for the safety analyses; • Removal of incidence rates and cumulative incidence rates. Consistent use of participants instead of subjects was applied throughout.	

7.2 Changes in Per-Protocol Planned Statistical Analyses

Per the Sponsor decision to perform a reduced and simplified analysis focusing on data from study 16996, the following deviations from the per-protocol planned analyses have been noted in this SAP:

- Section 4. Analysis Sets
    - Addition of of ENR and SAF-LTF analysis sets
    - Removal of SAF analysis set;
    - Accounting for the assignment of participants enrolled in 16996 from non-eligible feeder trials.

- Section 5. General Statistical Considerations
    - Removal of safety data combination between feeder studies and study 16996;
    - Description of limited data integration (including baseline characteristics and exposure);
    - Description of interim safety analyses to meet Health Authority requirements.

- Section 6. Statistical Methodology
    - Summary of all febrile neutropenia and hemorrhage events collected in study 16996 without regard to chemotherapy treatment;
    - Definition of 16996-emergent AEs.

7.3 References

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

8. Appendix

8.1 Adverse-Event Start Date Imputation

The general principle for imputing incomplete or missing AE start dates will be to assume that AEs are 16996-emergent, by imputing the start date at the earliest time in study 16996, whenever possible.

If the start date is completely missing, then the start date will be imputed using the date of informed consent to study 16996.

If the incomplete start date has day and month missing, then the following will be applied:

- If the year is same as the year of informed consent to study 16996, then the day and month of the date of informed consent to study 16996 will be assigned to the missing fields.
- If the year is prior to the year of informed consent to study 16996, then December 31 will be assigned to the missing fields.
- If the year is after the year of informed consent to study 16996, then January 01 will be assigned to the missing fields.

If the incomplete start date has missing day only, then the following will be applied:

- If the month and year are same as the year and month of informed consent to study 16996, then the date of informed consent will be assigned to the missing day.
- If the month and year are before the year and month of informed consent to study 16996, then the last day of the month will be assigned to the missing day.
- If the month and year are after the year and month of informed consent to to study 16996, then the first day of the month will be assigned to the missing day.