Summary Table of Study Protocol

Title	Prospective observational study to describe routine use of XGEVA® for prevention of skeletal-related events (SREs) in subjects with bone metastases from prostate carcinoma in Bulgaria
Protocol version identifier	20180095 version 1.0
Date of last version of the protocol	24 October 2018
EU Post Authorization Study (PAS) Register No.	N/A
Active Substance	Denosumab 120 mg, sc
Medicinal Product	XGEVA®
Product Reference	EU/1/11/703
Procedure Number	EMEA/H/C/2173/R/42
Joint PASS	No
Research Question and Objectives	The study will address the question of the use of XGEVA® for prevention of SREs in subjects with bone metastases from prostate carcinoma in Bulgaria. The primary objective is to describe real-life patterns of bone metastases management and routine use of XGEVA® for SRE prevention in subjects with bone metastases from hormone sensitive and castration-resistant prostate carcinoma. The secondary objectives are to estimate the incidence of SREs, and symptomatic SREs (SSEs), healthcare utilization and pain management.
Country of Study	Bulgaria
Author	PPD [redacted], M.D. Sr Medical Advisor Oncology Hematology Amgen (Europe) Bulgaria EOOD Viridian offices, 63 Kazbek Str, 1680 Sofia Bulgaria

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Europe B.V.
MAH Contact	Amgen Europe B.V. Minervum 7061 NL-4817 ZK Breda The Netherlands

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Investigator's Agreement

I have read the attached protocol entitled "Prospective observational study to describe routine use of XGEVA® for prevention of skeletal-related events (SREs) in subjects with bone metastases from prostate carcinoma in Bulgaria", dated 24 October 2018, and agree to abide by all provisions set forth therein.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my Subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Bulgaria EOOD.

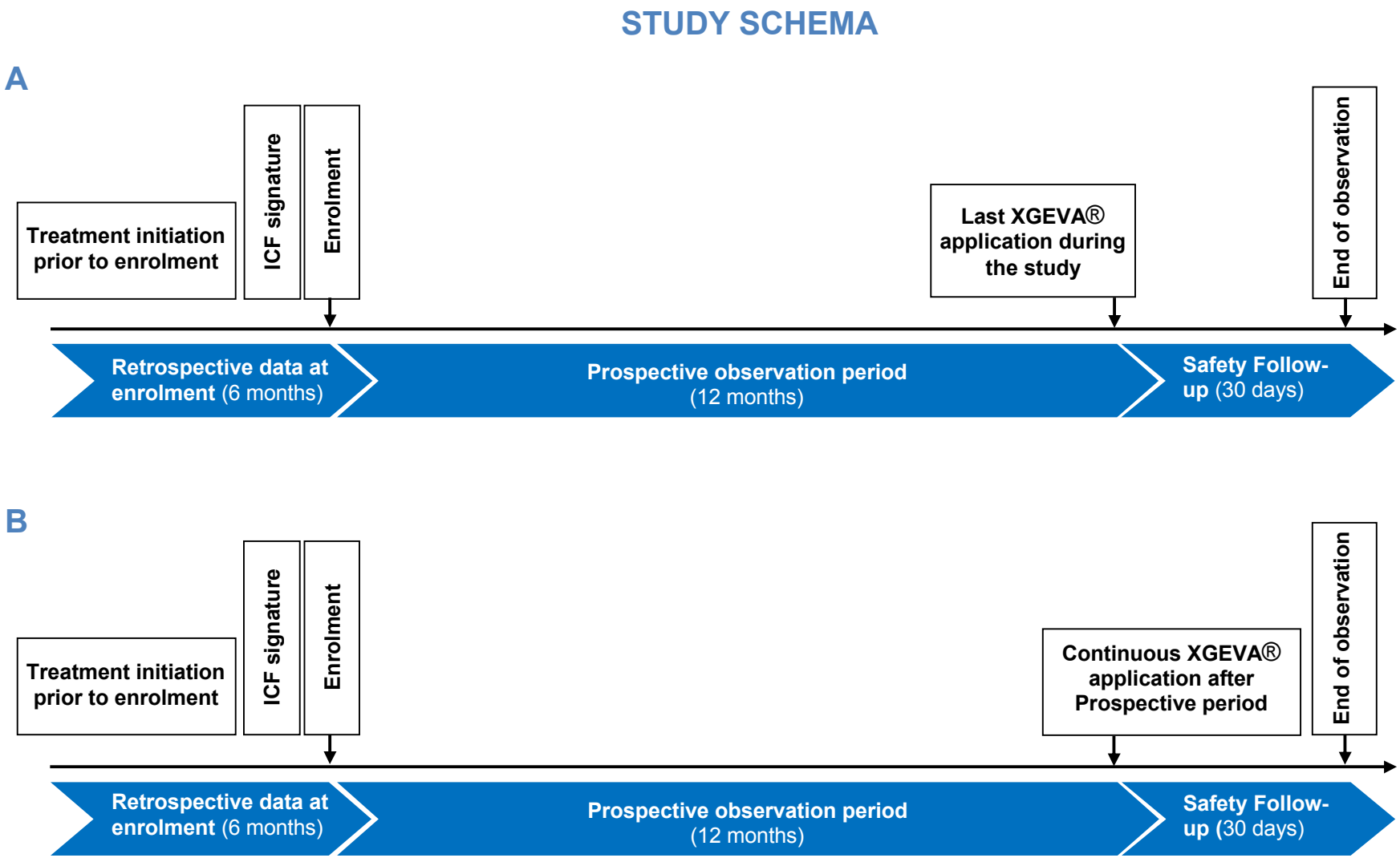
_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

Figure 1. Study Design Schema



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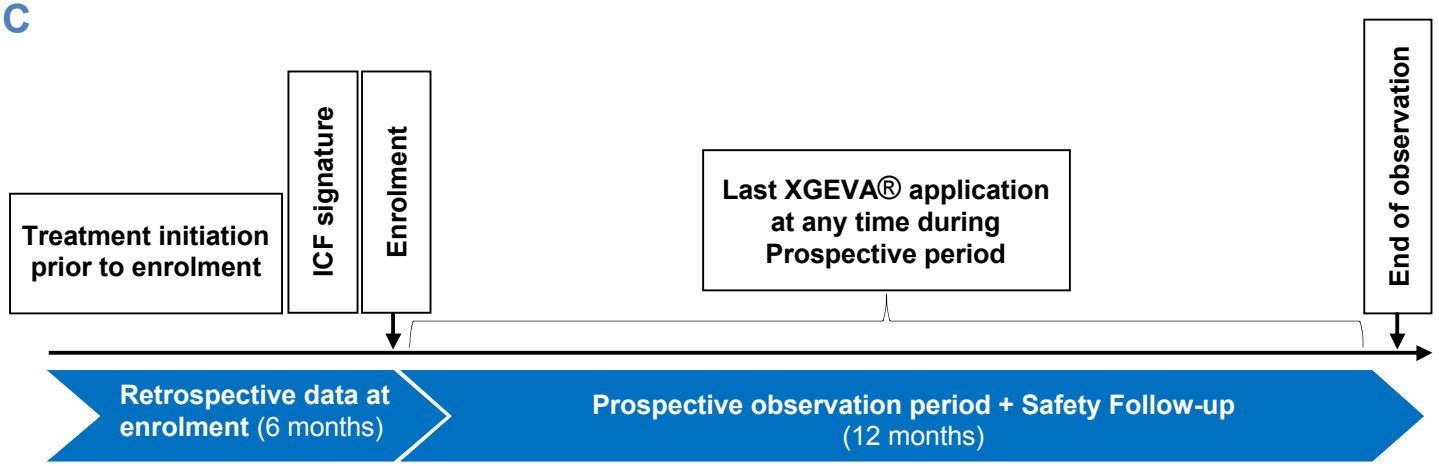

Remarks:

- Enrolment period will last 6 months.
- Data to be collected during each study period is described in the protocol.
- Data will be collected using EDC (electronic data capture) system named GoResearch™.

1. Table of Contents

2. List of Abbreviations and Terms

Abbreviation or Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
BALP	Bone-specific Alkaline Phosphatase
BMQ	Beliefs about Medicines Questionnaire
BPI	Brief Pain Inventory questionnaire
BTAs	Bone-Targeted Agents
CI	Confidence Intervals
CRPC	Castration-Resistant Prostate Carcinoma
CT	Computer Tomography
eCRF	electronic Case Report Form
ECOG performance status	Eastern Cooperative Oncology Group scale (from 0 to 5) assessing disease progression and daily living abilities of a patient, for more details see Appendix F
EDC	Electronic Data Capture
EHR	Electronic Health Records
ESMO	European Society for Medical Oncology
GFR	Glomerular Filtration Rate
HSPC	Hormone Sensitive Prostate Carcinoma
ICF	Informed Consent Form
IEC	Independent Ethics Committee
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCCN guidelines for prostate carcinoma	National Comprehensive Cancer Network guidelines for risk assessment of prostate carcinoma, for more details see Appendix G
PAMQ	Perceptions of Adherence Management Questionnaire

PSA	Prostate-Specific Antigen
RANKL	Receptor Activator of Nuclear factor-Kappa B (RANK) Ligand
sc	subcutaneously
SAP	Statistical Analysis Plan
SRE	Skeletal Related Event (nonsymptomatic pathological fracture, radiation to bone, spinal cord compression or surgery to bone)
SSE	Symptomatic Skeletal-related Event, including arthralgia, myalgia, increased bone pain
QoL	Quality of Life
End of Observation	The end of Safety Follow-up (Figure 1A,B) or the end of 12-month Prospective Observation period if XGEVA® was discontinued during the Observation period (Figure 1C) or the last visit before death, withdrawal of informed consent, or lost to follow-up, whichever occurs first
Prospective Observation period	Period between Enrolment Visit and start of Safety Follow-up defined as: 12 months of continuous XGEVA® administration (Figure 1A,B) with no longer than 60-day gap between doses or continuous XGEVA® administration until longer than 60-day gap in XGEVA® treatment followed by further data collection to the end of 12-month period (Figure 1C) or continuous XGEVA® administration until death or withdrawal of informed consent or loss-to follow-up, whichever occurs first
Retrospective period (baseline)	The period from the start of XGEVA® treatment to enrolment that may last from 1 to a maximum of 6 months
Safety Follow-up (SFU)	30 days of follow-up from last on-study XGEVA® administration at 12 months of observation period for subjects who reached 12 months of XGEVA® administration (Figure 1A) or continued XGEVA® treatment (Figure 1B). In case of discontinuation of XGEVA® during Prospective Observation period, further data will be collected until the end of 12-month observation period (Figure 1C).

3. Responsible Parties

Clinical Study Sponsor:	Amgen Bulgaria EOOD Viridian Offices, Manastirski Livadi West 63 Kazbek Str., fl. 5 1680 Sofia, Bulgaria
Key Sponsor contacts:	PPD, M.D. Sr Medical Advisor Oncology Hematology PPD Amgen (Europe) Bulgaria EOOD Viridian offices, 63 Kazbek Str 1680 Sofia Bulgaria

4. Abstract

Study Title

Prospective observational study to describe routine use of XGEVA® for prevention of skeletal-related events (SREs) in subjects with bone metastases from prostate carcinoma in Bulgaria

Study Background and Rationale

Prostate carcinoma is the most common cancer in men and the second leading cause of death due to cancer in Europe. Widely used hormone therapies are effective in hormone-sensitive prostate carcinoma (HSPC), but their efficacy decreases over time and may lead to castrate-resistant prostate carcinoma (CRPC). Patients suffering from HSPC and CRPC develop metastases to bones, which can cause many complications, including SREs. On that basis, the European Society for Medical Oncology (ESMO) 2014 guidelines recommend treating all patients with CRPC and bone metastases with bisphosphonates or denosumab, whether they are symptomatic or not.

Denosumab, a fully human antibody targeting receptor activator of nuclear factor-kappa B ligand, has been shown to be effective in SRE prevention, pain reduction, and improvement of health-related quality of life (QoL), but not overall survival in men with CRPC. Denosumab was approved in 2011 in the EU, and XGEVA® is currently indicated for prevention of SREs (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with advanced malignancies involving bone. According to the current summary of product characteristics XGEVA® is indicated also for treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The study will address the question of the use of XGEVA® for prevention of SREs in subjects with bone metastases from prostate carcinoma in Bulgaria. The study will also provide insight into the persistence and adherence to XGEVA® treatment observed in real-life clinical practice. The information gathered for a subject population representative of current clinical use of XGEVA® will be used for reimbursement negotiation by the Bulgarian heath authorities.

Research Question and Objectives

- Primary Objective

  To describe real-life patterns of bone metastasis management and routine use of XGEVA® for SREs prevention in subjects with bone metastases from prostate carcinoma.

- Secondary Objectives
  - To estimate the incidence of SREs and symptomatic SREs (SSEs) in subjects with bone metastases from HSPC and CRPC
  - To describe subject- and/or physician-reported factors that influence adherence to treatment, based on data obtained via specific questionnaires, namely:
    - Beliefs about Medicines Questionnaire (BMQ) completed by subjects and physicians,
    - Perceptions of Adherence Management Questionnaire (PAMQ) completed by physicians at two time points: after site initiation and prior to enrolment the first patient into the study and then after the last patient last visit (LPLV)
  - To describe healthcare utilization (hospitalisations for pathologic fractures, for surgery to bone, for spinal cord compression, and for radiotherapy to bone)
  - To describe pain management
- Hypothesis/Estimation

  This study is descriptive in nature; therefore, no formal hypothesis will be tested.

Study Design/Type

This is a multicentre, prospective, observational study in Bulgaria.

Study Population or Data Resource

The study will be conducted among adult subjects with bone metastases from HSPC and CRPC receiving XGEVA® in clinical routine practice. The observations will be made in 10 Bulgarian sites. The study will last 19 months: six months of the Retrospective period (before enrolment into the study), 12 months of the Prospective Observation period, and one month of the Safety Follow-up period (only for subjects who continued XGEVA® up to 12 months of the Prospective Observation period).

Summary of Patient Eligibility Criteria

Inclusion Criteria:

I. Patient at least 18 years old at the time of ICF signature
II. Patient with histologically or cytologically confirmed diagnosis of prostate carcinoma with at least one bone metastasis lesion confirmed by imaging (X-ray, MRI, or CT)
III. Patient received between one and three XGEVA® administrations in the timeframe of six months prior to enrolment
IV. Patient provided written informed consent

Exclusion Criteria:

I. Patient with bone metastases previously treated in the last six months with bisphosphonates or other bone-targeting agents (BTAs) for prevention of SREs in clinical trial or routinely
II. Patient with prostate carcinoma as a second primary malignancy
III. Patient with brain metastases
IV. Patient currently enrolled in trial with investigational drug for treatment / prevention of bone metastases and SREs

Safety Follow-up

Safety Follow-up will last 30 days after the Prospective Observation period for subjects who have reached 12 months of XGEVA® administration. In case of discontinuation of XGEVA® during the Prospective Observation period, further data will be collected until the end of a 12-month period. Relevant procedures to manage treatment-related ADRs/SADRs and AEs will be collected during this time.

Variables

- Outcome Variables

  The primary outcome variables will include demographics, clinical characteristics, and treatment patterns of subjects with bone metastases from HSPC and CRPC receiving XGEVA® in clinical routine practice.
  Key secondary outcomes will include details about SREs and SSEs, time from bone metastases diagnosis to XGEVA® initiation, factors that influence adherence to treatment evaluated by PAMQ and BMQ, hospitalisations, changes in pain severity assessed by Brief Pain Inventory (BPI) questionnaire, and pain medication.

- Exposure Variables

  The main exposure variables will be prior SRE, concomitant therapies, and type and location of investigational site.

- Other Covariates

  The potential influence of a demographic covariate (age) will be explored.

Study Sample Size

The targeted sample size is 100 subjects across 10 sites in Bulgaria. Because no prospectively formulated hypothesis will be tested, the sample size calculation is not based on statistical power calculations. The targeted sample size fulfils the requirements of country reimbursement authorities.

The exact method will be used to calculate 95% confidence intervals for binomial proportions. The sample size of 100 will determine the precision of the estimate, which is measured by the half-width of the 95% confidence interval.

Data Analysis

The analysis of this study will be descriptive in nature. Counts and percentages will be provided for categorical outcomes. Continuous outcomes will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles, and minimum and maximum values. Primary outcomes will be summarized using descriptive statistics. Secondary outcomes will be analysed using Andersen-Gill modification of the Cox proportional hazard method, treating death as competing risk (for SREs and SSEs) and will be summarized descriptively. Exploratory outcomes will be summarized using descriptive statistics. For each outcome parameter, the impact of covariates will be assessed using generalized linear models, when appropriate.