Summary Table of Study Protocol

Title	A two-stage, prospective observational study describing the use and effectiveness of XGEVA®/ANJIAWEI® for the prevention of skeletal related events in patients with bone metastases from solid tumors relative to ZOMETA® in the People's Republic of China
Protocol version identifier	20190036, Version **2.0**
Date of last version of the protocol	**04 June 2021**
EU Post Authorization Study (PAS) Register No	NA for initial protocol
Active Substances	denosumab or zoledronic acid
Medicinal Products	XGEVA®/ANJIAWEI® or ZOMETA®
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	Stage 1: Drug Use and Safety • Describe the use of XGEVA®/ANJIAWEI® and ZOMETA® administered for the prevention of skeletal-related events (SREs) among patients with bone metastases secondary to solid tumors (breast, prostate, or lung cancer) • Describe the comparability of prognosis for SREs at time of initiating a bone targeting agent (BTA) between patients who initiate XGEVA®/ANJIAWEI® and patients who initiate ZOMETA® • Describe the incidence of adverse events of special interest among XGEVA®/ANJIAWEI® patients Stage 2: Effectiveness for Prevention of Symptomatic SREs • Describe the effectiveness of XGEVA®/ANJIAWEI® relative to ZOMETA® for prevention of symptomatic SRE
Country of Study	People's Republic of China
Authors	PPD MD (Global Development), Amgen Inc. PPD (CfOR), Amgen Inc. PPD (Biostatistics), Amgen Inc.

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Inc. and Beigene Inc.
MAH Contact	PPD , MD Global Development, Amgen Inc.

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures (SOPs).

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Investigator's Agreement

I have read the attached protocol entitled, "A two-stage, prospective observational study describing the use and effectiveness of XGEVA®/ANJIAWEI® for the prevention of skeletal related events in patients with bone metastases from solid tumors relative to ZOMETA® in the People's Republic of China", dated **10 February 2023**, and agree to abide by all provisions set forth therein.

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 Inc.

Signature

Name of Investigator: Date (DD Month YYYY)

Title:

Name of Hospital/Site:

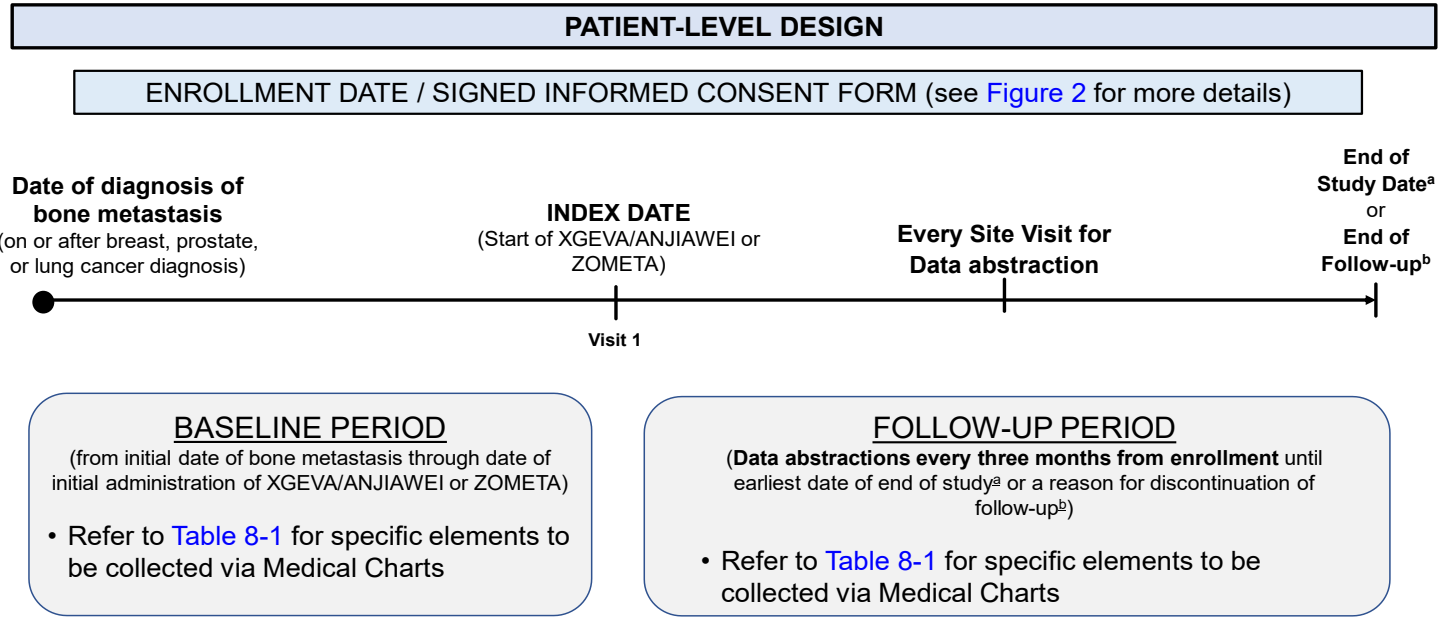
Address/City/State/Country:

Phone Number:

Email:

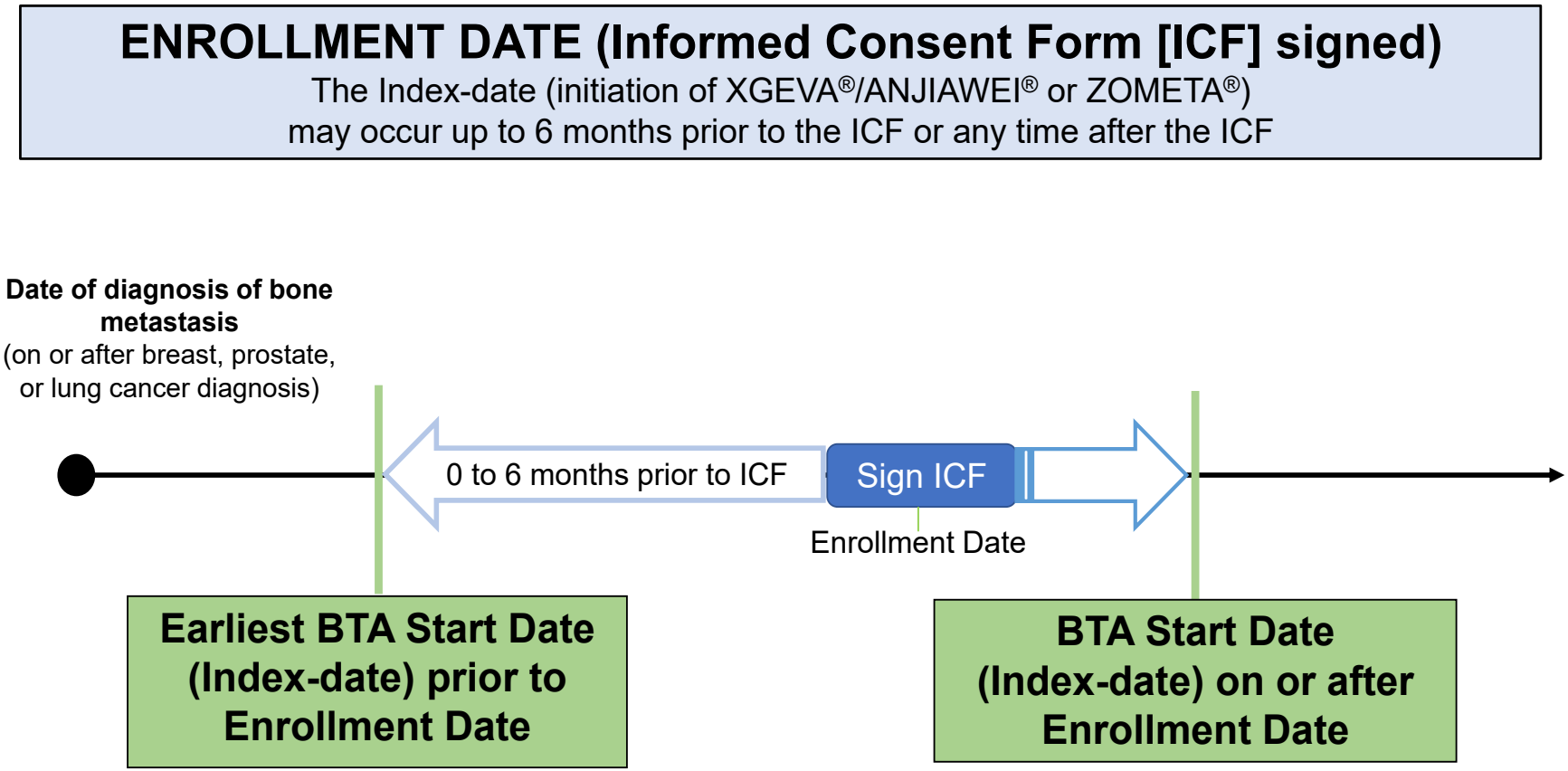
Study Design Schema

Figure 1. Study Design Schema – Patient Level Design



[a] End of Study date is defined as the date 60 months after the first patient is enrolled.
[b] Reasons for discontinuation of follow-up may include: switch to another type of BTA, discontinuation of BTA treatment, lost to follow-up, withdrawal of consent, or death.

Figure 2. Study Design Schema – Patient Enrollment/Consent and Index-Date



BTA = bone targeting agent; ICF = informed consent form

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2. List of Abbreviations

Abbreviation/Acronym	Definition
AAOMS	American Association of Oral and Maxillofacial Surgeons
AFF	atypical femoral fracture
ASBMR	American Society for Bone and Mineral Research
BTA	bone targeting agents
CDE	Center for Drug Evaluation
CRF	case report form
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EU	European Union
GCP	Good Clinical Practice
GCTB	giant cell tumor of bone
HGRAC	Human Genetics Resources Administration of China
HR	hazard ratio
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgG2	immunoglobulin G2
IPTW	inverse probability of treatment weights
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NA	not applicable
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
PAS	Post Authorization Study
PET	positron emission tomography
PMC	Post Marketing Commitment
PSM	propensity score-matching
PT	Preferred term
Q4W	Every 4 weeks

Abbreviation/Acronym	Definition
ONJ	osteonecrosis of the jaw
RANKL	receptor activator of nuclear factor kappa β ligand
RT	radiation therapy
RWE	real-world evidence
SAP	statistical analysis plan
SD	standard deviation
SMD	standardized mean difference
SOP	standard operating procedure
SRE	skeletal-related events
US/USA	United States/United States of America

3. Responsible Parties

PPD , Center for Observational Research Senior Manager, Amgen Inc., Thousand Oaks, USA.

4. Abstract

- **Study Title:**
  A two-stage, prospective observational study describing the use and effectiveness of XGEVA®/ANJIAWEI® for the prevention of skeletal related events in patients with bone metastases from solid tumors relative to ZOMETA® in the People's Republic of China
- **Study Background and Rationale:**
  Bone metastases are a common outcome in patients with solid tumors and are present in up to 70% of patients with advanced breast and prostate cancer and more than one-third of patients with advanced lung cancer (Coleman, 2006). Patients with bone metastases may experience local irreversible skeletal complications including pathologic fracture, spinal cord compression, and radiation or surgery to bone, known collectively as skeletal-related events (SREs). Skeletal-related events are indicators of poor prognosis and cause substantial pain and morbidity.

  In May 2019, the China National Medical Products Administration (NMPA) approved XGEVA®/ANJIAWEI® for giant cell tumor of bone (GCTB), and in November 2020, the China NMPA approved XGEVA®/ANJIAWEI® for the indication of bone metastasis from solid tumors and multiple myeloma.

  This is a Post Marketing Commitment (PMC) to assess the real-world use and effectiveness of XGEVA®/ANJIAWEI® for the prevention of SREs relative to ZOMETA®, in clinical practice of the People's Republic of China.
- **Study Feasibility Considerations:**
  The feasibility of this study to complete data collection and patient recruitment, is supported by:
  - Facilitating enrollment of local patients through leading academic clinicians that are treating patients with bone targeting agents (BTAs).
  - Using medical records as a practical mechanism for assessment of SREs.

- Extrapolating from other real-world studies in China which have enrolled hundreds of patients in the oncology setting, thus informing the feasibility of this PMC study.

- **Research Question and Objectives:**

Primary Objectives	Endpoints
Stage 1: Drug Use and Safety	
• Describe the use of XGEVA®/ANJIAWEI® and ZOMETA® administered for the prevention of skeletal-related events (SREs) among patients with bone metastases secondary to solid tumors (breast, prostate, or lung cancer)	• The frequency of administration and duration of treatment by XGEVA®/ANJIAWEI® and ZOMETA®
• Describe the comparability of prognosis for SREs at time of initiating a bone targeting agent (BTA) between patients who initiate XGEVA®/ANJIAWEI® and patients who initiate ZOMETA®	• Demographic and clinical characteristics (eg, comorbidities, prior skeletal-related events, tumor type) of patients that may be related to prognosis for SRE by treatment cohort (XGEVA®/ANJIAWEI® and ZOMETA®)
• Describe the incidence of adverse events of special interest among XGEVA®/ANJIAWEI® patients	• Adverse events of special interest (ie, osteonecrosis of the jaw, atypical femoral fracture [AFF], and hypocalcemia)
Stage 2: Effectiveness for Prevention of Symptomatic SRE	
• Describe the effectiveness of XGEVA®/ANJIAWEI® relative to ZOMETA® for prevention of symptomatic SRE	• Time to first symptomatic SRE. SRE is defined as 1 or more of the following: pathologic fracture (vertebral or non-vertebral), radiation therapy to bone, surgery to the bone, or spinal cord compression.

- **Hypothesis:**
  The analysis of all study endpoints will be descriptive in nature; there is no hypothesis being tested.
- **Study Design/Type:**
  This is a prospective, observational study of patients who are administered treatment with either XGEVA®/ANJIAWEI® or ZOMETA® for the prevention of SREs in the People's Republic of China.
- **Study Population or Data Resource:**
  This study plans to enroll a total of approximately 1000 patients diagnosed with bone metastases secondary to breast, prostate, or lung cancer and who are administered XGEVA®/ANJIAWEI® or ZOMETA® for prevention of SREs within the clinical setting of the People's Republic of China. Among the 1000 patients, a minimum of 100 patients for each tumor type (breast, prostate, lung) will be enrolled with approximately 500 patients enrolled for each treatment cohort (XGEVA®/ANJIAWEI® or ZOMETA®.
- **Summary of Patient Eligibility Criteria:**
  A summary of the inclusion criteria include:

- Patient has provided written informed consent (referred to as enrollment date).
- Diagnosis of bone metastasis secondary to breast, prostate, or lung cancer prior to initial use of BTA. Evidence of confirmed bone metastasis by either bone scan, skeletal survey, computerized tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, or clinical summary documentation.
- New user of a BTA for the prevention of SRE, specifically XGEVA®/ANJIAWEI® (brand name only) or ZOMETA® (brand name only).
- **Patient** age**s** ≥ 18 years as of enrollment date or index-date (whichever occurs first).
- A calculated serum creatinine clearance of ≥ 30 mL/minute using the Cockcroft-Gault formula.

The exclusion criteria include:

- Any prior use of bisphosphonate therapy or a receptor activator of nuclear factor kappa β ligand (RANKL) inhibitor for the purpose of prevention of SREs prior to index-date.
- Patients diagnosed with multiple myeloma.
- Patients with GCTB.
- At the time of signing the ICF, to the best of the patient's and investigator's knowledge, patients with: prior history or current evidence of osteonecrosis/osteomyelitis of the jaw; OR active dental or jaw condition which requires oral surgery, including tooth extraction or non-healed wound after dental/oral surgery; OR planned invasive dental procedure for the course of the study.
- Patients that are unlikely to continue receiving care at the enrolling site, based on the perspective and opinion of the investigator.

- **Baseline Period:**
  The baseline period is defined as the time between the date of initial diagnosis of bone metastasis (inclusive) and the date of BTA initiation (index-date).
- **Follow-up:**
  Follow-up begins on the index date (day 1) and continues until earliest of the following events: end of study (EOS) date, switch to another type of BTA (meaning, any deviation away from the BTA that was initiated at index-date, including switch from brand name to biosimilar), discontinuation of BTA treatment, lost to follow-up, withdrawal of consent, or death.

- **Variables:**
  - Exposure Assessment: BTA Treatment Exposure
    Bone targeting agent (XGEVA®/ANJIAWEI® or ZOMETA®) exposure will be assessed at the initial enrollment visit, as well as each subsequent clinic visit. The utilization information (date of exposure and drug) will be extracted from the patient medical record.

– Outcome Variables

BTA utilization outcomes include:

- Total duration of exposure to BTA (defined as the BTA-index date through the end of follow-up).
- The number of BTA administrations (defined as the number of administrations from BTA-index-date through the end of follow-up).

Safety Outcomes:

- Adverse events of special interest outcomes include osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), and hypocalcemia

Demographic and Clinical Characteristics and Prognostic Factors for SREs:

- The prognostic factors for SREs will include demographic and medical history, as well as the clinical, disease, and laboratory characteristics summarized in Table 8-1.

Outcomes Stage 2: Effectiveness of XGEVA®/ANJIAWEI® for prevention of SREs

The effectiveness endpoint of this study is "time to first symptomatic SRE". Skeletal-related event is defined as 1 or more of the following: pathologic fracture (vertebral or non-vertebral), radiation therapy to bone, surgery to the bone, or spinal cord compression (see Section 8.3.2.4 for more details).

- **Study Sample Size**

This is a descriptive study of respectively 1000 patients, which includes a minimum of 100 patients for each tumor type (breast, prostate, and lung) and approximately 500 patients per treatment cohort (XGEVA®/ANJIAWEI® or ZOMETA®). Assuming a 36-month enrollment duration and up to 60-month total study duration, the precision of the treatment effectiveness estimate measured as time to first symptomatic SRE is presented in Table 8-2 for different assumptions of hazard ratio (HR), median time to symptomatic SRE in the ZOMETA® cohort, potential annual dropout rates, total number of events.

- **Data Analysis**

The data will be analyzed in 2 stages.

Stage 1:

Stage 1 describes the baseline demographic and clinical characteristics of patients using XGEVA®/ANJIAWEI® and ZOMETA®, and describes the incidence of adverse events of special interest in patients using XGEVA®/ANJIAWEI®.

All descriptive statistics generated for this stage will include the following: continuous data will include mean, standard deviation, median, interquartile range (Q1 to Q3), and range, while categorical data will be summarized using frequency counts and percentages. Incidence of adverse events of special interest (ONJ, AFF, hypocalcemia) will be estimated as number of patients with adverse events of special interest events per 1000 person-years.

Before initiating Stage 2, the following assessments will be conducted to evaluate comparability of the 2 treatment cohorts:

- The overlap of the distribution of the estimated propensity score between the treatment cohorts (XGEVA®/ANJIAWEI® and ZOMETA®) will be assessed
- The standardized mean difference of baseline demographic and clinical characteristics between XGEVA®/ANJIAWEI® and ZOMETA® cohorts will be assessed
- The standardized mean difference in duration of BTA use for XGEVA®/ANJIAWEI® and ZOMETA® cohorts.

Stage 2:

If the treatment cohorts are comparable, based on results of the comparability evaluation assessments conducted in stage 1, then the effectiveness of XGEVA®/ANJIAWEI® relative to ZOMETA® for time to first symptomatic SRE will be estimated using the HR of XGEVA®/ANJIAWEI® compared with ZOMETA® and its 95% confidence interval. Additionally, Kaplan Meier curves and annualized event rates for each treatment cohort will also be estimated.

If the treatment cohorts are not comparable, then the relative effectiveness analyses will not be conducted; however, Kaplan Meier curves and annualized event rates will still be generated for each treatment group. Additional effectiveness measures could be considered (eg, to assess the SRE yearly event rate) within the same treatment cohort.

5. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	**10 February 2023**	**See Summary of Changes**	**Removal of inclusion criteria for life expectancy, Table 8-1, addition of new appendix F, safety language changes.**	**See Summary of Changes**

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Bone metastases are a common outcome in patients with solid tumors and occur in up to 70% of patients with advanced breast and prostate cancer, and more than one third of patients with advanced lung cancer (Coleman, 2006). Among patients diagnosed with solid tumors that metastasize to the bone, the outcome is the dysregulation of normal bone remodeling, consequently resulting in weakened bone structure and integrity, and increased risk for painful and irreversible skeletal complications. These complications include pathologic fracture, spinal cord compression, radiation to the bone (for severe pain), and surgery to the bone (stabilization), known collectively as skeletal-related

events (SREs). Skeletal-related events are indicators of poor prognosis; they cause substantial pain and morbidity and are associated with decreased quality of life.

Bone targeting agents (BTAs), such as the intravenous bisphosphonate, ZOMETA® (zoledronic acid), and receptor activator of nuclear factor kappa β ligand (RANKL) inhibitor XGEVA®/ANJIAWEI® (denosumab), are used for the prevention of SREs in patients with advanced cancers.

Previously conducted multi-country, randomized, double blind, active controlled, noninferiority trials have demonstrated that in patients with breast or castrate resistant prostate cancer, the median time to first SRE was longer with XGEVA®/ANJIAWEI® treatment than compared with zoledronic acid treatment (Fizazi et al, 2011; Stopeck et al, 2010). In breast cancer patients with metastatic bone disease, there was an observed 18% (hazard ration [HR]: 0.82; 95% CI 0.71 - 0.95) risk reduction of SREs in patients using XGEVA®/ANJIAWEI® compared to ZOMETA® (Stopeck et al, 2010). Similar results were observed among patients with castrate resistant prostate cancer, where the median time to first SRE with XGEVA®/ANJIAWEI® and ZOMETA® was 20.7 months and 17.1 months, respectively (HR: 0.82; 95% CI: 0.71 - 0.95) (Fizazi et al, 2011). Among a subgroup of solid tumor patients (excluding breast, prostate, and multiple myeloma cancer patients), the median time to first SRE with XGEVA®/ANJIAWEI® and ZOMETA® was 21.4 months and 15.4 months (HR: 0.81; 95% CI: 0.68 – 0.96) (Henry et al, 2014).

6.2 Rationale

XGEVA®/ANJIAWEI®(denosumab) is a human immunoglobulin G2 (IgG2) monoclonal antibody that binds to human RANKL. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

XGEVA® (denosumab) was first approved on 18 November 2010 (in the United States) for the prevention of SREs in patients with bone metastasis from solid tumors at a dose of 120 mg. Since then, XGEVA® has been approved in a total of 79 region/countries, which includes 28 of the European Union and 3 European Economic Area countries. Since XGEVA® was first approved for sale in November 2010, approximately 1 477 176 people have been prescribed XGEVA® 120 mg for treatment.

In May 2019, the China National Medical Products Administration (NMPA) approved XGEVA®/ANJIAWEI® for the following indication:

- Giant Cell Tumor of Bone (GCTB)
  - XGEVA®/ANJIAWEI® is indicated for the treatment of adults and skeletally mature (defined as at least 1 mature long bone and had a body weight ≥ 45 kg) adolescents with GCTB that is unresectable or where surgical resection is likely to result in severe morbidity
  - The recommended dose of XGEVA®/ANJIAWEI® is 120 mg administered every 4 weeks (Q4W) with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen

In November 2020, the China NMPA approved XGEVA®/ANJIAWEI® for the indication:

- Bone Metastasis from Solid Tumors and Multiple Myeloma
  - XGEVA®/ANJIAWEI® is indicated for the prevention of SREs in patients with bone metastasis from solid tumors and in patients with multiple myeloma.
  - The recommended dose of XGEVA®/ANJIAWEI® is 120 mg administered as a subcutaneous injection Q4W in the upper arm, upper thigh, or abdomen.

The rationale for this study is that it is a post marketing commitment (PMC) to assess the real-world use, safety, and effectiveness of XGEVA®/ANJIAWEI® for the prevention of SREs relative to ZOMETA®, in clinical practice in the People's Republic of China.

6.3 Feasibility Considerations

This is an observational, prospective, study of patients who are being prescribed either XGEVA®/ANJIAWEI® or ZOMETA® for the prevention of SREs in the post-marketing setting in People's Republic of China. Ultimately, the objective of this study is to evaluate the effectiveness of XGEVA®/ANJIAWEI® for the prevention of symptomatic SREs relative to ZOMETA® in Chinese patients with bone metastasis from solid tumors (breast, prostate, or lung cancer).

In order to inform strategies to address potential confounding (eg, differences in prognostic variables between treatment cohorts, such as extent of bone metastasis) when conducting the effectiveness analyses it is necessary to first understand the baseline demographic and clinical characteristics of patients prescribed either XGEVA®/ANJIAWEI® or ZOMETA®, and to understand the patterns of use of XGEVA®/ANJIAWEI® and ZOMETA®. Therefore, the study analysis will be conducted in 2 stages:

- Stage 1: Describe use of XGEVA®/ANJIAWEI® and ZOMETA®, baseline patient characteristics, and incidence of specific adverse events of interest
- Stage 2: Effectiveness of XGEVA®/ANJIAWEI® relative to ZOMETA® to prevent SREs, if deemed possible as outlined below in Section 8.7.1.1 “Monitoring for comparability during Enrollment”.

The feasibility of this study to complete data collection and patient recruitment, is supported by:

- Facilitating enrollment of local patients through leading clinicians that are treating patients with BTAs.
- Utilizing patient medical records, which provide a mechanism for a practical assessment of SREs.
- Extrapolating from other real-world studies in China which have enrolled hundreds of patients in the oncology setting, thus informing the feasibility of this PMC study.

Real World Evidence (RWE) study with an SRE endpoint conducted in China:

To inform both the feasibility of ascertaining SRE endpoints and the frequency of SRE endpoints within real-world clinical practice in Chinese cancer patients, we identified a published study that evaluated the association between BTAs and the incidence of SREs (Ding et al, 2012). Briefly, Ding et al, 2012 described tolerability, SREs, and adverse events among 181 breast cancer patients who had bone metastasis and received prolonged treatment (≥ 2 years) with a bisphosphonate. Effectiveness for 3 types of bisphosphonates was assessed by examining the incidence rates of SREs in months 0 to 24 versus ≥ 24 months. The study was conducted in 1 medical center, Cancer Hospital and Institute of the Chinese Academy of Medical Sciences, using data from January 2005 through May 2009 obtained through chart review. The 2-year cumulative incidence of SREs ranged from 22% to 43% in this study depending on type of bisphosphonate.

RWE study with an SRE endpoint conducted globally:

A prospective, observational study that included an SRE endpoint was conducted in centers across Germany, Italy, Spain, United Kingdom, Canada, and the United States (Hoefeler et al, 2014). In this study, the approach to data collection included baseline demographic and medical history collected at enrollment of patients with bone metastasis. In addition, the patients were followed prospectively through their medical records to identify the occurrence of SREs. Skeletal-related events were classified by the investigator as: pathologic fracture, radiation to bone, spinal cord compression, or surgery to bone.

Relevant examples of RWE studies with an effectiveness endpoint conducted in China:

Similar in approach to data accrual in the work by Ding et al, 3 studies have been conducted to obtain the real-world effectiveness of bevacizumab for advanced non-small cell lung cancer (NSCLC) in China (Li X et al, 2019; Qi et al, 2019; Xing et al, 2018). All 3 of these studies evaluated the real-world effectiveness (endpoint of progression free survival) and safety profile of bevacizumab in a Chinese cohort with advanced NSCLC through use of medical charts for data accrual and use of a 2-arm study design.
Qi et al, 2019 included a total of 415 patients (106 patients receiving bevacizumab and 309 patients not receiving bevacizumab) from 1 medical center, National Cancer Chinese Academy of Medical Sciences and Peking Union Medical College, using data from February 2010 to September 2017 obtained by chart review. To reduce the risk of confounding, propensity score-matching (PSM) was performed and 105 pairs were identified for analysis. The other studies used a similar approach and study design;
Li X et al, 2019 included a total of 233 patients over approximately a 5-year period; and Xing et al, 2018 included a total of 149 patients over approximately a 7-year period.

6.4 Statistical Inference (Estimation or Hypothesis)

The analysis of all study endpoints will be descriptive in nature; there is no hypothesis being tested.

7. Research Question and Objectives/Endpoints

Primary Objectives	Endpoints
Stage 1: Drug Use and Safety	
• Describe the use of XGEVA®/ANJIAWEI® and ZOMETA® administered for the prevention of skeletal-related events (SREs) among patients with bone metastases secondary to solid tumors (breast, prostate, or lung cancer)	• The frequency of administration and duration of treatment by XGEVA®/ANJIAWEI® and ZOMETA®
• Describe the comparability of prognosis for SREs at time of initiating a bone targeting agent (BTA) between patients who initiate XGEVA®/ANJIAWEI® and patients who initiate ZOMETA®	• Demographic and clinical characteristics (eg, comorbidities, prior skeletal-related events, tumor type) of patients that may be related to prognosis for SRE by treatment cohort (XGEVA®/ANJIAWEI® and ZOMETA®)
• Describe the incidence of adverse events of special interest among XGEVA®/ANJIAWEI® patients	• Adverse events of special interest (ie, osteonecrosis of the jaw, atypical femoral fracture [AFF], and hypocalcemia)

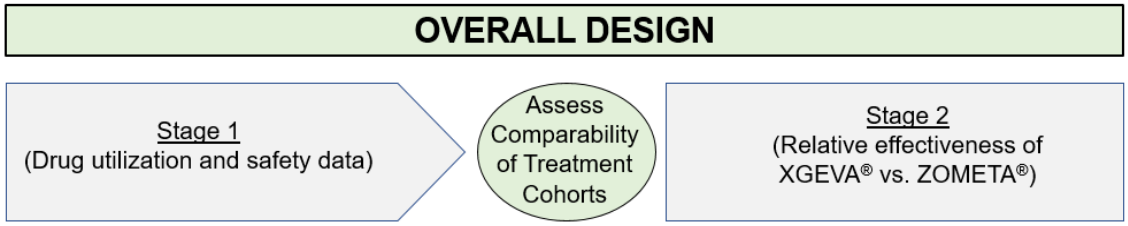
Primary Objectives	Endpoints
Stage 2: Effectiveness for Prevention of Symptomatic SRE	
• Describe the effectiveness of XGEVA®/ANJIAWEI® relative to ZOMETA® for prevention of symptomatic SRE	• Time to first symptomatic SRE. SRE is defined as 1 or more of the following: pathologic fracture (vertebral or non-vertebral), radiation therapy to bone, surgery to the bone, or spinal cord compression.

8. Research Methods

8.1 Study Design

This study is a two-stage, prospective observational study assessing therapy use, safety, and effectiveness among patients in the People's Republic of China who are administered either XGEVA®/ANJIAWEI® (denosumab 120 mg Q4W) subcutaneously or ZOMETA® (4 mg Q4W) intravenously for the prevention of SREs in the post-marketing setting in the People's Republic of China. The study analysis will be conducted in 2 stages. In the first stage, data on drug use will be collected to describe how XGEVA®/ANJIAWEI® and ZOMETA® are used in routine clinical practice in the People's Republic of China. Data on adverse events of special interest will be collected for XGEVA®/ANJIAWEI® treated patients. In the second stage, analyses describing the effectiveness of XGEVA®/ANJIAWEI® relative to ZOMETA® will be performed; the second stage will be conditional on demonstrating in the first stage how potential confounding can be addressed.

Figure 3. Overall Design Schema



Note: Monitoring of patient enrollment will be conducted on a continual basis approximately every 3 to 6 months (and throughout entire duration of study execution) after the first initial patient has been enrolled in the study (see Section 8.7.1.1 for more details).

8.2 Setting and Study Population

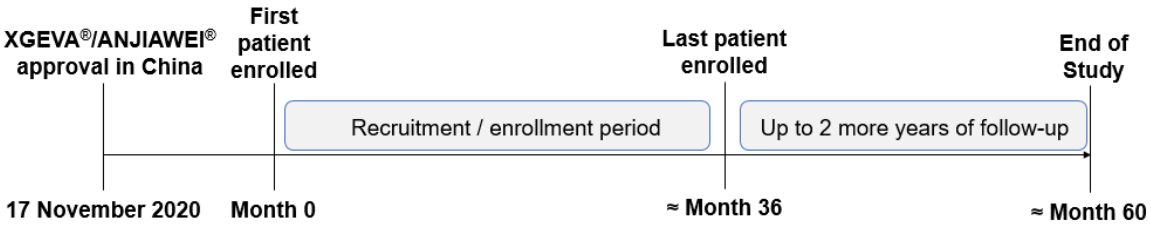
This study plans to enroll a total of approximately 1000 patients diagnosed with bone metastases secondary to breast, prostate, or lung cancer and who are administered XGEVA®/ANJIAWEI® or ZOMETA® for prevention of SREs within the clinical setting of

the People's Republic of China. Among the 1000 patients enrolled, a minimum of 100 (10%) patients for each tumor type (breast, prostate, lung) will be enrolled, and 500 patients will be enrolled in each treatment cohort (XGEVA®/ANJIAWEI® and ZOMETA®, respectively). All eligible patients will be identified by the recruiting physician either after XGEVA®/ANJIAWEI® or ZOMETA® treatment is initiated, or when plans for treatment initiation have been decided (Figure 2). In the rare event that a patient signs the informed consent form (ICF) prior to the planned initiation of XGEVA®/ANJIAWEI® or ZOMETA®, but does not receive at least 1 administration of XGEVA®/ANJIAWEI® or ZOMETA®, the patient will remain in the study; however, a patient-replacement that meets all inclusion and exclusion study criteria, can be enrolled.

8.2.1 Study Period

Study initiation and patient enrollment is planned to be executed following the approval of the protocol by China Center for Drug Evaluation (CDE) and Human Genetics Resources Administration of China (HGRAC), and upon completion of site(s) initiation. Patient enrollment will stop after meeting sample size requirements of approximately 1000 (500 per treatment cohort). The total study period is anticipated to be 60 months which includes the 36 months of patient enrollment (on a rolling basis) and execution of patient follow-up time.

Figure 4. Study Period Schema



At the time of signing the ICF, the patient will be considered enrolled in the study (this represents the study enrollment date). The date a patient initiates the incident BTA (ZOMETA® or XGEVA®/ANJIAWEI®) represents the index-date. The index-date can occur on or after the Enrollment Date or between 0 to 6 months prior to the Enrollment Date if the patient initiated the BTA at the investigator site where the ICF was signed and there is sufficient evidence of BTA administration available in the medical record (See Figure 2). While patients can be identified retrospectively for enrollment consideration in

this study (See Figure 2), the collection of retrospective data will begin only after the patient signs the ICF.

As depicted in Figure 1 and Figure 2, the baseline period includes data collected from initial diagnosis of bone metastasis to the date of BTA initiation (referred to as index-date), as described below in Section 8.2.4. For the follow-up period, data will be collected for up to 60 months following the date of the first patient enrolled, as described below in Section 8.2.5.

8.2.2 Selection and Number of Sites

Up to 50 sites will be selected to participate in this study, in order to meet the criteria for sample size. The process for site selection will include investigator interest; investigator access to prescribe either ZOMETA® or XGEVA®/ANJIAWEI®; potential ability of a site to enroll patient(s); experience conducting study enrollment, execution, and electronic case report form (eCRF) completion; and adequate facilities and staffing, to complete required study activities.

Study site(s) may be closed to enrollment if the site does not identify and enroll patients for study inclusion within 3 months of site initiation. Sites will be monitored for patient enrollment activity and to ensure accurate completion of eCRFs.

8.2.3 Patient Eligibility

After the decision is made by the physician and the patient to use a BTA according to local guidelines and approved indication, patients will be asked to consent to study participation by providing consent themselves or by their legally authorized representative.

8.2.3.1 Inclusion Criteria

1. Patient has provided written informed consent (referred to as enrollment date).
2. Diagnosis of bone metastases secondary to breast, prostate, or lung cancer prior to initial use of a BTA. Evidence of confirmed bone metastasis by either bone scan, skeletal survey, computerized tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, or clinical summary documentation.
3. New user of a BTA, specifically XGEVA®/ANJIAWEI® (brand name only) or ZOMETA® (brand name only), for the prevention of SREs, after the decision is made by the physician and the patient to use a BTA according to local guidelines and approved indication (Index-date is the date of initiating the incident BTA).
    a. Among the patients with an index-date between 0 to 6 months prior to ICF, the patient must have initiated the BTA at the investigator site where the ICF was signed.

4. Patient ages ≥ 18 years as of enrollment date or index-date (whichever occurs first)
7. A calculated serum creatinine clearance of ≥ 30 mL/minute using the Cockcroft-Gault formula

8.2.3.2 Exclusion Criteria

1. Any use of a BTA, including bisphosphonate therapy or a RANKL inhibitor, for the purpose of prevention of SREs prior to index-date.
2. Patients diagnosed with multiple myeloma.
3. Patients with GCTB.
4. At the time of ICF, to the best of the patient's and investigator's knowledge, patients with: prior history or current evidence of osteonecrosis/osteomyelitis of the jaw; OR active dental or jaw condition which requires oral surgery, including tooth extraction or non-healed wound after dental/oral surgery; OR planned invasive dental procedure for the course of the study.
5. Patients that are unlikely to continue receiving care at the enrolling site, based on the perspective and opinion of the investigator.

8.2.4 Baseline Period

Upon enrollment in this study, the patient's medical record will be reviewed to obtain information on demographic characteristics, physical measurements, medical history and comorbid conditions, prior medication exposure, laboratory values, and clinical and diagnostic characteristics. All baseline covariates outlined in Table 8-1 will be collected via medical record data abstraction upon study enrollment visit, based on treatment index-date.

The baseline period is defined as the time between the date of initial diagnosis of bone metastasis (inclusive) and the date of BTA initiation (index-date). During this time period the most proximal value of each baseline covariate, relative to the index-date, will be captured.

8.2.5 Study Follow-up

Follow-up begins on the index date (day 1) and continues until earliest of the following events: end of study (EOS) date, switch to another type of BTA (meaning, any deviation away from the BTA that was initiated at index-date, including switch from brand name to biosimilar), discontinuation of BTA treatment, lost to follow-up, withdrawal of consent, or death.

Clinical assessment information that is ascertained during the course of standard-of-care will be collected by either the treating physician, site representative, or delegate, into the eCRF forms from patients' medical records, during and up through the end of follow-up.

If a patient does not return to the site for 100 consecutive days, the site may be contacted to confirm if the patient did in fact not return to the site for care or determine if the site failed to retrieve clinical assessment information.

Definitions:

- End of Study Date: defined as 60 months after the first subject enrolled in the study.
- Switch to another type of BTA: defined as a change in BTA-therapy away from the BTA used at index-date, including switch from brand name to biosimilar. The date of BTA-switch is defined as the day prior to administration of the new BTA therapy or 30 days after the last administration date of the BTA used at index-date, whichever occurs first.
- Discontinuation of BTA: A patient that discontinues using the BTA is defined as a patient that satisfies both criteria:
  - 1) a patient that did not receive an administration of either the BTA that was used at index-date, nor a different BTA (which would indicate a switch to another type of BTA), within the 0 to 100 days following the last administration date of BTA; and
  - 2) had ≥ 1 site visit within 0 to 100 days following the last administration date of BTA.

  The date of discontinuation is defined as either (*whichever occurs first)*:
  - 30 days after the last date of BTA administration;
  - the date of the last recorded site visit.
- Loss to follow-up: defined as a patient that does not return to the site within 100 days of the last administration date of BTA. The date of loss-to-follow-up is defined as the date associated with the last site visit of the administered BTA.
- Death: in the event of death, the end date of follow-up would be defined as 30 days after the last administration date of the BTA or date of death, whichever occurs first.

At each site visit for a patient, clinical assessment for outcomes of interest and data collection by site, delegate, or treating physician will be extracted from the patient medical record and will take place according to the schedule outlined in Table 8-1, throughout follow-up for the patient. There will not be a requirement for a minimum number of site visits after enrollment in the study.

8.3 Variables

8.3.1 Exposure Assessment: BTA Treatment Exposure

New use of XGEVA®/ANJIAWEI® or ZOMETA® is the exposure of interest. This is defined as initiation of treatment with XGEVA®/ANJIAWEI® or ZOMETA® for prevention of SREs, with no previous use of either of these medications or of other BTAs for this indication of SREs prior to the index-date, during the baseline time period (date from the initial date of bone metastasis diagnosis and the index-date). Assuming the patient

satisfies all inclusion and exclusion criteria, exposure is defined as receiving at least 1 administered dose of XGEVA®/ANJIAWEI® or ZOMETA®.

Bone targeting agent (XGEVA®/ANJIAWEI® or ZOMETA®) exposure will be assessed at the initial enrollment visit, as well as each subsequent clinic visit. The utilization information (date of exposure and drug) will be extracted from the patient medical record, as described below in Table 8-1.

8.3.2 Outcome Assessment

8.3.2.1 Definition of BTA Utilization

Drug utilization outcomes include:

- Total duration of exposure to BTA (defined as the index date through the end of follow-up).
- The number of BTA administrations (defined as the number of administrations from index-date through the end of follow-up).

8.3.2.2 Definition of Adverse Events of Special Interest

Safety Outcomes:

- Adverse events of special interest outcomes include:
  - Osteonecrosis of the Jaw (ONJ)
  - Atypical Femoral Fracture (AFF)
  - Hypocalcemia

All experienced adverse events of special interest will be captured during a patient's time of follow-up. Refer to Section 8.3.2.5.

8.3.2.3 Definition of Prognostic Factors for SREs

Patient Demographics and Medical History Characteristics:

- The prognostic factors of SREs will include demographic and medical history, as well as the clinical, disease, and laboratory characteristics summarized below in Table 8-1.

8.3.2.4 Definition of SREs

The key outcome of this study is "time to first symptomatic SRE". A SRE is defined as 1 or more of the following: pathologic fracture (vertebral or non-vertebral); radiation therapy to bone, surgery to the bone, or spinal cord compression. All SREs will be captured for each patient during eligible patient follow-up time, thus a patient may experience $>$ 1 SRE. A new SRE event is defined by occurrence $\geq$ 21 days after the

preceding SRE-event. The earliest captured SRE during the patient's follow-up time will be reported and identified as the first symptomatic SRE.

Definitions:

- Pathologic fractures are those bone fractures that occur spontaneously or are not due to major trauma. The nature of the trauma, whether major or otherwise, will be determined by investigator.
- Surgery to bone (including vertebroplasty) includes procedures to set or stabilize a fracture or to prevent an imminent fracture or spinal cord compression.
- Radiation therapy to bone includes radiation for pain control (including use of radioisotopes), to treat or prevent pathologic fractures, or to treat or prevent spinal cord compression.
- Spinal cord compression events must be confirmed using appropriate radiographic imaging (eg, MRI or CT scans).

These events, as well as clinical sequelae associated with hypercalcemia, will be captured on the eCRF.

8.3.2.5 Adjudication Process for Suspected ONJ and AFF Adverse events

To identify potential events of ONJ, a broad search strategy encompassing a variety of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) will be employed. Events identified with this strategy would be submitted for external expert adjudication to determine whether the events meet the American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria for ONJ (Ruggiero et al, 2014).

For potential AFF events, adjudication will be performed using a pre-defined AFF criteria (American Society for Bone and Mineral Research [ASBMR] 2013 AFF definition) (Appendix D). If an event is adjudicated positively for ONJ or AFF, events will be upgraded to a serious adverse event if not already reported as such and reported to the regulatory agencies and study investigators.

8.3.3 Covariate Assessment

The factors outlined in the Table 8-1 below are covariates (as well as exposures and outcomes) that will be gathered at study enrollment and, when specified, at each subsequent site visit. These factors are believed to be potential risk factors or confounders for the outcome of interest, SREs. The schedule of collection of each covariate is also presented in the Table 8-1 below.

A list of baseline covariates that may be used to calculate the propensity score will be presented in the Statistical Analysis Plan (SAP), however a broad category of covariates that will include:

- Demographic characteristics
- Geographical and socioeconomic information about the patient
- Laboratory tests and measurements
- Medical and comorbid history
- Systemic anticancer therapy
- Cancer diagnostic information
- Bone metastasis information (including time from bone metastasis diagnosis to initiation of BTA treatment, site(s) of bone metastases and/or number of bone metastases).

Table 8-1. Schedule of Data Collection

		Enrollment	
GENERAL ASSESSMENTS			
Eligibility Review		X	
Informed Consent		X	
DATA COLLECTED (If available in Medical Record)		**Upon study enrollment to reflect time at initiating XGEVA®/ANJIAWEI® or ZOMETA® (Retrospective Chart Review)**	**Data abstraction** **Data abstraction every 3 months (±14 days) through End of Follow-up**
Demographic characteristics:	• Age (continuous) • Sex (male, female) • Distance from home to site/treatment	X (Any time during baseline, with the most proximal to/on index-date)	-
Socioeconomic:	• Province of patient • Education level	X (Any time during baseline, with the most proximal to/on index-date)	-
	• Insurance type		-
Physical measurements:	• Height • Weight	X (Any time during baseline, with the most proximal to/on index-date)	-
Smoking status	• Current, Former, or Never Smoker; Not reported	X (Any time during baseline, with the most proximal to/on index-date)	-

Table 8-1. Schedule of Data Collection

DATA COLLECTED (If available in Medical Record)		Index-date/Baseline Prior to Index-date (Retrospective Chart Review)	Data abstraction Data abstraction every 3 months (±14 days) through End of Follow-up
Relevant medical history for SRE:	• Osteoporosis • Renal impairment): – (if renal impairment is present: Define CKD Stage 1, 2, 3, 4, 5)	X (Any time during baseline, with the most proximal to/on index-date)	-
	• Reproductive status of female patient: – Childbearing (potentially), pregnant, surgically sterile, infertile (medically verified) Menstrual Status: – Menstruation, perimenopausal, post-menopausal (surgically or naturally)		
Supplemental bone therapy medication	• Exposure to calcium • Exposure to vitamin D	X (Any time during the baseline, with the most proximal to/on index-date)	X Note: **Data abstraction** during follow-up
Prior SRE History	• Prior bone fracture • Prior radiation therapy for bone pain • Prior surgery to bone • Prior spinal cord compression	X (Any time during baseline)	-
Laboratory values[a]	• Serum Calcium • Serum Creatinine	X (Any time during the baseline, with the most proximal to/on index-date)	X Note: **Data abstraction** during follow-up
Treatments	• Use of Opioid Medications	X (Any time during the baseline, with the most proximal to/on index-date)	X Note: **Data abstraction** during follow-up
	• Currently undergoing systemic anticancer therapy	X (At index-date of initiation of BTA)	X Note: **Data abstraction** during follow-up
	• Treatment with BTA: XGEVA®/ANJIAWEI®; ZOMETA® – Dates of each administration	X	X Note: **Data abstraction** during follow-up

Table 8-1. Schedule of Data Collection

DATA COLLECTED (If available in Medical Record)		Index-date/Baseline Prior to Index-date (Retrospective Chart Review)	Data abstraction Data abstraction every 3 months (±14 days) through End of Follow-up
Tumor characteristics	• ECOG score • Tumor type: (Breast, Prostate, or Lung Cancer) – Date of initial cancer diagnosis – For Breast cancer: Hormone receptor status • Metastasis sites: – Date of bone metastasis diagnosis – Site(s) of bone metastases • Number of bone metastases	X (Any time during baseline, with the most proximal to/on index-date)	-
Skeletal-related events (measured for each individual SRE in both treatment cohorts)	• SRE: – Radiation therapy to the bone (radioisotopes) – Symptomatic pathological fracture – Surgery to the bone – Spinal cord compression	-	X Note: **Data abstraction** during follow-up; Capture all occurrences of an SRE
XGEVA®/ANJIAWEI® patients only: AEs and AEs of special interest (measured for each individual AEs of special interest)	• Adverse Events, including AEs of special interest in particular: – Osteonecrosis of the Jaw – Atypical Femoral Fracture – Hypocalcemia	-	X Note: **Data abstraction** during follow-up; Capture all occurrences of an AE/AEs of special interest

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AE = adverse event; BTA = bone targeting agent; CKD = chronic kidney disease; ECOG = Eastern Cooperative Oncology Group; SRE = skeletal-related events
[a]The laboratory values should only be collected if they are outside of the normal range and considered an AE.

8.3.4 Validity and Reliability

The data collected for this study will be derived from patient medical records and used to populate eCRFs with clear instructions for site investigators. Clear instructions will be provided to investigators regarding eCRF completion for accuracy of data extraction from medical records.

8.4 Data Sources

Patient data will be collected by investigators, delegates, or site staff at the enrollment visit and subsequently at routine clinical visits. The investigator, delegates, or site staff will enter the information into the eCRF. The data to be entered into the eCRF will be obtained from paper or electronic medical records, depending on the site method of documentation. All **abnormal** laboratory and **diagnostic** imaging will be collected as per the site's clinical standard of measurement and will be transcribed into the study database **as per CRF guidelines**.

8.5 Study Size

The achievable sample size will, in part, depend on the extent of XGEVA®/ANJIAWEI® use in clinical practice in the People's Republic of China. For time to first symptomatic SRE, the precision of the effectiveness measure which would be achievable in the study of 1000 patients (500 patients in each treatment cohort) is presented below.

This is a descriptive study. The sample size calculations shown below are not intended for hypothesis testing in either the overall population or any specific cancer type subgroup. Table 8-2 provides estimates of achievable precision, expressed as 95% confidence interval, for the HR for time to first symptomatic SRE in patients treated with XGEVA®/ANJIAWEI® compared to those treated with ZOMETA®, under the following assumptions: approximately 500 patients per treatment cohort; a 36-month enrollment duration and up to 60-month total study duration; median time to symptomatic SRE in the ZOMETA® cohort, annual dropout rate, and total number of events, varying within the ranges provided in Table 8-2.

Table 8-2. Precision for Treatment Effectiveness Estimate of Time to First Symptomatic SRE (Sample Size: N = 500 per Cohort)

HR of XGEVA®/ANJIAWEI® Compared with ZOMETA®	Median Time to First Symptomatic SRE in ZOMETA® Cohort (Months)	Yearly Dropout Rate	Total Events	95% CI for HR
0.75	20	40%	388	(0.615, 0.915)
0.75	20	50%	330	(0.604, 0.931)
0.75	30	40%	292	(0.596, 0.943)
0.75	30	50%	245	(0.584, 0.963)
0.75	50	40%	195	(0.566, 0.993)
0.75	50	50%	161	(0.551, 1.021)
0.85	20	40%	404	(0.699, 1.033)
0.85	20	50%	344	(0.688, 1.050)
0.85	30	40%	305	(0.679, 1.064)
0.85	30	50%	256	(0.665, 1.086)
0.85	50	40%	204	(0.646, 1.118)
0.85	50	50%	169	(0.629, 1.149)
0.95	20	40%	418	(0.784, 1.151)
0.95	20	50%	357	(0.772, 1.169)
0.95	30	40%	318	(0.763, 1.184)
0.95	30	50%	267	(0.747, 1.208)
0.95	50	40%	214	(0.727, 1.242)
0.95	50	50%	177	(0.708, 1.276)

CI = confidence interval; HR = hazard ratio; SRE = skeletal-related events

8.6 Data Management

Data will be abstracted by physician, site, or delegate staff from patient records into an electronic database provided by Amgen. Protocol-specific training and eCRF completion instructions will be provided to all site staff or delegates tasked with patient data abstraction. The Amgen/Beigene representative(s) and regulatory authority inspectors are responsible for contacting and visiting the physician for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that patient confidentiality is respected.

Each patient will be assigned a unique identification number at the time of enrollment. This unique identification number will be used to link data to subsequent data entries. The data will be abstracted by physician, delegate, or site staff from patient's medical

records into a web based electronic data capture (EDC) system/form that will record site enrollment, case identification, patient selection, and study progress at the site and patient level. The EDC system (*Rave-Medidata*) will include eCRFs designed to capture the variables and outcomes of interest. The data collected for this study will be derived from medical records that are kept per routine clinical practice for the documentation and decision-making for a patient's care. The sponsor, or designated vendor, will provide protocol-specific training on the eCRFs to all study site abstractors (physician, delegate, site staff) in advance of the study data collection period to ensure clarity on the questions and accuracy of the data to be captured.

8.6.1 Obtaining Data Files

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's "audit trail."
- To ensure the quality of clinical data across all patients and sites, a clinical data management review is performed on patient data received. During this review, patient data are checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system for site resolution.
- The physician will be required to sign the Investigator Signature Form for this EDC study. This signature indicates that the physician inspected or reviewed the data in the eCRF, the data queries and agrees with the content.

8.6.2 Linking Data Files

Not applicable.

8.6.3 Review and Verification of Data Quality

Upon data entry, all data will be checked to ensure validity. Data will be evaluated for outliers and missing information. In the event of outliers, inconsistent, invalid, or missing data, sites will be queried for clarification and the patient medical records will be referenced to resolve any errors, inconsistencies, or attempt to populate missing data.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Monitoring Patient Enrollment

During the 36-month enrollment phase, to monitor and inform any potential modifications of the inclusion and/or exclusion criteria with the intention of making both treatment

cohorts more comparable. Approximately every 3 to 6 months (and throughout entire duration of study execution), patient enrollment will be monitored for the following:

- Treatment allocation (XGEVA®/ANJIAWEI® and ZOMETA®)
- Tumor allocation (breast, prostate, and lung)
- Patient replacement (for those patients who enroll but subsequently do not receive BTA treatment)

If modification is needed, the protocol will be amended. For purposes of transparency, BeiGene/Amgen plan to seek prior China CDE advice and recommendations on necessary modifications to protocol.

8.7.1.2 Primary Analysis:

The primary analysis will be conducted after the last patient completes the study follow-up, as outlined in Section 8.2.5. The primary analysis will be comprised of 2 stages.

Stage 1:

Stage 1 describes the utilization of XGEVA®/ANJIAWEI® and ZOMETA® among patients with bone metastases secondary to breast, prostate, or lung cancer; assesses the comparability of baseline characteristics and prognostic factors for SREs at the time of initiating a BTA between patients using XGEVA®/ANJIAWEI® and ZOMETA®; and describes the incidence of adverse events of special interest in patients using XGEVA®/ANJIAWEI®.

The following assessments will be conducted to evaluate comparability between the 2 treatment cohorts:

- The overlap of the distribution of the estimated propensity scores between the 2 treatment cohorts will be assessed
- The standardized mean difference (SMD) of baseline demographic and clinical characteristics between XGEVA®/ANJIAWEI® and ZOMETA® cohorts will be assessed.
- The SMD in duration of BTA use for XGEVA®/ANJIAWEI® and ZOMETA® cohorts.

Stage 2:

If the treatment cohorts are comparable based on the results of the comparability assessments conducted in Stage 1, then the effectiveness of XGEVA®/ANJIAWEI® relative to ZOMETA® for time to first symptomatic SRE will be estimated using the HR of XGEVA®/ANJIAWEI® relative to ZOMETA® and its 95% confidence interval (see the

planned analysis method in Section 8.7.2.5). The Kaplan Meier curve and yearly event rates in each treatment cohort will also be estimated.

If the 2 treatment cohorts are not comparable, then the relative effectiveness analysis will not be conducted; however, Kaplan Meier curve and yearly event rate in each treatment cohort will be estimated. Additional effectiveness measures could be considered (eg, to assess the SRE yearly event rate) within the same treatment cohort.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

All analyses will be descriptive, and no formal hypothesis testing is planned. The analysis plan will be fully described in a written and approved SAP. Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the patient population and treatment cohorts.

Patients that completed the ICF and enrolled in the study but did not receive at least 1 administration of the BTA (either ZOMETA® or XGEVA®/ANJIAWEI®) will not be included in the analyses, unless otherwise specified.

Continuous variables will be reported as mean, standard deviation (SD), median, range, and interquartile range (Q1 to Q3), where appropriate. Categorical variables will be summarized as frequency counts and percentage.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Attempts to collect missing data and incomplete data will be resolved by using the patient medical records and through site queries. Handling of missing or incomplete data in the analysis will be detailed in the SAP.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Patient enrollment by site and investigator, month/year of enrollment, and by month/year of index-date, will be summarized.

8.7.2.3.2 Description of Patient Characteristics

Patient baseline characteristics (including demographics, baseline medications, surgical procedures, and other clinical and tumor characteristics) will be summarized using descriptive statistics. Refer to Table 8-1 for a schedule of data collection.

8.7.2.4 Analysis of the Primary Endpoints: Stage 1

The primary objectives of Stage 1 are to:

- describe the demographic and clinical characteristics that are potentially related to prognosis for SREs in patients using XGEVA®/ANJIAWEI® or ZOMETA®
- describe the utilization of XGEVA®/ANJIAWEI® and ZOMETA®; and
- (for XGEVA®/ANJIAWEI® patients only): describe the incidence rates of adverse events of special interest (ie, ONJ, AFF, and hypocalcemia)

For the utilization of XGEVA®/ANJIAWEI® and ZOMETA®, the following measurements will be summarized: duration of treatment and number of administrations. Supplemental bone therapy medication (Vitamin D, Calcium) use will be summarized by treatment cohort.

As previously referenced, all baseline demographic, clinical, and medical history characteristics, and characteristics measured during follow-up, that are potentially related to prognosis for SREs (eg, age, comorbidities, prior SRE experienced, tumor type, number of bone metastasis sites) will be summarized using descriptive statistics.

To assess the comparability of baseline demographic and clinical characteristics between XGEVA®/ANJIAWEI® and ZOMETA® cohorts, SMD will be used. Standardized mean differences are intuitive indices which measure the effect size between 2 groups/cohorts. Compared to a t-test or Wilcoxon rank-sum test, they are independent of sample size, and therefore more appropriate to be adopted in real-world analyses of large data. In brief, the SMD for binary variables is the absolute difference in proportions of the variable between exposed (XGEVA®/ANJIAWEI® in this study) and non-exposed subjects (ZOMETA®) standardized to the variation in the variable (ie, the standard deviation). It has a minimum value of 0 (“perfect” balance) but no maximum value. For continuous variables, SMD is the absolute difference in the means of variables in the two treatment cohorts standardized to the variation (Austin, 2009). A standardized difference of 0.1 (10 percent) denotes meaningful imbalance in the baseline covariate (Normand et al, 2001).

The propensity score is a balancing score and conditional on the propensity score, the distribution of observed baseline covariates will be similar between treatment cohort of interest (XGEVA®/ANJIAWEI®) and the comparator cohort (ZOMETA®). The distribution of the propensity score in XGEVA®/ANJIAWEI® vs. ZOMETA® will be described and graphically illustrated. In addition to SMD, a common summary statistic in

pharmacoepidemiology, a propensity score will be calculated for each patient in the study using multivariate logistic regression analysis, conditional on baseline covariates.

Evaluation of differences in baseline demographic and clinical characteristics between patients initiating XGEVA®/ANJIAWEI® and those initiating ZOMETA®, through SMD for individual variables and visual assessment of the extent of overlap between propensity score distributions, will permit an assessment of comparability between these 2 treatment cohorts, and thus, feasibility of proceeding to Stage 2 (ie, comparative analysis).

For the Stage 1 safety endpoint, which is the incidence of adverse events of special interest, the analysis set will include all patients that have received at least 1 administration of XGEVA®/ANJIAWEI®. Descriptive information on the incidence of the adverse events of special interest and outcomes in patients will be calculated for the entire analysis set (collectively), and then further by each specific identified adverse event of special interest, and presented as incidence rate and 95% confidence interval. The incidence rate calculation will be the total number of patients with an adverse event of special interest event divided by the total number of at-risk person-years in the XGEVA®/ANJIAWEI® cohort, per 1000 person-years of follow-up.

8.7.2.5 Analysis of the Primary Endpoints: Stage 2

The endpoint for Stage 2 is time to first symptomatic SRE, which is defined as the time from the index date to the date of first occurrence of on-study symptomatic SRE.

In each treatment cohort, the Kaplan-Meier curve will be estimated and graphically displayed. The Kaplan-Meier estimates with 95% confidence intervals at prespecified time points and annualized event rate will be calculated by treatment cohort.

If the 2 treatment cohorts are comparable per Section 8.7.2.4, the effectiveness of XGEVA®/ANJIAWEI® relative to ZOMETA® for prevention of symptomatic SREs will be evaluated for the time to first symptomatic SRE. The HR of XGEVA®/ANJIAWEI® compared with ZOMETA® and its 95% confidence interval will be estimated using a Cox proportional hazards model. Adjustment for potential confounding will be performed by applying the propensity scores to inverse probability of treatment weights (IPTW).

If the 2 treatment cohorts are not comparable, comparative effectiveness analysis will not be performed.

Table 8-3. Summary of Analysis for Outcomes of Interest

Outcomes of Interest	Analysis Method	Analysis time Point
Baseline demographics	Descriptive statistics on continuous data will include mean, SD, median, interquartile range: Q1 to Q3, and range, while categorical data will be summarized using frequency counts and percentages.	Baseline
Utilization of XGEVA®/ANJIAWEI® or ZOMETA®	Descriptive statistics on continuous data will include mean, SD, median, interquartile range: Q1 to Q3, and range, while categorical data will be summarized using frequency counts and percentages.	Index-date to End of Follow-up Time
Incidence of adverse events of special interest	Descriptive statistics: N, total number of cases, total at-risk person-time in each cohort, and incidence rate per 1000 person-years Presented as all adverse events of interest; by individual adverse event: osteonecrosis of the jaw, AFF, and hypocalcemia	Time at risk for adverse events: Index-date to End of Follow-up Time OR first occurrence event of adverse event
XGEVA®/ANJIAWEI® vs ZOMETA®: time to first SREs	Kaplan Meier curve and yearly event rate will be estimated in each treatment cohort. If the 2 treatment cohorts are comparable, the HR with 95% confidence interval will be estimated using a PS method based on the IPTW-weighted Cox proportional hazard model. If the 2 treatment cohorts are not comparable, comparative effectiveness analysis will not be performed.	Time at risk for First-SRE: Index-date to End of Follow-up Time (time at risk for this outcome is censored at the occurrence of the first SRE)

AE = adverse event; AFF = atypical femoral fracture; IPTW = inverse probability of treatment weighting; PS = propensity score; SD = standard deviation**; SREs = skeletal related events**.

8.7.2.5.1 Sensitivity Analysis

If the two treatment cohorts are comparable, to assess consistency of findings, sensitivity analyses may be performed for time to first symptomatic SRE using different methods for propensity score adjustments (eg, using a Cox proportional hazards model stratified by the propensity score quintiles or using a Cox proportional hazards model adjusted using the continuous propensity score as a covariate to estimate the HR and 95% confidence interval).

Additionally, for the planned analyses in stage 1 and stage 2, a sensitivity analysis may be performed that would truncate follow-up time for patients with BTA-treatment patterns that had gaps in BTA prescriptions that exceeded 45 days between dates of BTA-administrations, given that the study design allows for up to 100 days between administrations (eg, a patient received a BTA medication in month January, February,

March, but then has a gap until June, the patient follow-up time would be truncated at the end of March).

8.7.2.5.2 Subgroup Analysis

For the planned analyses in stages 1 and stage 2, subgroup analyses may be conducted, if sample size permits. The subgroup analyses may include the presentation of results by the subgroups of tumor type (breast, prostate, lung), or calendar year of index date. Additional subgroup analyses may also be conducted, for example: by age-group (categorized), number of bone metastases (categorized), anticancer therapy (yes; no), or baseline SREs (yes; no).

8.7.3 Analysis of General Adverse Events

Adverse events and **treatment-emergent adverse events as reported by the investigator**, other than the adverse events of special interest (ONJ, AFF, and hypocalcemia) will be coded using the most current version of the MedDRA, at the time of database development. Patient incidence rates of all adverse events will be tabulated by system organ class and PT. Tables of fatal adverse events, serious adverse events, **treatment-emergent adverse events as reported by the investigator,** and adverse events leading to withdrawal from treatment will also be provided.

8.8 Quality Control

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the patient eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Documents to be maintained for the study are as follows:

- Patient files containing the completed eCRF, ICFs, as applicable, and patient identification list

- Study files containing the protocol with all amendments, copies of pre-study documentation, and all correspondence to and from the Independent Ethics Committee (IEC) or other relevant ethical review board and Amgen

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available. Retention of study documents will be governed by the contractual agreement with Amgen.

Amgen retains all data, programs, and outputs generated for the study. At study close, data are uploaded from the electronic clinical database and stored in accordance with Amgen SOPs. Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard programming procedures will apply.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

8.9.1.1 Measurement Error(s)/Misclassification(s)

The quality of data will be reflective of clinical practice. There is the potential for information of study interest not to be captured or inconsistently captured in clinical practice. In addition, potential errors may occur in extraction of data from the medical records.

We anticipate minimal influence from misclassification given that we are seeking adjudication for adverse events of special interest (in particular, ONJ and AFF).

The study data are being extracted from the patient's medical records, thus missing data and errors in recording may occur. There may also be variance of recording practices between the medical staff and sites, however, given the prevalent use of electronic medical records and consideration in site selection, we anticipate the variance of recording practices to be minimal. Lastly, the quality of data for classification of patient exposures and measurement of covariates is reliant on the accuracy of reporting and record of information by the treating physicians and site staff.

8.9.1.2 Information Bias

Information bias may occur if, for example, the data for patients with more complications were recorded with more (or potentially less) detail. Imprecise date of outcome events may limit precision of time-to-event analyses. Information about patients' treatment outside of the specific cancer treatment site may also not be captured in the available medical record. To help mitigate this potential bias, attempts to limit missing information due to a patient seeking treatment to outside sites has been built into the study; for

example, by discontinuing follow-up if a patient does not return to the site at least every 100 days.

8.9.1.3 Selection Bias

This study is a prospective observational study in the real-world setting. The inclusion/exclusion criteria are intended to enroll patients initiating XGEVA®/ANJIAWEI® or ZOMETA®. Consecutive enrollment will be performed to potentially reduce selection bias between the two drug cohorts. Both the inclusion criteria and study design including patients representing each tumor type should also reduce selection bias. However, because the study requires patients to complete the ICF, not all patients may elect to sign and participate in this study, which may lead to a lack of patient representation in this study relative to all patients that may use a BTA.

8.9.1.4 Confounding

This is an observational study of clinical practice and the practice of medicine may lead to different patient types receiving different treatments. The treatment is determined by the treating physician, according to local guidelines, and approved XGEVA®/ZOMETA® indication. Imbalance of baseline characteristics (for example by tumor type or duration of time to initiate BTA) between the 2 treatment cohorts may lead to bias for estimation of outcomes. The propensity score method may help reduce bias by creating quasi-randomization between 2 treatment cohorts. The propensity scores can be used in the relevant primary and sensitivity analyses.

8.9.2 External Validity of Study Design

The patient population come from sites that have agreed to participate in this study and thus the results may not be generalizable to all sites with BTA use in the People's Republic of China. Additionally, patients that have agreed to participate in this study may be different from a patient not consenting to participate.

8.9.3 Analysis Limitations

Although the propensity score method may reduce confounding bias by creating quasi-randomization between the two treatment cohorts, the propensity score method will not be able to account for unobserved or unknown baseline characteristics that have an impact on either the treatment determination or the clinical outcomes of interest.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

The eCRF will be designed to minimize missing data by providing comprehensive eCRF completion guidelines to the investigator/site. Some patients may drop out of the study,

creating incomplete data for the study endpoint assessments. However, measures described in the research methods (Section 8), attempt to limit or reduce the risk of missing or incomplete data.

8.10 Other Aspects

8.10.1 Language

All written information and other materials to be used by patients and investigative staff must use language and vocabulary that are clearly understood.

9. Protection of Human Subjects

9.1 Informed Consent

An initial sample ICF is provided for the investigator or designee to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the sponsor, Amgen/BeiGene Study Manager, to the investigator or designee. The written ICF is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the study, the investigator or designee will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study.

The acquisition of informed consent is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

9.2 Independent Ethics Committee (IEC)

A copy of the protocol proposed ICF, and other written patient information must be submitted to the IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and ICF must be received by the sponsor before site is initiated.

The investigator must submit and, where necessary, obtain approval from the IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The investigator is to notify the IEC or other relevant ethical review board of deviations from the protocol or serious

adverse events occurring at the site and other adverse event reports received from the sponsor, in accordance with local procedures.

The investigator is responsible for obtaining annual IEC or other relevant ethical review board approval/renewal throughout the duration of the study. Copies of the Investigator's Reports, where applicable by local regulations and the IEC or other relevant ethical review board continuance of approval must be sent to the sponsor.

9.3 Patient Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to the sponsor.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to the sponsor (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC direct access to review the subject's original medical records for verification of data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

9.4 Subjects Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the patient does not wish to or is unable to continue further study participation. **Subject** data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be

included after withdrawal of consent. The investigator is to discuss with the patient appropriate steps for withdrawal of their consent from the study.

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

10.1 Definition of Reportable Events

10.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

10.1.2 Serious Adverse Events

A serious adverse event/serious adverse device effect is any adverse event/adverse device effect as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an “other medically important serious event” that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for “serious” is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

“Other medically important serious events” refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

10.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose/underdose, whether accidental or intentional, misuse, addiction, or abuse involving an Amgen product,
- Use of an Amgen product while pregnant and/or breast feeding,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Accidental or Occupational exposure,
- Any lack or loss of intended effect of the product(s).

10.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) or combination product(s) includes investigational product.

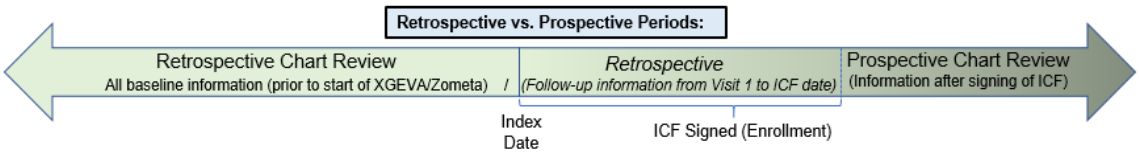
Amgen will collect complaints on the following product:

- XGEVA®/ANJIAWEI®

10.2 Safety Collection, Recording, and Submission to Amgen Requirements

This study is collecting information from patient medical records. The collection of safety information from the medical record will have both retrospective and prospective periods relative to the date of enrollment (Figure 5).

Figure 5. Retrospective vs. Prospective Periods



ICF = Informed Consent Form.

10.2.1 Retrospective Chart Review

The potential retrospective period is defined as the time from diagnosis of bone metastasis to the time of signing of the ICF. This study is analyzing secondary data from

medical records. The safety outcomes that are listed in Section 8.3.2.2 will be documented and analyzed in this study. These will be reported in aggregate in the final study report as rates. See Section 8.3.2 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Reportable events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

10.2.2 Prospective Chart Review

The prospective period (or follow-up period) is defined as the time from the signing of the ICF to final study contact/EOS. This study is collecting information from patients and healthcare professionals prospectively. All reportable events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to XGEVA®/ANJIAWEI® will be collected from signing of ICF to final study contact/end of study. The Investigator is responsible for ensuring that all reportable events they become aware of during study period, are recorded in the patient's appropriate study documentation. **It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.** If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the patient's records after the patient ends the study. All reportable events must be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within the timelines stated in Table 10-1 below.

Table 10-1. Types of Safety Data to be Collected and Reported and Timeframe

Reportable Events/Event Type	Reporting Time Frame[a]
• Serious Adverse Events (related and non-related) • Product Complaints (serious and non-serious) • Other Safety Findings (serious and non-serious) • Pregnancy and/or Lactation Exposure	• Within 1 business day from when Investigator first becomes aware of the event
• Non-serious Adverse Events (related and non-related)	• Within 15 calendar days from when Investigator first becomes aware of the event

[a] Please note, more stringent reporting timelines may apply per local requirements

Reportable events that are suspected to be related to any **Amgen** medicinal product, **combination product or device** where there is no exposure to XGEVA®/ANJIAWEI® (eg, ZOMETA®) **should** be **spontaneously** reported to **Amgen within 1 business day**

of investigator/vendor awareness. A list of all Amgen medicinal products can be found in the **following link: https://wwwext.amgen.com/amgen-worldwide**.

To spontaneously report a reportable event to Amgen, refer to the following link to locate your Local Amgen contact information by country: https://wwwext.amgen.com/contact-us/product-inquiries.

Additional details on what to collect and report to Amgen for the reportable event can be found in the following link: https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting.

If the EDC system is unavailable to the site staff, the reportable events listed in the table above must still be reported to Amgen within the specified reporting timeframes stated. For studies using Amgen's EDC system where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See Appendix C for sample Safety Report Form(s), Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix E for sample Pregnancy and Lactation Notification Forms. The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

10.2.3 Collection of Pregnancy and Lactation Information

Female Subjects Who Become Pregnant

Investigator will collect pregnancy information on any female subject who becomes pregnant following exposure to XGEVA®/ANJIAWEI® through 5 months after the last dose.

Information will be recorded on the Pregnancy Notification Form (see Appendix E). The worksheet must be submitted to Amgen Safety within 1 business day of when Investigator first becomes aware of the subject's pregnancy (Note: Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide Investigator with a consent form and questionnaire to collect additional information. After obtaining

the female subject's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant following exposure to XGEVA®/ANJIAWEI® through 5 months after the last dose of XGEVA®/ANJIAWEI®. This information will be forwarded to Amgen Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Amgen Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is considered another safety finding, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the Investigator will report the event as a serious adverse event.

Male Subjects with Partners who Become Pregnant or Were Pregnant at the Time of Enrollment

In the event a male subject fathers a child following exposure to XGEVA®/ANJIAWEI®, and for an additional 5 months after discontinuing XGEVA®/ANJIAWEI®, the information will be recorded on the Pregnancy Notification Form. The form (see Appendix E) must be submitted to Amgen Safety within 1 business day of when the Investigator first becomes aware of the pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide Investigator with a consent form and questionnaire to collect additional information. The Investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

Investigator will collect lactation information on any female subject who breastfeeds while taking XGEVA®/ANJIAWEI® through 5 months after the last dose.

Information will be recorded on the Lactation Notification Form (see Appendix E) and submitted to Amgen Safety within 1 business day of when the Investigator's first becomes aware of the lactation exposure.

With the female subjects signed consent for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking XGEVA®/ANJIAWEI® through 5 months after discontinuing XGEVA®/ANJIAWEI®.

10.2.4 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IECs, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IEC or other relevant ethical review board of reportable events in accordance with local procedures and statutes.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

The sponsor may amend the protocol at any time. **When** the sponsor amends the protocol **and distributes the protocol amendment to the sites,** written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IEC must be informed of all amendments and give approval **for all protocol amendments that sponsor provides to the site**. The Investigator must send a copy of the approval letter from the IEC to the sponsor.

The sponsor reserves the right to terminate the study at any time. Both the sponsor and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IEC in writing of the study's completion or early termination and send a copy of the notification to the sponsor.

12. Plans for Disseminating and Communicating Study Results

The results of this study will be submitted for publication.

12.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

13. References

American Society for Bone and Mineral Research (ASBMR) 2013 AFF definition

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14. Appendices

Appendix A. List of Stand-alone Documents

None.

Appendix B. ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A two-stage, prospective observational study describing the use and effectiveness of XGEVA®/ANJIAWEI® for the prevention of skeletal related events in patients with bone metastases from solid tumors relative to ZOMETA® in the People's Republic of China

EU PAS Register® number:
Study reference number (if applicable):

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☐	☐	☐	
2.1.2 The objective(s) of the study?	☐	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☐	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☐	

Comments:

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☐	☐	☐	
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☐	☐	☐	
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☐	
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☐	

Comments:

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

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☐	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☐	
5.3	Is exposure categorised according to time windows?	☐	☐	☐	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☐	

5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☐	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☐	
6.2	Does the protocol describe how the outcomes are defined and measured?	☐	☐	☐	
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☐	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☐	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☐	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☐	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☐	

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☐	

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☐	
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☐	
	9.1.3 Covariates and other characteristics?	☐	☐	☐	
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☐	
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☐	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☐	
	9.3.3 Covariates and other characteristics?	☐	☐	☐	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☐	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☐	☐	☐	
10.2	Is study size and/or statistical precision estimated?	☐	☐	☐	
10.3	Are descriptive analyses included?	☐	☐	☐	
10.4	Are stratified analyses included?	☐	☐	☐	
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☐	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☐	
10.7	Does the plan describe methods for handling missing data?	☐	☐	☐	
10.8	Are relevant sensitivity analyses described?	☐	☐	☐	

Comments:

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

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☐	
12.1.2 Information bias?	☐	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☐	

Comments:

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

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

Appendix C. Sample Safety Reporting Form(s)

ATTENTION: CONTACT PVOPS CSL PRODUCT REPRESENTATIVE FOR STUDY SPECIFIC FORM

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for Observational Research Studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions
The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

What to report on this form:

- All adverse events associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol
- The following safety findings are to be reported on this form as events regardless of association with an adverse event
  - Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product
  - Transmission of infectious agents
  - Reports of uses outside the terms for authorized use of the product including off label use
  - Occupational exposure
  - Any lack or loss of intended effect of the product(s)
  - Product complaint ONLY IF ASSOCIATED WITH AN ADVERSE EVENT

The following should not be reported on this form and should be reported via the normal process set up for the study

- Pregnancy and lactation reports
- Product complaints without association with an AE

1. Site Information
   Site Number* – Enter your assigned site number for this study
   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested
2. Subject Information
   Subject ID Number* – Enter the entire number assigned to the subject
   Age at event onset, Sex, and Race – Enter the subject's demographic information
   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.

3. Adverse Event
   Provide the date the Investigator became aware of this Information
   Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started rather than the date of diagnosis or hospitalizion. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**
   Date Ended – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.
   Is event serious?* – Indicate Yes or No. This is a mandatory field.
   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   Immediately life-threatening: Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

FORM-099346 *Instructions Page 1 of 2* *Version 1.0 Effective Date 01 February 2016*

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

4. **IP Administration including Lot # and Serial # when known / available.**
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to Amgen drug under study* – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event – Enter the code for the outcome of the event at the time the form is completed if outcome is known.
   Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

5. **Hospitalization**
   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

6. **Amgen drug Under Study Administration including Lot # and Serial # when known / available.**
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
7. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
8. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
9. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
10. **Other Relevant Tests**
    Indicate if there are any tests, including any diagnostics or procedures.
    For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

11. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

A Study 20190036 AMG 162 (Xgeva)	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM/Study manager/Author prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of drug under study	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that theEvent may have been caused by Amgen drug under study or an Amgen device used to administer the Amgen drug under study?								**Outcome of Event** ·Resolved ·Not resolved ·Fatal ·Unknown	Check only if event is related to study procedure eg, biopsy
						<drug/device> No✓	<drug/device> Yes✓	<drug/device> No✓	<drug/device> Yes✓	<drug/device> No✓	<drug/device> Yes✓	<drug/device> No✓	<drug/device> Yes✓		
				☐ Yes ☐ No											
				☐ Yes ☐ No											
				☐ Yes ☐ No											

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

A Study 20190036 AMG 162 (Xgeva)	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

5. Was drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

Amgen Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<< Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test / Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

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Page 2 of 3

A Study 20190036 AMG 162 (Xgeva)	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

The Common Terminology Criteria for Adverse Events (CTCAE) is be used. The CTCAE is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Appendix E. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20190036

Study Design: ☐ Interventional ☑ Observational (If Observational: ☑ Prospective ☑ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20190036

Study Design: ☐ Interventional ☑ Observational (If Observational: ☑ Prospective ☑ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix F. NCI CTCAE v5.0 electrolyte abnormalities

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypercalcemia	Corrected serum calcium >ULN to 11.5 mg/dL; >ULN to 2.9 mmol/L; ionized calcium >ULN to 1.5 mmol/L	Corrected serum calcium >11.5 to 12.5 mg/dL; >2.9 to 3.1 mmol/L; ionized calcium >1.5 to 1.6 mmol/L; symptomatic	Corrected serum calcium >12.5 to 13.5 mg/dL; >3.1 to 3.4 mmol/L; ionized calcium >1.6 to 1.8 mmol/L; hospitalization indicated	Corrected serum calcium >13.5 mg/dL; >3.4 mmol/L; ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Hyperkalemia	>ULN to 5.5 mmol/L (mEq/L)	>5.5 to 6.0 mmol/L (mEq/L)	>6.0 to 7.0 mmol/L (mEq/L); hospitalization indicated	>7.0 mmol/L (mEq/L); life-threatening consequences	Death
Hypermagnesemia	>ULN to 3.0 mg/dL; >ULN to 1.23 mmol/L		>3.0 to 8.0 mg/dL; >1.23 to 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Hypernatremia	>ULN to 150 mmol/L (mEq/L)	>150 to 155 mmol/L (mEq/L)	>155 to 160 mmol/L (mEq/L); hospitalization indicated	>160 mmol/L (mEq/L); life-threatening consequences	Death

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated (eg, dialysis)	Death
Hyperuricemia	>ULN without physiologic consequences		>ULN with physiologic consequences	Life-threatening consequences	Death
Hypocalcemia	Corrected serum calcium <LLN to 8.0 mg/dL; <LLN to 2.0 mmol/L; ionized calcium <LLN to 1.0 mmol/L	Corrected serum calcium <8.0 to 7.0 mg/dL; <2.0 to 1.75 mmol/L; ionized calcium <1.0 to 0.9 mmol/L; symptomatic	Corrected serum calcium <7.0 to 6.0 mg/dL; <1.75 to 1.5 mmol/L; ionized calcium <0.9 to 0.8 mmol/L; hospitalization indicated	Corrected serum calcium <6.0 mg/dL; <1.5 mmol/L; ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Hypokalemia	<LLN to 3.0 mmol/L (mEq/L)	<LLN to 3.0 mmol/L (mEq/L); symptomatic; intervention indicated	<3.0 to 2.5 mmol/L (mEq/L); hospitalization indicated	<2.5 mmol/L (mEq/L); life-threatening consequences	Death

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypomagnesemia	<LLN to 1.2 mg/dL; <LLN to 0.5 mmol/L	<1.2 to 0.9 mg/dL; <0.5 to 0.4 mmol/L	<0.9 to 0.7 mg/dL; <0.4 to 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Hyponatremia	<LLN to 130 mmol/L (mEq/L)	125 to 129 mmol/L (mEq/L) and asymptomatic	125 to 129 mmol/L (mEq/L) symptomatic; 120 to 124 mmol/L regardless of symptoms	<120 mmol/L (mEq/L); life-threatening consequences	Death
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences	Death

Page 3 of 3