Summary Table of Study Protocol

Title	The use and safety of XGEVA or Zoledronic acid in clinical practice among Chinese patients with bone metastases from breast, lung, or prostate cancer – a retrospective cohort study within Taiwan's Health Insurance Research Database
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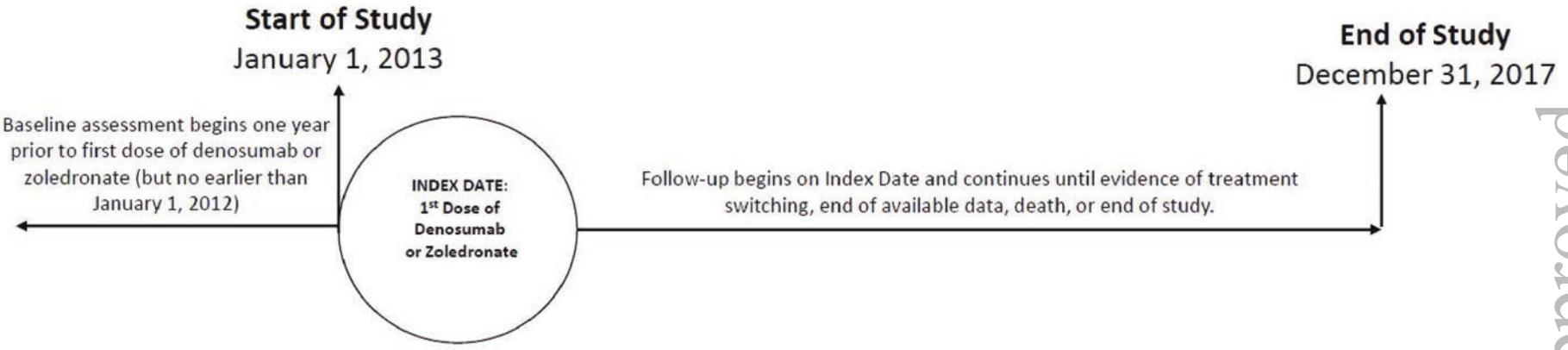
Signature

Name of Investigator <<*Coordinating Investigator*>>

Date (DD Month YYYY)

Figure 1: Study Design Schema



1. Table of Contents

List of Tables

List of Figures

List of Appendices

2. List of Abbreviations

AFF	Atypical femur fracture
BM	Bone metastasis(es)
FDA	Food and Drug Administration
MOHW	Ministry of Housing and Works
NHI	National Health Institute
NHIRD	National Health Insurance Research Database
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IV BP	Intravenous bisphosphonate
ONJ	Osteonecrosis of the jaw
RWD	Real world data
SCC	Spinal cord compression
SRE	Skeletal-related event
TCR	Taiwan Cancer Registry
US	United States
ZA	Zoledronic acid

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4. Abstract

Study Title

The use and safety of XGEVA or Zoledronic acid in clinical practice among Chinese patients with bone metastases from breast, lung, or prostate cancer – a retrospective cohort study within Taiwan's Health Insurance Research Database

Study Background and Rationale

Denosumab (XGEVA) was approved for use in Taiwan in 2012. Its utilization and safety in clinical practice have yet to be characterized within a Chinese population. Given the duration of time since approval and the number of patients who have used XGEVA in clinical practice, there is now an opportunity to examine and characterize the utilization and safety of XGEVA among Chinese cancer patients in routine real-world clinical practice. The data from this study will provide valuable information on patients who are often excluded from clinical trials, as well as evidence related to the use of XGEVA in clinical practice. The safety of XGEVA is currently being characterized through pharmacovigilance activities in countries where XGEVA is approved. Information from this study will provide a systematic evaluation of safety rates as means to evaluate if safety among Chinese patients is consistent with Western populations. Obtaining this information is the first step for future comparative effectiveness studies of XGEVA in mainland China. There is an unmet need in mainland China for improved treatments for patients with BM following diagnosis of breast, prostate, and lung cancer. We anticipate using these results as a component of our application for SRE indication in mainland China.

Research Question and Objectives

All objectives will be conducted in the total population and separately by cancer type.

Primary Objectives:

1. Describe the use of XGEVA and Zoledronic acid among breast, lung, and prostate cancer patients following diagnosis of incident bone metastases (BMs).
2. Characterize the safety of XGEVA among patients with breast cancer, prostate cancer, and lung cancer, as measured by the incidence of osteonecrosis of the jaw (ONJ), atypical femur fracture (AFF), and hypocalcemia and descriptively compare these outcomes with results obtained from the registrational trials in the United States as well as other real-world studies.

Hypothesis/Estimation

Primary objective #1 (use of XGEVA and Zoledronic acid) is descriptive and formal hypothesis testing will not be implemented.

Primary objective #2 (safety of XGEVA) will estimate the incidence rates of three important identified risk factors in the Global Risk Management Plan for XGEVA, including ONJ, AFF, and hypocalcemia. We will summarize the incidence rates of these endpoints, but formal hypothesis testing will not be implemented.

Study Design/Type

Retrospective cohort.

Study Population or Data Resource

The study population will include patients in Taiwan's National Health Insurance Research Database (NHIRD) who were diagnosed with bone metastasis secondary to breast or prostate cancer who were newly treated with XGEVA or Zoledronic acid between January 1, 2013 and December 31, 2017.

The National Health Insurance Program of the Taiwan Bureau of National Health Insurance, serves a population of more than 23 million through a single-payer national health insurance program for medical and dental care. Records of all healthcare claims reimbursed by the National Health Insurance Program since 1995 though the current date minus an approximate 18-month lag are centralized for research in the NHI data. The database includes patient-level demographic characteristics and longitudinal information of diagnoses and procedures occurring in both ambulatory and inpatient settings and of therapies dispensed at the pharmacy or administered in the physician's office. NHI data through December 2017 will be included in this study.

Summary of Patient Eligibility Criteria

- Diagnosis of BM secondary to breast, prostate, or lung cancer and prior to initial use of XGEVA or Zoledronic acid.
- New user of XGEVA or Zoledronic acid during study period (January 1, 2013 to December 21, 2016)
    - New user of either therapy will be defined as not having been treated with any bone targeting agent therapy prior to treatment initiation with XGEVA or Zoledronic acid.
- At least one year of data available prior to initial administration of XGEVA or Zoledronic acid.
- 18 or older at diagnosis of BM.

Exclusion Criteria

- Patients with diagnosis of giant cell tumor of the bone, or multiple myeloma (to ensure that included subjects are receiving XGEVA for the indication of the treatment of BM from solid tumors).
- Evidence of XGEVA or Zoledronic acid use prior to BM diagnosis.

Variables

1. *Objective #1*
    - Use of XGEVA or Zoledronic acid will be characterized as follows:
        - Describe the mean number XGEVA or Zoledronic acid prescriptions per patient
        - Characterize the treatment duration from first dose to last dose of XGEVA or Zoledronic acid
        - Describe the proportion of patients discontinuing XGEVA or Zoledronic acid for more than 90 days
        - Describe the proportion of patients who switch therapies
        - Estimate the time from initial therapy to the switching of therapy
2. *Objective #2*
    - The incidence of ONJ, AFF, and hypocalcemia will be reported per 100 person-years of follow-up. The incidence rates of these outcomes will then be descriptively compared to those obtained in the registrational trials in the United States.

Follow-up

- *Primary Objective #1* - patients will be followed from date of initial treatment with XGEVA or Zoledronic acid to the first of any of the following: evidence of switching therapy, end of available data, death, or end of study. The Index Date is the date of first treatment with XGEVA or Zoledronic acid.
- *Primary Objective #2* - patients will be followed from date of initial treatment with XGEVA until the earliest date of a safety endpoint, evidence of switching therapy, end of available data, death, or end of study. The Index Date is the date of first treatment with XGEVA or Zoledronic acid.

Study Sample Size to Assess Safety

Assuming the mean follow-up duration is about 1.0 year, a study size of 2000 person-years of observation (2000 patients * 1.0 year), we anticipate >99% probability of detecting at least one event given the true incidence is 1 per 100 person-years and an 86% probability of detecting at least one case given the true incidence is 1 per 1000 person-years. A study size of 4000 person-years of observation (4000 patients * 1.0 year) will provide 98% probability of detecting at least one case given the true incidence is 1 per 1000 person-years.

Data Analysis

- *Primary Objectives #1* – The use of XGEVA or Zoledronic acid will be examined for all patients from drug initiation through discontinuation. Outcomes will include duration of use in weeks and total number of doses.
- *Primary Objective #2* - The safety of XGEVA will be examined for all patients from initiation of XGEVA through end of the available data or death. To evaluate safety,

we will summarize the number of patients with ONJ, AFF, and hypocalcemia and we will estimate the incidence of the three safety outcomes as the total number of patients with a specific event meeting the case definition per 1,000 person-years of follow-up:

$$\frac{Total\ number\ of\ the\ patients\ with\ safety\ event}{Total\ patient\ years\ in\ the\ cohort} \text{ X } 1{,}000$$

- We will then descriptively compare these outcomes with results obtained from the registrational trials in the United States as well as other real-world studies.

5. Amendments and Updates

None.

6. Milestones

Milestone	Planned date
Start of data collection (defined as start of data extraction)	Q4 2019
End of data collection (defined as analytical dataset is available for analysis)	Q2 2020
Primary analyses completion date	Q1 2020
Final report of study results	Q2 2020

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Bone metastasis (BM) is a common indicator of disease progression for patients with breast and prostate cancer, with as many as 70% of breast cancer patients (Theriault et al, 2012) and 90% of prostate cancer patients (Bubendorf et al, 2000) experiencing this complication. Patients diagnosed with solid tumors that metastasize to the bone are at an elevated risk for painful and irreversible skeletal-related events (SREs) including fractures, bone pain, spinal cord compression (SCC), and hypercalcemia. One study of routine clinical practice in the United States (U.S.) found that 63% of breast, 59% of lung, and 52% of prostate cancer patients experienced a SRE either at diagnosis of bone metastasis (BM) or over patient follow-up (13.6 months for breast, 3.1 months for lung, and 16.6 months for prostate) (Oster et al, 2013). SREs are a burden on the healthcare system, resulting in high costs and decreased quality of life in patients (McDougall et al, 2016).

Intravenous bisphosphonates (IV BPs; zoledronic acid [ZA]) are approved for use in Taiwan for the prevention of SREs in patients with advanced cancers. The receptor activator of nuclear factor κ B ligand (RANKL) inhibitor, denosumab (XGEVA, Amgen), was approved for prevention of SREs in solid tumors in Taiwan in 2012 but is not available to patients in mainland China.

Cancer treatment has improved in China, which translates to more survivors and longer survival times; however, there is still substantial unmet need in this population. Areas of unmet need range widely and include support with physical and daily living activities, support with healthcare after primary treatment, and psychological support (Bonevski et al, 2000; Ho et al, 2018).

In China, the recommended management of malignant tumor bone metastases is a multidisciplinary team approach. Treatment goals include: 1) control of the primary cancer; 2) prevention of SREs; and 3) relieve pain, preserve mobility and function, and improve quality of life (Chinese Anticancer Association, 2015; Sun et al, 2014; Committee of Rehabilitation and Palliative Care China, 2014). Since SREs are associated with diminished quality of life and survival, prevention of SREs plays an important role in the management of patients with bone metastases.

In the last two decades, bisphosphonates have become established as a valuable additional approach to the range of current treatments. Following the launch of bisphosphonates in China, they have become a standard of care in the treatment of

malignant tumor bone metastasis to prevent SREs in daily practice. Local Chinese guidelines recommend that bisphosphonate treatment should be initiated once malignant bone metastasis is confirmed (Chinese Anticancer Association, 2015; Sun et al, 2014; Committee of Rehabilitation and Palliative Care China, 2014). In particular, third-generation bisphosphonates (including zoledronic acid) have shown significantly improved efficacy and have been widely used (80%) for the treatment of bone metastases (Yang et al, 2016). Zoledronic acid is considered the standard of care, with demonstrated efficacy across tumor types (Kohno, 2005; Saad, 2002; Rosen, 2004） and greater potency compared to other bisphosphonates (Gutta, 2007） .

7.2 Rationale

Denosumab (XGEVA) was approved for use in Taiwan in 2012. Its utilization and safety in clinical practice has yet to be characterized within a Chinese population. Given the duration of time since approval and the number of patients of who have used XGEVA in clinical practice, there is now an opportunity to examine and characterize the utilization and safety of XGEVA among Chinese cancer patients in routine real-world clinical practice. Evidence from real-world patient experiences provide a valuable opportunity to evaluate the utilization and safety of drugs and devices in populations outside of the clinical trial setting and to better understand populations and outcomes typically excluded from clinical study (Sherman et al, 2016).

The utilization of XGEVA has been documented in Western populations. One US study of patients initiating XGEVA or IV BP therapy found that XGEVA patients were older, less likely to switch therapies, and more compliant than IV BP patients, receiving a median of 7 administrations over the first 12 months versus 4 for IV BP patients (Hernandez et al, 2014). A second US study of patients initiating therapy with XGEVA or Zoledronic acid similarly found greater compliance in XGEVA-treated patients, and also found that time to non-persistence was significantly longer for XGEVA patients (25.9 months versus 17.2 months for ZA) (Qian et al, 2017).

The safety of XGEVA is currently being characterized through pharmacovigilance activities in countries where XGEVA is approved and it was extensively studied in three global, phase 3 clinical trials in breast cancer (Stopeck et al, 2010), prostate cancer (Fizazi et al, 2011), other solid tumors (excluding breast and prostate cancer) and multiple myeloma (Henry et al, 2011), and an open label extension safety study (Stopeck et al, 2016). Information from the current study will provide a systematic evaluation of safety rates among Chinese patients and it will descriptively evaluate if they are

consistent with Western populations. Obtaining this information is the first step for future comparative effectiveness studies of XGEVA in mainland China. There is an unmet need in mainland China for improved treatments for patients with BM following diagnosis of breast, prostate, and lung cancer. We anticipate using these results as a component of our application for SRE indication in mainland China.

Table 1 summarizes the approval dates and reimbursement status of XGEVA or Zoledronic acid. XGEVA was approved for use in Taiwan in 2012; however, the utilization and safety of XGEVA in clinical practice has yet to be characterized within a Chinese population. Given the duration of time since approval and the number of patients of who have used XGEVA in clinical practice, there is now an opportunity to examine the utilization XGEVA or Zoledronic acid and to characterize the safety of XGEVA among Chinese cancer patients in routine real-world clinical practice. In this study, we will characterize the use of XGEVA or Zoledronic acid in this population and describe the safety of XGEVA.

Table 1. Summary of approval dates and reimbursement status of XGEVA and Zoledronic acid

	XGEVA		Zoledronic Acid	
	Indication Approval Date in Taiwan	Reimbursement Status in Taiwan	Indication Approval Date in Taiwan	Reimbursement Status in Taiwan
Breast Cancer	June 14, 2012	Jan 1, 2013	May 30, 2003	Dec 1, 2004
Prostate Cancer	June 14, 2012	Jan 1, 2013	May 30, 2003	Dec 1, 2004
Lung Cancer	June 14, 2012	Dec 1, 2015	May 30, 2003	N/A

7.3 Statistical Inference (Estimation or Hypotheses)

Primary objective #1 (use of XGEVA or Zoledronic acid) is descriptive and formal hypothesis testing will not be implemented.

Primary objective #2 (safety of XGEVA) will estimate the incidence rates of three important identified risk factors in the Global Risk Management Plan for XGEVA, including ONJ, AFF, and hypocalcemia. We will summarize the incidence rates of these endpoints and descriptively compare the rates of these outcomes with those obtained in the registrational trial in the United States, but formal hypothesis testing will not be implemented.

8. Research Question and Objectives

All objectives will be conducted in the total population and separately by cancer type.

Primary Objectives:

1. Describe the utilization of XGEVA or Zoledronic acid among breast, lung, and prostate cancer patients following diagnosis of incident bone metastases (BMs).
2. Characterize the safety of XGEVA among patients with breast cancer, prostate cancer, and lung cancer, as measured by the incidence of osteonecrosis of the jaw (ONJ), atypical femur fracture (AFF), and hypocalcemia and descriptively compare the rates of these outcomes with those obtained in the registrational trial in the United States.

9. Research Methods

9.1 Study Design

Retrospective cohort study.

9.2 Setting and Study Population

The study population will include patients diagnosed with bone metastasis secondary to breast, prostate or lung cancer who are newly treated with XGEVA or Zoledronic acid in Taiwan between January 1, 2013 and December 31, 2016, with an assessment of safety until December 31, 2017.

Taiwan Department of Statistics, Ministry of Health and Welfare is the unit designated by the government to manage health and social welfare statistical databases, and to develop data platform for academic research. Through the services provided by the Health and Welfare Data Science Center (HWDSC) of the Department of Statistics, researchers may access a wide range of health and welfare data, including claims, mortality (with cause of death) and Taiwan Cancer Registry (TCR). The HWDSC staff encrypt the national ID for all individuals according to a secured encryption algorithm that is not made known to the public. The encrypted ID is unique for all individuals and will be used for linkage between databases.

National Health Insurance claims data

Taiwan National Health Insurance (NHI) started in 1995 and is a publicly funded single payer health insurance program for all residents. Health insurance for individuals is required by law and coverage is more than 99%. The majority of health care providers in Taiwan contract with the National Health Insurance Agency in Taiwan to provide a wide range of medical services. Geographic locations of health care claims are broadly

classified into 6 regions in Taiwan. Salary range, which serves as the basis for enrollees' premium calculation, can serve as a proxy indicator for socioeconomic status. Bundled payment according to the Diagnosis-Related Group system only applies in limited number of disease conditions, therefore detailed drug use information during hospitalization is also available. An added advantage of the NHI data source is the low membership turnover rate, which is particularly important for long term follow-up study.

Mortality data

The household registration system in Taiwan maintains birth, marital status, and death information and is administered by the Department of Household Registration, Ministry of the Interior. Death certificates are collected through this system and transferred to the Ministry of Housing and Works (MOHW) for coding of cause of death (in International Classification of Disease-10 (ICD-10) system) and maintenance of the mortality database. This study will utilize the cause of death data files in years 2000-2016, primarily focusing on the date of death of study subjects.

Taiwan Cancer Registry data

In Taiwan, the population-based cancer registry was founded in 1979. Since then, the registry collected basic information, referred to the "20 items short-form system," on incident cancer cases (including cancer-in-situ) within 1 year after the initial diagnosis from hospitals with more than 50-bed capacity throughout the country. Recorded items include date of birth, gender, time and method of diagnosis, cancer site and morphology, treatment summary and death. From 2002 onward, a "long-form" system was established to collect more detailed information of cancer staging, treatment and follow-up data from hospitals with more than 500 new cancer cases diagnosed annually. The number of recorded items increased from 20 to 65 in 2002, further to 95 in 2007, and to 114 in 2011. In 2003, Cancer Control Act was introduced with all reporting hospitals mandated to submit cancer patient information to the cancer registry. To ensure quality of cancer registries and enhancing the quality of cancer registry data, Taiwan Society of Cancer Registry was established in 2006, conducting random medical record review to ensure data accuracy since 2010. TCR data from 2000 through 2014 will be utilized for this study.

9.2.1 Study Period

January 1, 2013 – December 31, 2017

9.2.2 Patient Eligibility

9.2.2.1 Inclusion Criteria

- Diagnosis of BM secondary to breast, prostate, or lung cancer and prior to initial use of XGEVA or Zoledronic acid.
- New user of XGEVA or Zoledronic acid during study period (January 1, 2013 to December 21, 2016)
    - New user of either therapy will be defined as not having been treated with any bone targeting agent therapy prior to treatment initiation with XGEVA or Zoledronic acid.
- At least one year of data available prior to initial administration of XGEVA or Zoledronic acid.
- 18 or older at diagnosis of BM.

9.2.2.2 Exclusion Criteria

- Patients with diagnosis of giant cell tumor of the bone, or multiple myeloma (to ensure that included subjects are receiving denosumab for the indication of the treatment of BM from solid tumors).
- Evidence of XGEVA or Zoledronic acid use prior to BM diagnosis.

9.2.3 Baseline Period

A baseline period of one year prior to initial administration of XGEVA or Zoledronic acid will be examined for all patients.

9.2.4 Study Follow-up

- *Primary Objective #1* - patients will be followed from date of initial treatment with XGEVA or Zoledronic acid to the first of any of the following: evidence of switching therapy, end of available data, death, or end of study. The Index Date is the date of first treatment with XGEVA or Zoledronic acid.
- *Primary Objective #2* - patients will be followed from date of initial treatment with XGEVA until the earliest date of a safety endpoint, evidence of switching therapy, end of available data, death, or end of study. The Index Date is the date of first treatment with XGEVA or Zoledronic acid.

9.3 Variables

9.3.1 Descriptive Variables

9.3.1.1 Primary Objective #1 – Use of XGEVA or Zoledronic acid

This study will describe the use of XGEVA or Zoledronic acid among breast, lung, and prostate cancer patients following diagnosis of incident bone metastases. NHI-specific drug codes within the NHI database will be used to identify medication use. The following items be evaluated in the exposure assessment during the study period:

- Describe the average number of XGEVA or Zoledronic acid prescriptions per patient.

- Characterize the treatment duration from first dose to last dose of XGEVA or Zoledronic acid.
- Describe the proportion of patients discontinuing XGEVA or Zoledronic acid. Discontinuation of therapy will be defined as not having received a prescription for that therapy within a 90-day window following the date of the previous prescription.
- Describe the proportion of patients who switch therapies. Switching therapy will be defined as receiving a prescription for the alternate therapy within a 90-day window following the date of the previous prescription.
- Calculate the time from initial therapy to the switching of therapy.

9.3.2 Outcome Assessment

9.3.2.1 Primary Objective #2

Three safety outcomes in this study are important identified risks in the Global Risk Management Plan for XGEVA. Outcomes will be identified by published algorithms.

- Osteonecrosis of the Jaw (ONJ) is generally associated with tooth extraction or local infection with delayed healing. The AAOMS clinical definition for ONJ includes exposed bone or bone that can be probed through a fistula in the maxillofacial region that has persisted for longer than 8 weeks in a patient without prior of radiation to jaws or metastatic disease to the jaws (Ruggiero et al, 2014). For the case definition in this study, the following three-step algorithm was applied (Lin et al, 2014):
    1. Identify patients that could be a case of ONJ by having inpatient or outpatient codes for aseptic necrosis of the jaw, inflammatory conditions of the jaw, periapical abscess with sinus, or alveolitis of jaw (Lin et al, 2014) (see Appendix A);
    2. Among these potential ONJ cases, identify cases with a persistent diagnosis record ≥ 8 weeks and no gaps > 30 days between diagnosis;
    3. Among these potential ONJ cases with a persistent diagnosis, identify cases with concomitant use of broad-spectrum oral antibiotics, including penicillin, cephalosporin, clindamycin, and fluoroquinolone therapies.
- Atypical femur fracture (AFF) is a no trauma or minimal trauma fracture occurring along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. For the clinical definition, these fractures have a characteristic appearance on imaging with a simple transverse or oblique fracture with breaking of the cortex and diffuse cortical thickening of the proximal femoral shaft (Shane et al, 2014) (see Appendix A).

- Hypocalcemia can be caused by the use of denosumab. The case definition is a patient receiving inpatient or emergency room care with a primary diagnosis for hypocalcemia (see Appendix A). This definition does not include secondary diagnoses of hypocalcemia, which are likely to represent a consequence of underlying diseases such as chronic renal failure, malabsorption, or hypoparathyroidism.

9.3.3 Characterizing Treated Populations

The baseline period (i.e., 12 months prior to index date) of one dose of therapy will be used to describe patient and disease characteristics of those initiating XGEVA or Zoledronic acid. Covariates include age at index date, calendar year of index date, urbanization level of residence, history of SREs, time from bone metastases to time of therapy with denosumab or zoledronic acid, co-morbidities (see Appendix B) that are risk factors for fracture. Descriptive variables will be used to summarize these variables among patients treated with XGEVA or Zoledronic acid.

9.3.4 Validity and Reliability

The NHI data have been used extensively for conducting high-quality, large, population-based studies of drug safety in the fields of osteoporosis (Lin et al, 2014; Lin et al, 2011), cardiovascular health (Lee et al, 2015; Hsieh et al, 2017), and oncology (Chien et al, 2016). In addition to NHI data access, researchers can assess the original data source to validate the diagnosis, procedures, comorbidities, and prescriptions recorded in the NHI data. Examples of this validation process in Taiwan confirmed more than 85% of diagnoses within NHI data for acute myocardial infarction (Cheng et al, 2014) and stroke (Cheng et al, 2011). Algorithms will be used to identify the variables for ONJ, and AFF because these specific case definitions are not specifically coded in the data source. The specific ICD-9-CM and ICD-10-CM codes that will be used in this study are summarized in Appendix A.

9.3.4.1 ONJ

The case definition of ONJ will include first a sensitive algorithm to identify suspected cases within the inpatient and outpatient data. Criteria for being a confirmed case, include (Ruggiero et al, 2014):

- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

9.3.4.2 AFF

The case definition of AFF leading to hospitalization will be based on a validated algorithm to identify non-traumatic subtrochanteric or diaphyseal fractures of the femur, which are sites where AFFs occur (Narongroeknawin et al, 2012).

9.3.4.3 Hypocalcemia

Presence of hypocalcemia will be identified by primary diagnosis of the condition using ICD-9-CM and ICD-10-CM codes.

9.4 Data Sources

The National Health Insurance Program of the Taiwan Bureau of National Health Insurance, serves a population of more than 23 million through a single-payer national health insurance program for medical and dental care. Nearly all (99.9%) of the population of Taiwan has health insurance through the National Health Insurance Program. Records of all healthcare claims reimbursed by the National Health Insurance Program since 1995 though the current date minus an approximate 18-month lag are centralized for research in the National Health Insurance Research Database (NHI). The NHI data includes patient-level demographic characteristics and longitudinal information of diagnoses and procedures occurring in both ambulatory and inpatient settings and of therapies dispensed at the pharmacy or administered in the physician's office. The NHI data have been used extensively for conducting high-quality, large, population-based studies of drug safety in the fields of osteoporosis (Lin et al, 2011; Lin et al, 2014), cardiovascular health (Lee et al, 2015; Hsieh et al, 2017), and oncology (Chien et al, 2016). NHI data through December 2016 are included in this study.

In the NHI data, patient privacy is protected by anonymizing patient records and allowing researchers to only see aggregate data without any information that could identify individuals. Taiwanese researchers affiliated with academic institutions have access to the NHI data, including the Institute of Clinical Pharmacy and Pharmaceutical Sciences at National Cheng Kung University in Taiwan. National Cheng Kung University has experienced scientists and a team of analysts to manage the data center and to partner on research collaborations with industry.

In addition to NHI access, these sites can assess the original data source to validate the diagnosis, procedures, comorbidities, and prescriptions recorded in the NHI data. Examples of this validation process in Taiwan confirmed more than 85% of diagnoses within the NHI data for acute myocardial infarction (Cheng et al, 2014) and stroke (Cheng et al, 2011).

9.5 Study Size

The study size is dependent on the number of patients treated with XGEVA in clinical practice.

For the characterization of safety in the XGEVA treated group, assuming the mean follow-up duration is about 1.0 year, a study size of 2000 person-years of observation (2000 patients * 1.0 year) in this group will provide >99% probability of detecting at least one event given the true incidence is 1 per 100 person-years and provide 86% probability of detecting at least one case given the true incidence is 1 per 1000 person-years. A study size of 4000 person-years of observation (4000 patients * 1.0 year) in this group will provide 98% probability of detecting at least one case given the true incidence is 1 per 1000 person-years.

9.6 Data Management

All analyses will be conducted by the Taiwanese collaborators using Jigsaw version 2.0 and R version 3.4.5. As required by privacy laws in Taiwan, the Taiwanese collaborators will have sole access to the data for this study.

9.6.1 Obtaining Data Files

Per government regulation, all data processing will be carried out at the Health and Welfare Data Science Center (HWDSC). Patient-level data are not allowed to be brought outside of the HWDSC. Aggregated results and graphs are released after review by HWDSC. All analyses will be led by Dr. PPD .

9.6.2 Linking Data Files

Records of all healthcare claims reimbursed by the National Health Insurance Program since 1995 though the current date minus an approximate 18-month lag are centralized for research with the NHI data. Data from the various clinical databases in Taiwan have already been linked prior to use.

9.6.3 Review and Verification of Data Quality

Data will be reviewed by the statistician at the time of the initial data pull for analysis. The data will be assessed for completeness and accuracy, and any variables with a significant amount of missingness (>20%) or with unlikely or impossible values will be assessed further in conjunction with the study team. Variables may be excluded from analysis if found to be incomplete or inaccurate at the time of data query. No imputations will be conducted for missing data.

9.7 Data Analysis

9.7.1 Planned Method of Analysis

All analyses will be conducted for the entire cohort and separately for each tumor type.

9.7.1.1 Description of Study Enrollment

Flow charts, starting with the number of all XGEVA or Zoledronic acid users in the data source and ending with the number of XGEVA or Zoledronic acid users included in study, will be used to describe the application of inclusion and exclusion criteria.

9.7.1.2 Description of Patient Characteristics

Patient demographics and clinical history during the baseline period will be summarized for all patients and separately for patients in the XGEVA treated group and the Zoledronic acid treated group, by cancer type. Continuous variables will be presented as number, mean with standard deviation, and median with interquartile range. Categorical variables will be presented as number and percentage.

9.7.1.2.1 Primary Objectives #1– Use of XGEVA and Zoledronic acid

Use of XGEVA or Zoledronic acid will be examined for all patients who meet the inclusion criteria during the study period. Continuous variables will be presented as number, mean with standard deviation, and median with interquartile range. Categorical variables will be presented as number and percentage for the following:

- Describe the mean number of XGEVA or Zoledronic acid prescriptions per patient
- Characterize the treatment duration from first dose to last dose of XGEVA or Zoledronic acid
- Describe the proportion of patients discontinuing XGEVA or Zoledronic acid
- Describe the proportion of patients who switch therapies
- Estimate the time from initial therapy to the switching of therapy

9.7.1.2.2 Primary Objective #2 – Safety of XGEVA

Primary Objective #2 - The safety of XGEVA will be examined for all patients from initiation of XGEVA through end of the available data or death. To evaluate safety, we will summarize the number of patients with ONJ, AFF, and hypocalcemia and we will estimate the incidence of the three safety outcomes as the total number of patients with a specific event meeting the case definition per 1,000 person-years of follow-up:

$$\frac{Total\ number\ of\ the\ patients\ with\ safety\ event}{Total\ patient\ years\ in\ the\ cohort} \text{ X } 1{,}000$$

To descriptively compare these outcomes, we will generate a summary table that provides the results of each event in this study and the studies that are summarized in Table 2.

Table 2. Summary of results from ONJ, AFF, and hypocalcemia in registrational trials and real-world studies.

Data Source	XGEVA patients in study	Osteonecrosis of the jaw		Atypical Femur Fracture[a]		Hypocalcemia	
		Rate[b] per 100 person-years	95% CI	Rate[b] per 100 person-years	95% CI	Rate[b] per 100 person-years	95% CI
Sweden [c]	350	2.0	(1.1, 3.5)	NR	NR	NR	NR
Denmark [c]	676	3.2	(2.3, 4.4)	NR	NR	NR	NR
Norway [c]	316	2.3	(1.2, 4.0)	NR	NR	NR	NR
US, Amgen-sponsored RCT - BrC [e]	1026	2.0% [d]	NR	NR	NR	5.5% [d]	NR
US, Amgen-sponsored RCT - PrC [f]	950	2.3% [d]	NR	NR	NR	12.7% [d]	NR
US, Amgen-sponsored RCT - OST & MM [g]	878	1.1% [d]	NR	NR	NR	10.8% [d]	NR
US, open label extension [h]	465 denosumab/denosumab; 452 ZA/denosumab [d]	4.3% in denosumab/denosumab; 5.5% in ZA/denosumab [d,i]	NR	NR	NR	3.1% in denosumab/denosumab; 5.5% in ZA/denosumab [d,i]	NR
US, retrospective, hospital-based [j]	106	NR	NR	NR	NR	34.9% [k]	NR
US, integrated RCT analysis [l, m]	5723	1.8% [d, l]	NR	NR	NR	12.4% [d, m, n]	NR
US, retrospective, hospital-based [o]	253	NR	NR	0.4% [d]	0.1%–2.2%	NR	NR

Table 2. Summary of results from ONJ, AFF, and hypocalcemia in registrational trials and real-world studies.

Data Source	XGEVA patients in study	Osteonecrosis of the jaw		Atypical Femur Fracture[a]		Hypocalcemia	
		Rate[b] per 100 person-years	95% CI	Rate[b] per 100 person-years	95% CI	Rate[b] per 100 person-years	95% CI
Spain, retrospective, hospital outpatient [p]	104	12.5% [q]	NR	NR	NR	38.5% [r]	NR

AFF = atypical femur fracture; US = United States; NR = Not reported; BrC = Breast cancer; PrC = Prostate cancer; OST = Other solid tumors; MM = Multiple myeloma

[a] Nontraumatic subtrochanteric and diaphyseal fracture are sites where AFF may occur.

[b] Incidence rate.

[c] Study 20101363 Annual Interim Report Year 6.

[d] Cumulative incidence of new cases at end of study follow up.

[e] Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, De Boer RH, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010;28(35):5132–9.

[f] Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomized, doubleblind study. Lancet. 2011;377(9768):813–22.

[g] Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, et al. Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma. J Clin Onc 2011; 29 (9): 1125-1132.

[h] Stopeck AT, Fizazi K, Body JJ, Brown JE, Carducci M, Diel I, et al. Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. Support Care Cancer. 2016;24(1):447–55.

[i] "Denosumab/denosumab" refers to patients who continued on denosumab in extension trial; "ZA/denosumab refers to patients who were assigned to ZA but switched to denosumab in extension trial.

[j] Yerram P, Kansagra S, Abdelghany O. Incidence of hypocalcemia in patients receiving denosumab for prevention of skeletal-related events in bone metastasis. J Oncol Pharm Pract. 2017 Apr;23(3):179-184. doi: 10.1177/1078155216628325. Epub 2016 Jun 23. PubMed PMID: 26830549.

[k] Cumulative incidence within 30 days of denosumab administration.

[l] Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol. 2012;23:1341–7.

[m] Body JJ, Bone HG, de Boer RH, Stopeck A, Van Poznak C, Damião R, Fizazi K, Henry DH, Ibrahim T, Lipton A, Saad F, Shore N, Takano T, Shaywitz AJ, Wang H, Bracco OL, Braun A, Kostenuik PJ. Hypocalcaemia in patients with metastatic bone disease treated with denosumab. Eur J Cancer. 2015 Sep;51(13):1812-21. doi:10.1016/j.ejca.2015.05.016. Epub 2015 Jun 17. PubMed PMID: 26093811.

[n] Cumulative incidence of hypocalcaemia, defined as grade 2 or higher.

[o] Yang SP, Kim TWB, Boland PJ, Farooki A. Retrospective review of atypical femoral frature in metastatic bone disease patients receiving denosumab therapy. The Oncologist 2017; 22: 438-444.

[p] Manzaneque A, Chaguaceda C, Mensa M, Bastida C, Creus-Baró N. Use and safety of denosumab in cancer patients. Int J Clin Pharm. 2017 Jun;39(3):522-526. doi: 10.1007/s11096-017-0455-1. Epub 2017 Apr 5. PubMed PMID: 28382583.

[q] Cumulative incidence after a median of 11 administrations of denosumab (range, 3-22).

[r] Cumulative incidence after a median of 4 administrations of denosumab (range, 1-33).

9.8 Quality Control

Statistical analyses on the final analytical datasets will be conducted by two persons and crosschecked for quality assurance.

9.9 Limitations of the Research Methods

9.9.1.1 Information Bias

It is possible that there are errors in the data entered into the EMR at the various sites that report into the NHI data. This is one unavoidable limitation of using a secondary data source comprised of EMR data. Since the NHI data is a national healthcare database and represents 99% of the population, we do not anticipate that errors in data entry would differ in any meaningful way that would alter use and safety assessments.

9.9.1.2 Selection Bias

We do not anticipate that selection bias will impact this study, as the NHI data is a national database, representing over 99% of the Taiwanese population. However, the patients included in this study will be selected based on the set of inclusion and exclusion criteria that have been outlined in section 9.2.2.1 and 9.2.2.2, respectively.

9.9.2 External Validity of Study Design

The NHI data includes all healthcare information for all patients in Taiwan; results from analysis of this database should be an accurate reflection of healthcare in Taiwan. Because patients in Taiwan are ethnically Chinese, there is no reason to expect substantive differences between safety in Taiwanese patients compared with patients in mainland China.

10. Protection of Human Subjects

10.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The study protocol will be reviewed by the IRB of National Cheng Kung University in Taiwan.

10.2 Confidentiality

No patient identifiers are present in the NHIRD. All data are de-identified, stripped of any identifying information. Furthermore, the use of the NHIRD is limited to a small number of carefully selected academic researchers.

11. Collection, Recording, and Reporting of Safety Information

This study is analyzing secondary data from NHIRD. The safety outcomes that are listed in section Outcome Assessment 9.3.2.1 will be analyzed in this study. These will be reported in aggregate in the final study report as incidence rates. See

section Outcome Assessment 9.3.2.1 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen 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 IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

The study protocol and the Observational Research Study Report (ORSR) of results will be submitted to the China Center for Drug Evaluation. No other public disclosure of the results is planned.

13.1 Publication Policy

This study is being conducted for registrational purposes only and we do not anticipate submitting the results for publication in the peer-reviewed literature. Results may be made public if required by the ENCEPP. Authorship of any reports resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

1. 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.

14. References

Bonevski, B; Sanson-Fisher, R., Hersey, P., Paul, C., Foot, G. Assessing the perceived needs of patients attending an outpatient melanoma clinic. *Journal of Psychosocial Oncology*, 17 (2000), pp. 101-118.

Bubendorf L, Schopfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Human pathology* 2000;31(5):578-83.

Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf*. 2011;20:236-242.

Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YH. Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. *J Epidemiol*. 2014;24:500-507.

Chien HC, Kao Yang YH, Bai JP. Trastuzumab-Related Cardiotoxic Effects in Taiwanese Women: A Nationwide Cohort Study. *JAMA Oncol*. 2016;2:1317-1325.

Chinese Anticancer Association. Chinese Anticancer Association guideline and norm on the diagnosis and treatment of breast cancer (version 2015). *China Oncology.* 2015;25:692-754. (In Chinese)

Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R, Goessl C. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011 Mar 5; 377(9768):813-22.

Gutta R, Louis PJ. Bisphosphonates and osteonecrosis of the jaws: science and rationale. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007;104(2):186 193

Henry DH, Costa L, Goldwasser F, Hirsh V, Prausova J, Scagliotti GV, Sleeboom H, Spencer A, Vadhan-Raj S, von Moos R, Willenbacher W, Woll PJ, Wang J, Jun S, Damsey R, Yeh H. Randomized, double-blind study of denomusab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Onc* 2011;29:1125-1132.

Hernandez RK, Quigley J, Pirolli M, Quach D, Chen KS, Arellano J, Liede A (2014) Patients with bone metastases from solid tumors initiating treatment with a bone-targeted agent in 2011: a descriptive analysis using oncology clinic data in the US. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer* 22(10):2697–2705.

Ho PJ, Gernaat SAM, Hartman M, Verkooijen HM. Health-related quality of life in Asian patients with breast cancer: a systematic review. BMJ Open. 2018;8(4):e020512.

Hsieh H, Hsu JC, Lu CY. 10-year trends in statin utilization in Taiwan: a retrospective study using Taiwan's National Health Insurance Research Database. BMJ Open 2017; 7(5): e014150.

Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized placebo-controlled trial. *J Clin Oncol* 2005;23:3314-21.

Lee YH, Hsu YN, Yu IL, Phan DV, Chou P, Chan CL, Yang NP. Treatment incidence of and medical utilization for hospitalized subjects with pathologic fractures in Taiwan-Survey of the 2008 National Health Insurance data. *BMC Health Serv Res*. 2011; 11: 230.

Lee CC, Lee MT, Chen YS, Lee SH, Chen YS, Chen SC, Chang SC. Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. *JAMA Intern Med*. 2015;175:1839-1847.

Lin TC, Yang CY, Yang YH, Lin SJ. Alendronate adherence and its impact on hip-fracture risk in patients with established osteoporosis in Taiwan. *Clin Pharmacol Ther* 2011;90:109-116.

Lin TC, Yang CY, Kao Yang YH, Lin SJ. Incidence and risk of osteonecrosis of the jaw among the Taiwan osteoporosis population. *Osteoporos Int*. 2014;25:1503-1511.

Lin JN, Chen HJ, Yang CH, Lai CH, Lin HH, Chang CS, Liang JA. Risk of osteoporosis and pathologic fractures in cancer patients who underwent hematopoietic stem cell transplantation: a nationwide retrospective cohort study. *Oncotarget*. 2017 May 23; 8(21): 34811–34819.

Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, Richardson GE, Siena S, Maroto P, Clemens M, Bilynskyy B, Charu V, Beuzeboc P, Rader M, Viniegra M, Saad F, Ke C, Braun A, Jun S. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomized, phase 3 trials. *Eur J Cancer* 2012;48:3082-3092.

Lipton A, Fizazi K, Stopeck AT, Henry DH, Smith MR, Shore N, Martin M, Vadhan-Rajh S, Brown JF, Richardson GE, Saad F, Yardley DA, Zhoum K, Balakumaran A, Braun A. Effect of denosumab versus zoledronic acid in preventing skeletal-related events in patients with bone metastases by baseline characteristics. *European Journal of Cancer* 2016;53:75-83.

McDougall JA, Bansal A, Goulart BHL, McCune JS, Karnopp A, Fedorenko C, Greenlee S, Valderrama A, Sullivan SD, Ramsey SD. The Clinical and Economic Impacts of Skeletal-Related Events Among Medicare Enrollees With Prostate Cancer Metastatic to Bone. *The Oncologist* 2016;21(3):320-326.

Narongroeknawin P, Patkar NM, Shakoory B, et al. Validation of diagnostic codes for subtrochanteric, diaphyseal, and atypical femoral fractures using administrative claims data. *J Clin Densitom*. 2012;15:92-102.

Oster G, Lamerato L, Glass AG, Richert-Boe KE, Lopez A, Chung K, Richhariya A, Dodge T,Wolff GG, Balakumaran A, Edelsberg J (2013) Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer* 21(12):3279–3286.

Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate for the treatment of bone metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J* 2001;7:377-87.
Rosen LS, Gordon DH, Dugan W, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004;100:36-43.

Ruggiero S, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F. American Association of Oral and Maxillofacial Surgeons position paper on medication related osteonecrosis of the jaw--2014 update. *J Oral Maxillofac Surg*. 2014;72:1938-1956.

Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94:1458-68.

Shane E, Burr D, Abrahamsen B, Adler RA, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2014 Jan;29(1):1-23

Sherman, RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence — What is it and what can it tell us? *N Engl J Med* 2016;375:2293-2297.

Stopeck AT, Lipton A, Body J, Steger GG, Tonkin K, de Boer RH, Lichinitser M, Fujiwara Y, Yardley DA, Viniegra M, Fan M, Jiang Q, Dansey R, Jun S, Braun A. Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study. *J Clin Oncol* 2010;28:5132-5139.

Sun Y, Guan Z, Liao M, et al. Expert consensus on the diagnosis and treatment of bone metastases in lung cancer. *Zhonqquo Fei Ai Za Zi*. 2014;17(2)57-72

Theriault RL. Biology of bone metastases. *Cancer control : journal of the Moffitt Cancer Center* 2012;19(2):92-101.

The Committee of Rehabilitation and Palliative Care, China. Chinese expert consensus statement on clinical diagnosis and treatment of malignant tumor bone metastasis and bone related diseases. Beijing: Peking University of Medicine Press. 2014. (in Chinese)

Qian Y, Bhowmik D, Kachru N, Hernandez RK. Longitudinal patterns of bone-targeted agent use among patients with solid tumors and bone metastases in the United States. *Support Care Cancer* 2017 Jun;25(6):1845-1851.

Yang Y, Ma Y, Sheng J, et al. A multicenter, retrospective epidemiologic survey of the clinical features and management of bone metastatic disease in China. *Chin J Cancer*. 2016;35:40.

15. Appendices

Appendix A. ICD-9-CM and ICD-10-CM diagnosis codes for safety outcomes

Osteonecrosis of the Jaw

Case definition is inpatient or outpatient care for any of the following diagnosis:

ICD-9-CM	Description
525.9	Unspecified disorder of the teeth and supporting structure
526.4	Inflammatory conditions of jaw
526.89	Other specified diseases of the jaws
526.9	Unspecified disease of the jaws
528.9	Other and unspecified diseases of the oral soft tissues
730.00	Acute osteomyelitis, site unspecified
730.08	Acute osteomyelitis involving other
730.10	Chronic osteomyelitis, site unspecified
730.18	Chronic osteomyelitis involving other specified sites
730.20	Unspecified osteomyelitis, site unspecified
733.40	Aseptic necrosis of bone, site unspecified
733.45	Osteonecrosis of the jaw
733.49	Aseptic necrosis of other bone sites
733.90	Disorder of bone and cartilage, unspecified
ICD-10-CM	**Description**
M27.2 (K10.2)	Inflammatory conditions of jaws
M27.3 (K10.3)	Alveolitis of jaws
M87.180	Osteonecrosis due to drugs, jaw
M87.08 M87.28 M87.38 M87.88	Idiopathic aseptic necrosis of bone, other site; Osteonecrosis due to previous trauma, other site; Other secondary osteonecrosis, other site; Other osteonecrosis, other site;
(K10.8)	Other specified disease of jaws

Atypical Femoral Fracture

Case definition includes inpatient care for any of the following diagnosis:

ICD-9-CM	Description
820.22	Closed fracture of subtrochanteric section of neck of femur
821.00	Closed fracture of unspecified part of femur
821.01	Closed fracture of shaft of femur
ICD-10-CM	**Description**
S72.2--A	Closed subtrochanteric fracture of femur -- initial encounter
S72.3--A	Closed fracture of shaft of femur -- initial encounter

AND no concurrent major trauma codes

ICD-9-CM	Description	ICD10
E800-E848	Railway accidents, motor vehicle accidents, other road vehicle accidents; water transport accidents; air transport accidents; other vehicle accidents	V00 – V99

Hypocalcemia

Case definition includes inpatient care with a PRIMARY diagnosis of:

ICD-9-CM	Description
275.41	Hypocalcemia
ICD-10-CM	**Description**
E83.51	Hypocalcemia

Appendix B. Comorbidities of Interest

History of co-morbidities	History of medication use
Cataract	Alpha-blockers
Chronic obstructive pulmonary disease	Antidiabetic agents
Congestive heart failure	Antihistamines
Dementia	Antiparkinsons
Depression	Antipletelets
Diabetes mellitus	Antithrombotic agents
Dyslipidemia	Arrhythmic medications
Gastrointestinal bleeding	Calcium channel blockers
Glaucoma	Gastroesophageal reflux medications
Hemorrhagic stroke	Gout medications
Hypertension	Lipid lowering agents
Ischemic heart disease	Nonsteroidal anti-inflammatory drugs
Renal failure	Osteoporosis medications
Ischemic stroke	Propulsives
Macular degeneration	Renin-angiotensin system inhibitors
Osteoarthritis	Respiratory Medications
Parkinson disease	Systemic corticosteroids
Peptic ulcer	Thiazide diuretics
Pneumonia	Beta-blockers
Rheumatoid arthritis	
Schizophrenia	

Appendix C. ENCePP Checklist for Study Protocols

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]	☒	☐	☐	6.0
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

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)	☒	☐	☐	7.1 7.2 7.3 8.0
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?	☐	☐	☒	

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.3
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7.1.2.2
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)	☐	☐	☒	N/A

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4
4.2 Is the planned study population defined in terms of:				9.2
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)	☒	☐	☐	9.2

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)	☒	☐	☐	9.2.2.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.2.2.1
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.2.2.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

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?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	N/A
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	N/A
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9.1.2
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9.1.1
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.9.2

Section 8: Effect 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)	☐	☐	☒	N/A

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)	☒	☐	☐	9.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.2
9.1.3 Covariates?	☒	☐	☐	9.2
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
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.2
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.2
9.3.3 Covariates?	☒	☐	☐	9.2

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6.1

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.1
10.2 Are descriptive analyses included?	☒	☐	☐	9.1.1.1
10.3 Are stratified analyses included?	☐	☐	☒	N/A
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	N/A
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6.3
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6.3
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.6.3

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?	☒	☐	☐	9.9.1.2 9.9.1.1
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, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	N/A

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	N/A
13.3 Have data protection requirements been described?	☒	☐	☐	10.2

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	15.0

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)?	☒	☐	☐	13.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13.1