Summary Table of Study Protocol

Title	A Real-world, Prospective, Observational Study of Prolia® (Denosumab) in Chinese Women With Postmenopausal Osteoporosis (PMO)
Protocol version identifier	20180401**, Version 2.0**
Date of last version of the protocol	**04 February 2019**
EU Post Authorization Study (PAS) Register No	**EUPAS37579**
Active Substance	Denosumab
Medicinal Product	Denosumab; Prolia®
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	To estimate the incidence rates of adverse events, serious adverse events, and adverse drug reactions among PMO patients receiving Prolia® according to the China Prescribing Information in a postmarketing setting
Country(ies) of Study	China
Author	PPD

Investigator's Agreement

I have read the attached protocol entitled 'A Real-world, Prospective, Observational Study of Prolia® (Denosumab) in Chinese Women with Postmenopausal Osteoporosis (PMO)', dated **08 March 2023**, and agree to abide by all provisions set forth therein.

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

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

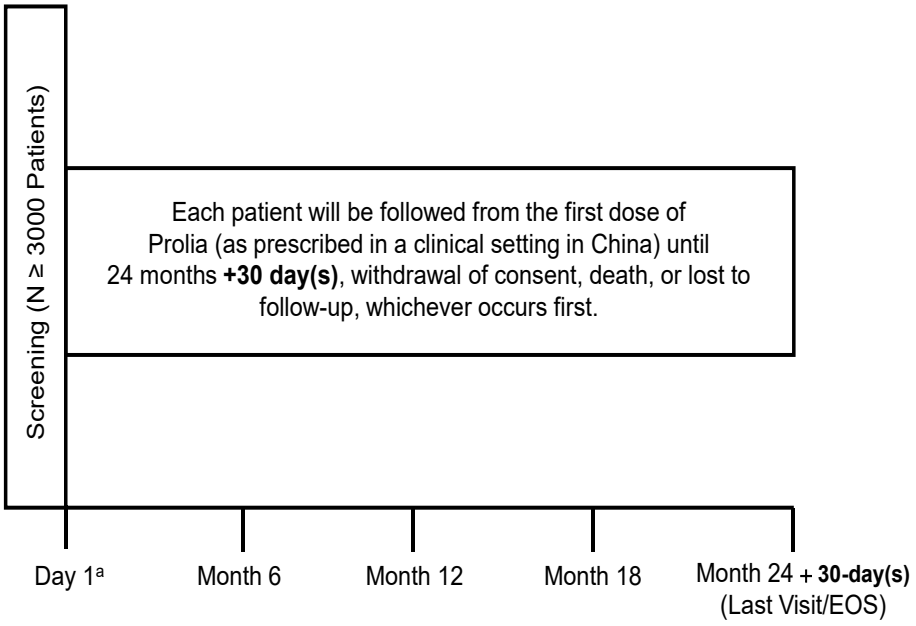
at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Study Design Schema



[a] Screening and Day 1 could occur on same day.

1. Table of Contents

List of Tables

List of Appendices

2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
ADR	adverse drug reaction
BMD	bone mineral density
BMI	body mass index
CA	Calcium
CRF	case report form
CRO	clinical research organization
COVID-19	**coronavirus disease 19**
CTCAE	Common Terminology Criteria for Adverse Events
DXA	dual-energy x-ray absorptiometry
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
End of study	defined as up to 24 months after the last patient enrolled/followed up, whichever occurs later
End of study for an individual patient	Defined as the last day the patient is assessed for collection of data
Enrollment	defined as the date the patient provides written consent and meets the inclusion criteria
EOS	end of study
EU	European Union
Follow-up period	up to 24 months + **30 day(s)** starting from day 1, withdrawal of consent**,** or death
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
NA	not applicable
NMPA	National Medical Products Administration
PAS	postauthorization study
PI	Prescribing Information
PMC	postmarketing commitment
PMO	postmenopausal osteoporosis

Abbreviation or Term	Definition/Explanation
Primary completion	defined as the date when the last patient is assessed for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary final analysis, whether the study concluded as planned in the protocol or was terminated early
Q6M	every 6 months
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
SC	Subcutaneous**(ly)**
SOP	Standard Operating Procedures
Study day 1	defined as the first day that protocol-required therapy (Prolia®) is/are administered to the patient (day 1 and enrollment could fall on the same day)
US	United States

3. Responsible Parties

Sponsor	Amgen Biotechnology Consultation (Shanghai) Co., Ltd Room 1501, Platinum Tower No. 233 Taicang Road Huangpu District Shanghai, 200020 P.R. China

The list of investigators is at Amgen and is available upon request.

4. Abstract

- **Study Title**

A Real-world, Prospective, Observational Study of Prolia® (Denosumab) in Chinese Women with Postmenopausal Osteoporosis (PMO)

- **Study Background and Rationale**

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and susceptibility to fracture. Osteoporosis is one of the leading causes of significant morbidity and disability in the aging population and contributes to the increasing economic burden on the healthcare system.

According to the National Survey of Osteoporosis, conducted by China National Health Commission, the prevalence of osteoporosis in Chinese population older than 50 years is 19.2% (6% in male, 32.1% in female); the prevalence of osteoporosis in population older than 65 years is 32.0% (10.7% in male, 51.6% in female). Compar**ing** these prevalence number**s** with those in the global publication, it was found that the prevalence of osteoporosis in Chinese men is similar to that in other countries, however, the prevalence of osteoporosis in women is significantly higher than that in European and American countries, similar to that in **other** Asian countries such as Japan and South Korea. The disease awareness and bone mineral density (BMD) testing rate are low in China; the disease awareness in population older than 20 years is only 11.7%, the BMD test rate in population older than 20 years is 2.8%, and 3.7% in population older than 50 years (National Survey of Osteoporosis, China National Health Commission 2018).

Previous studies demonstrated the ability of denosumab to prevent vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis. Reductions in fracture risk due to denosumab were statistically significant, clinically meaningful, and consistent across subjects with a wide range of fracture risk and baseline characteristics. Denosumab's specific mechanism of action reduces bone turnover in a coupled and dynamic manner, results in clinically meaningful increases in BMD, and improves measures of bone strength. These skeletal benefits of denosumab were obtained with a safety profile similar to that of placebo. Denosumab, administered subcutaneous**ly** (SC) at a dose of 60 mg every 6 months (Q6M) (Prolia), is effective and well tolerated for the treatment of PMO (Study 20030216 [FREEDOM] Clinical Study Report).

Considering the need for osteoporosis treatment options in China, this postmarketing commitment (PMC) study **of** Prolia in China is intended to satisfy local regulatory requirements and further evaluate safety and effectiveness of Prolia to treat osteoporosis in postmenopausal women in Mainland China.

- **Research Question and Objective(s)**

Primary Objective(s)

- To estimate the incidence rates of adverse events, serious adverse events, and adverse drug reactions (ADRs) among PMO patients receiving Prolia according to the China Prescribing Information (PI) in a postmarketing setting

Secondary Objective(s)

- To describe the effectiveness of Prolia by assessing the percent change from baseline in BMD of the lumbar spine and/or total hip and/or femoral neck (if BMD available and performed per local standard of care)
- To describe the incidence of clinical fractures during treatment with Prolia
- To describe characteristics of patients receiving Prolia in the postmarketing setting

- **Hypothesis(es)/Estimation**

There is no hypothesis to be tested and the study will provide descriptive data on use of Prolia; the incidence of adverse events, **serious adverse events,** and ADRs; BMD at the lumbar spine, total hip, and femoral neck; clinical fractures, and patient characteristics in the postmarketing setting.

- **Study Design/Type**

This study is a real-world, prospective, single arm, observational multi-center study in postmenopausal women with osteoporosis who are being prescribed Prolia on label (per the China Prolia PI) in a postmarketing setting in Mainland China. No study drug will be provided by Amgen. There will be no control group.

- **Study Population or Data Resource**

Study enrollment will be offered to patients meeting the eligibility criteria at participating sites in China. Enrollment will stop after approximately 12 months once the enrolled sample size is at least 3000. The goal of this study is to capture at least 3000 patients who are prescribed Prolia in a clinical setting in China.

- **Summary of Patient Eligibility Criteria**

  Inclusion Criteria

  - Postmenopausal women who are eligible to receive Prolia (on label) in the postmarketing setting in China
  - Consent to participate in this study

  Exclusion Criteria

  Subjects are excluded from the study if any of the following criteria apply:

  - **Previously received or receiving any denosumab or biosimilar therapy**
  - **Patients currently enrolled in another study involving any investigational procedure, device, or drug**

- **Baseline Period**

The baseline period is defined as up to 6 months before the first dose of Prolia and including the date of the first dose of Prolia. Entries recorded during this baseline period in a subject's chart will be reviewed to obtain information on demographic characteristics, lifestyle variables, BMD, medical history, physical examination, concomitant therapy, and laboratory values.

- **Follow-up**

Each patient will be followed from the first dose of Prolia until the end of the 24-month + **30 day(s)** period, withdrawal of consent, death, or loss to follow-up (eg, patients transferring to another clinic), whichever occurs first. Administration of the first dose of Prolia will occur on day 1. Patients will be informed to visit Principal Investigator Q6M for next injection and data collection, until the end of study (EOS), regardless of the treatment status. The frequency of follow-up visits, except for months 6, 12, and 18 (provided the patient continues treatment with Prolia), is at the discretion of the investigator.

- **Variables**

Primary Endpoint

- Adverse events, **serious adverse event,** and ADRs (including seriousness and causality to drug). Subject level incidence will be reported and summarized by classification according to the adverse event coding.

Secondary Endpoints

- Percent change from baseline in BMD at 24 months (or as close as possible to the last dose of Prolia) (measured by dual-energy x-ray absorptiometry [DXA] scan) of the lumbar spine and/or total hip and/or femoral neck.
- Clinical fractures during treatment with Prolia. Fractures include **clinical** vertebral, non-vertebral, and hip fractures recorded and evaluated from day 1 through the end of **the** follow up period.
- Characteristics of patients receiving Prolia in the postmarketing setting.

- **Study Sample Size**

Amgen will enroll at least 3000 eligible patients to obtain safety information. A total of 3000 patients will enable the study to have a 95% chance to detect at least one adverse event if the true event rate is 0.1%.

- **Data Analysis**

Descriptive analysis of the collected safety and effectiveness endpoints will be conducted **as needed** and **at** final analysis when all patients have had the opportunity to complete the final study visit. No hypothesis testing will be performed. Categorical outcomes will be summarized by the number and percentage of subjects in each category. Continuous outcomes will be summarized by the number of nonmissing values, mean, standard deviation, median, lower and upper quartiles, and minimum and maximum values. For the incidence, 95% CI will be presented based on an exact method.

5. Amendments and Updates

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	08 March 2023	See summary of changes		

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to increased bone fragility and susceptibility to fracture. Osteoporosis risk increases with age and women are more likely than men to develop osteoporosis, particularly during the postmenopausal period. Other risk factors include Caucasian and Asian ethnicity, family history, low calcium and vitamin D intake, smoking, and alcohol intake.

Osteoporosis is one of the leading causes of significant morbidity and disability in the aging population and contributes to the increasing economic burden on the healthcare system.

According to the National Survey of Osteoporosis, conducted by China National Health Commission, the prevalence of osteoporosis in Chinese population older than 50 years is 19.2% (6% in male, 32.1% in female); the prevalence of osteoporosis in population older than 65 years is 32.0% (10.7% in male, 51.6% in female). Compar**ing** these prevalence number**s** with those in the global publication, it was found that the prevalence of osteoporosis in Chinese men is similar to that in other countries, however, the prevalence of osteoporosis in women is significantly higher than that in European and American countries, similar to that in **other** Asian countries such as Japan and South Korea. The disease awareness and BMD testing rate are low in China; the

disease awareness in population older than 20 years is only 11.7%, the BMD test rate in population older than 20 years is 2.8%, and 3.7% in population older than 50 years (National Survey of Osteoporosis, China National Health Commission 2018).

Osteoporosis presents a major public health issue as the world's population ages. The morbidity and mortality associated with osteoporotic related fractures is devastating in terms of disability to an individual and cost to the global economy. The osteoporotic hip and vertebral fractures caused excess mortality rates in this population of Mainland China. The current diagnosis and medical treatment following the fragility fractures is still insufficient in Mainland China (Wang et al, 2015). The rate of fracture has been rising very rapidly with females showing a higher fracture incidence than males in those aged 50 years and over in China (Xia et al, 2012). The osteoporosis-related fractures cause a substantial economic burden which will markedly increase over the coming decades in China justifying the need for effective treatments (Si et al, 2015).

Previous studies demonstrated the ability of denosumab to prevent vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis. Reductions in fracture risk due to denosumab were statistically significant, clinically meaningful, and consistent across subjects with a wide range of fracture risk and baseline characteristics. Denosumab's specific mechanism of action reduces bone turnover in a coupled and dynamic manner, results in clinically meaningful increases in BMD, and improves measures of bone strength. These skeletal benefits of denosumab were obtained with a safety profile similar to that of placebo. Denosumab, administered SC at a dose of 60 mg Q6M (Prolia), is effective and well tolerated for the treatment of PMO (Study 20030216 [FREEDOM] Clinical Study Report). Denosumab provides an opportunity for a safe, convenient, and effective therapeutic option with a rapid onset of action.

Denosumab is a fully human monoclonal antibody that binds with high affinity (dissociation equilibrium constant [Kd] 3 x 10^{-12} M) and specificity to receptor activator of nuclear factor kappa-B ligand (RANKL) which neutralizes the activity of RANKL, thereby preventing activation of its receptor, receptor activator of nuclear factor kappa-B (RANK), on the surface of precursor and mature osteoclasts. As a consequence, bone resorption is reduced. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian Chinese hamster ovary cells. It consists of 2 heavy chains of the immunoglobulin G2 subclass and 2 light chains of the kappa subclass which are covalently linked through disulfide bonds. Prolia is formulated for SC

injection and is administered at a dose of 60 mg Q6M for PMO indication. Prolia is colorless to slightly yellow, clear to slightly opaque, and practically free from particle injectable solution in a colorless and clear prefilled syringe.

Prolia is currently indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fractures.

6.2 Rationale

Considering the need for osteoporosis treatment options in China, this PMC study **of** Prolia in China is intended to satisfy local regulatory requirements and further evaluate safety and effectiveness of Prolia to treat osteoporosis in postmenopausal women in Mainland China.

6.3 Statistical Inference (Estimation or Hypothesis[es])

This regulatory PMC is a prospective, observational, multicenter study in patients who are being treated with Prolia. There is no hypothesis to be tested and the study will provide descriptive data on use of Prolia; the incidence of adverse events, **serious adverse events,** and ADRs; BMD at the lumbar spine, total hip, and femoral neck; clinical fractures, and patient characteristics in the postmarketing setting.

6.4 COVID-19

Amgen closely monitors the coronavirus disease 19 (COVID-19) pandemic around the world. As part of this effort, Amgen performs a rigorous assessment, considering the study design, patient safety, public health risk, benefit-risk assessment, as well as the burden on country healthcare systems. Decisions are made on a study-by-study and country-by-country basis to minimize risk to patients and avoid undue burden on healthcare facilities.

Subjects who display symptoms consistent with COVID-19 infections or who have tested positive for COVID-19 should contact the investigator to ensure appropriate care as well as documentation and management of study activities.

Amgen considers that it is important to continue the proposed development of Prolia in this study in order to advance potential therapy options for patients as rapidly as possible, while balancing this with appropriate measures to monitor and mitigate the potential impact of COVID-19.

7. Research Question and Objectives

7.1 Primary

The primary objective is to:

- estimate the incidence rates of adverse events, serious adverse events, and ADRs among PMO patients receiving Prolia according to the China Prescribing Information (PI) in a postmarketing setting.

7.2 Secondary

The secondary objectives of the study are to:

- describe the effectiveness of Prolia by assessing the percent change from baseline in BMD of the lumbar spine and/or total hip and/or femoral neck (if BMD available and performed per local standard of care)
- describe the incidence of clinical fractures during treatment with Prolia
- describe the characteristics of patients receiving Prolia in the postmarketing setting

8. Research Methods

8.1 Study Design

This study is a real-world, prospective, single arm, observational multi-center study in postmenopausal women with osteoporosis who are being prescribed Prolia on label (per the China Prolia PI) in a postmarketing setting in Mainland China. No study drug will be provided by Amgen China. There will be no control group. Since osteoporosis is a common condition, it seems prudent to capture adverse events with frequencies as low as 1 in 1000. The goal of this study is to capture at least 3000 patients who are prescribed Prolia in a clinical setting in China. If patients meet the inclusion criteria (Section 8.2.3.1)**, none of the exclusion criteria (Section 8.2.3.2)** and sign the informed consent, they will be considered enrolled. Patients will be seen by their physician per local standard of care and receive Prolia on label.

The primary endpoints of this study include: adverse events, serious adverse events, and ADRs.

The secondary endpoints of this study include: percent change from baseline in BMD at 24 months (or as close as possible to the last dose of Prolia) (measured by dual-energy x-ray absorptiometry [DXA] scan) of the lumbar spine and/or total hip and/or femoral neck; clinical fractures; and baseline characteristics (eg, demographic, medical history, prior-treatment).

All data collected for this study will be extracted from the information generated or gathered through routine medical practice.

The enrollment period will stop approximately 12 months once the enrolled sample size is at least 3000. Each patient will be followed from the first dose of Prolia (as prescribed in a clinical setting in China) until the end of the 24-month + **30-day(s)** period, or death, withdrawal of consent, or loss to follow-up (eg, patients transferring to another clinic), whichever occurs first. The frequency of follow-up visits, except for months 6, 12, and 18 (provided the patient continues treatment with Prolia), is at the discretion of the investigator.

The overall study design is described by a study schema. For a full list of study procedures, including the timing of each procedure, please refer to the schedule of assessments in Table 8-1.

Table 8-1. Schedule of Assessments

Data Collection[l]	Screening/Day1[a]	Month 6	Month 12	Month 18	Month 24/Last Visit/EOS
Informed consent[i]	X	-	-	-	-
Eligibility	X	-	-	-	-
Demographics[b]	X	-	-	-	-
Physical measurements (height, weight)	X	-	-	-	-
Lifestyle variables[c]	X	-	-	-	-
BMD by DXA[d,e]	X[e]	-	X	-	X
Medical history[f]	X	-	-	-	-
Prolia Treatment	X	X	X	X	X
Treatment status[k]	-	X	X	X	X
Laboratory Values[g]	X	-	-	-	-
Concomitant therapies review[h]	X	X	X	X	X
Adverse events (including clinical fractures **and ADRs**)[j]	X	X	X	X	X
Serious adverse events	X	X	X	X	X

Footnotes defined on next page

BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; EOS = end of study**; ICF = Informed consent form**

[a] Screening and day 1 could occur on the same day.

[b] Age.

[c] Lifestyle variable**s** include smoking (past and present), alcohol intake, exercise.

[d] DXA of lumbar spine, and/or femoral neck and/or total hip; frequency of BMD measurement according to local clinical practice.

[e] BMD value most proximal to start of Prolia and within past 6 months before the first dose of Prolia and including the date of the first dose of Prolia.

[f] See Section 8.3.2.8.

[g] Laboratory values most proximal to start of Prolia and within past 6 months before the first dose of Prolia and including the date of the first dose of Prolia will be considered as baseline.

[h] Concomitant medications, including therapy name, indication, dose, unit, frequency, route of administration, and start and stop date will be collected:

- Concomitant use of calcium and/or vitamin D
- Concomitant use of other osteoporosis treatment(s)
- Concomitant use of other medications (eg, steroid, anti-inflammation, and anti-diabetic agents, hypertension agents).

[I] After the initial denosumab prescription, the informed consent and patient enrollment procedures can be completed within 4 weeks; these steps can be completed on the same day, depending on clinic protocol and patient preference.

[j] Patients education will be provided at the time of ICF signature. Then **adverse events, Serious adverse events and ADRs** will be reported by patients during follow up visits.

[k] Treatment status of on treatment, consent withdrawn, death, or lost to follow-up will be collected.

[l] This study is intended to collect available data until 24 months + **30 day(s)** after the enrollment. Sites will use different methods, such as phone call, to remind patients for follow-up. Patients with eventual no-show will be considered as lost to follow-up.

8.2 Setting and Study Population

The study population comprises patients treated with Prolia in a clinical setting which includes any primary through tertiary healthcare setting where Prolia is prescribed. Patients will be screened for eligibility, receive a single dose of Prolia during their initial visit/day 1 (which could be the same day as screening), and return for follow-up visits at the discretion of the investigator based on the patient's course of treatment. According to the China Prolia PI, Prolia is administered Q6M; thus, patients who remain on treatment will have up to 4 follow-up visits during the 24-month + **30 day(s)** follow-up period (See Section 8.2.1). The safety and effectiveness data will be collected up to 24 months + **30 day(s)**, withdrawal of consent, death, or lost to follow up, whichever occurs first.

8.2.1 Study Period

The total study duration is estimated to be 36 months. Enrollment will stop after approximately 12 months once the enrolled sample size is at least 3000. This will allow 24 months + **30-day(s)** follow-up of the last enrolled patient, analysis, and reporting in preparation for re-examination by the National Medical Products Administration (NMPA). Each patient will be followed from the first dose of Prolia until the end of the 24 month + **30-day(s)** period, withdrawal of consent, death, or lost to follow-up (eg, patients transferring to another clinic), whichever occurs first. The frequency of

follow-up, except for months 6, 12, and 18 (provided the patient continues treatment with Prolia), is at the discretion of the investigator.

This study is intended to collect available data until 24 months + **30-day(s)** after the enrollment. Sites will use different methods, such as phone call, to remind **patients of** follow-up **visits**. Eventually, **patients who do not return for follow-up visits** will be **considered** as lost to follow-up.

Definitions:

Screening/Enrollment: Defined as the date the patient provides written consent and meets the eligibility criteria (see Section 8.2.3).

Study day 1: Defined as the first day that protocol-required therapy (Prolia) is administered to the patient (day 1 and screening could fall on the same day).

Follow-up period: Up to 24 months + **30-day(s)** starting from day 1, until withdrawal of consent, death, or lost to follow up.

End of study (EOS): defined as up to 24 months + **30-day(s)** after the last patient enrolled/followed up, whichever occurs later. This definition also coincides to end of follow-up period.

End of study for an individual patient: Defined as the last day the patient is assessed for collection of data.

Primary completion: Defined as the date when the last patient is assessed for the final collection of data for the primary endpoint(s), for the purposes of conducting the final analysis, whether the study concluded as planned in the protocol or was terminated early.

8.2.2 Selection and Number of Sites

Sites will be eligible to participate in the study if they are listed among the sites to receive and administer Prolia according to the formulary. Approximately 65 sites will be enrolled to participate.

Site selection will be carried out according to normal site evaluation processes. Selection will be based on interest in study participation, and willingness and capacity to comply with protocol and data entry conventions. Sites will be considered active after fulfilling all legal, regulatory and ethical requirements.

To ensure that the recruitment strategy has as little impact on routine practice as possible, the decision to treat the patient with denosumab will be made independently of, and before, enrollment in the study. After the initial denosumab prescription, the informed consent and patient enrollment procedures can be completed within 4 weeks; these steps can be completed on the same day, depending on clinic protocol and patient preference.

8.2.3 Subject/Patient/Healthcare Professional Eligibility

8.2.3.1 Inclusion Criteria

- Postmenopausal women who are eligible to receive Prolia (on label) in the postmarketing setting in China
- Consent to participate in this study

8.2.3.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

- **Previously received or receiving any denosumab or biosimilar therapy.**
- **Patients currently enrolled in another study involving any investigational procedure, device, or drug.**

8.2.4 Baseline Period

The baseline period is defined as up to 6 months before the first dose of Prolia and including the date of the first dose of Prolia. Entries recorded during this baseline period in a patient's chart will be reviewed to obtain information on demographic characteristics, lifestyle variables, BMD, medical history, physical examination, concomitant therapy, and laboratory values. Summaries of baseline characteristics will reflect patient status on the date of the first dose of Prolia (eg, age).

8.2.5 Study Follow-up

Each patient will be followed from the first dose of Prolia until the end of the 24-month + **30 day(s)** period, withdrawal of consent, death, or loss to follow-up (eg, patients transferring to another clinic), whichever occurs first. Administration of the first dose of Prolia will occur on day 1. Patients will be informed to visit Principal investigator Q6M for next injection and data collection, until the EOS, regardless of the treatment status. The frequency of follow-up visits, except for months 6, 12, and 18 (provided the patient continues treatment with Prolia), is at the discretion of the investigator.

8.3 Variables

8.3.1 Outcome Assessment

8.3.1.1 Primary Endpoint

Adverse events, **serious adverse events,** and ADRs (including seriousness and causality to drug), will be collected as they become available throughout the follow-up period and reported. Subject incidence will be reported and summarized by classification according to the adverse event coding.

8.3.1.2 Secondary Endpoints

- Percent change from baseline in BMD at 24 months (or as close as possible to the last dose of Prolia) (measured by DXA scan) of the lumbar spine and/or total hip and/or femoral neck.
- Clinical fractures during treatment with Prolia. Fractures include **clinical** vertebral, non-vertebral, and hip fractures recorded and evaluated from day 1 through the end of **the** follow up period.
- Characteristics of patients receiving Prolia in the postmarketing setting.

8.3.2 Other Assessments

8.3.2.1 Demographics

Patients' age will be collected at screening/day 1.

8.3.2.2 Physical Measurements

Height (in centimeters) and weight (in kilograms) should be measured without shoes at screening/day 1.

8.3.2.3 Lifestyle Variables

Lifestyle variables include smoking (past and present), alcohol intake, and exercise will be collected during screening/day 1.

8.3.2.4 Safety Data

For the safety assessment, all adverse events**, Serious Adverse Events and ADRs** are collected on day 1 and as they become available throughout the follow-up period. Standardized case report forms (CRFs) will be used for reporting.

8.3.2.5 Prolia Treatment

Prolia is administered Q6M according to the China PI in a postmarketing setting.

8.3.2.6 Treatment Status

Treatment continuation or discontinuation will be assessed using end of treatment CRFs. If discontinued, the reason for discontinuation (ie, safety event, disease progression,

death, or loss to follow-up) will be documented. This form should be collected upon treatment discontinuation or completion at the last visit.

8.3.2.7 BMD

BMD will be measured using DXA scans and processed locally during routine clinical visits. Dual-energy x-ray absorptiometry of lumbar spine, and/or femoral neck and/or total hip will be measured at screening/day 1, month 12, and month 24/EOS. Method of assessment will be per the site's clinical standard for measuring BMD of the lumbar spine, total hip, and femoral neck. Measurement method, machine type, and specific site (lumbar spine, total hip, and femoral neck) of measurement will be collected. BMD will be reported using structured CRFs.

8.3.2.8 Medical and Medication History

Medical history of disease (for prior therapies include therapy name, indication, dose, unit, frequency, route of administration, and start and stop date):

- history of drug allergies
- fracture history (prevalent fractures, site of prevalent fracture, number of prevalent vertebral fractures)
- renal impairment (chronic kidney disease, estimated glomerular filtration rate [eGFR])
- hepatic impairment (Child-Pugh class A, B, or C)
- prior use of calcium and/or vitamin D
- prior use of bisphosphate preparations
- prior use of other osteoporosis treatment(s)
- serum calcium and vitamin D levels
- other medical conditions associated with the safety and efficacy of Prolia therapy for the patients
    - including conditions and drug treatments that influence bone metabolism
    - history of dental procedures (checklist of relevant conditions to be provided in CRF)

8.3.2.9 Laboratory Values

Clinical laboratory values will be collected at baseline and during other routine visits as deemed necessary by the investigator and processed locally (serum creatinine, liver function, parathyroid hormone, serum calcium level, and vitamin D levels should be collected at baseline). Laboratory values most proximal to start of Prolia and within past 6 months before the first dose of Prolia and including the date of the first dose of Prolia will be considered as baseline.

8.3.2.10 Concomitant Therapy

Concomitant use of calcium and/or vitamin D, osteoporosis treatment(s), and other treatments (eg, steroid, anti-inflammation, and anti-diabetic agents, hypertension agents, etc) including therapy name, indication, dose, unit, frequency, route of administration, and start and stop date will be collected at baseline and during the follow up period.

8.3.3 Subgroup Assessment

The following variables would be used to summarize selected outcomes as the subgroup analysis:

- Age at baseline (years)
- Body mass index (BMI) at baseline
- History of osteoporosis therapy use (prior and/or concomitant bisphosphonate or other treatment use)
- Hepatic impairment (Child-Pugh class A, B, or C) at baseline
- Renal function at baseline (stage of chronic kidney disease based on estimated GFR)
- **Any historical osteoporosis** fracture or without **historical osteoporosis** fracture

8.3.4 Validity and Reliability

Efforts will be made to collect complete data through the use of clear instructions to investigators regarding the completion of CRFs.

8.4 Data Sources

Patient data will be collected by investigators or site staff at routine clinical visits or as reported in between visits by the patient and captured on the electronic CRF (eCRF). The investigator or site staff will ask specific questions of the patients to assess for any potential occurrence of safety events. BMD will be collected by DXA per the site's clinical standard of measurement. All laboratory values (serum creatinine, liver function, parathyroid hormone, serum calcium level, and vitamin D levels) will be transcribed into the Amgen database.

8.5 Study Size

Amgen will enroll at least 3000 eligible patients to obtain safety information. A total of 3000 patients will enable the study to have a 95% chance to detect at least one adverse event if the true event rate is 0.1%.

8.6 Data Management

Standard Amgen processes for clinical trial and data management will be used in this study.

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 CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the patient's CRF 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.

Elements to include:

- Patient files containing completed CRFs, informed consent forms, and patient identification list.
- Study files containing the protocol with all amendments, copies of prestudy documentation, and all correspondence to and from the Independent Ethics Committee (IEC) and Amgen.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available. Retention of study documents will be governed by the PMC Agreement.

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.

8.6.2 Linking Data Files

Not applicable.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Final Analysis

The final analysis will be conducted when all patients have had the opportunity to complete the last protocol-specified assessment in the study.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

The statistical analysis in this PMC study will be descriptive in nature, and no hypothesis testing will be performed. Categorical outcomes will be summarized by the number and percentage of subjects in each category. Continuous outcomes will be summarized by the number of nonmissing values, mean, standard deviation, median, lower and upper quartiles, and minimum and maximum values. For the incidence, 95% CI will be presented based on an exact method.

For subjects who are prematurely withdrawn, reasons for withdrawal will be described.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Patients may have missing data points for a variety of reasons. Data may be missing due to patient's early withdrawal from study, a missed visit, or nonevaluability of an endpoint at a particular time point. In general, analyses will be based on available data. Missing baseline and postbaseline BMD data will not be imputed. Other non-key baseline variable missing will be reported as appropriate.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Subject/Patient Characteristics

Demographic and baseline characteristics collected (see Section 8.3.2) will be tabulated descriptively.

8.7.2.4 Analysis of the Primary and Secondary Endpoint(s)

8.7.2.4.1 Analysis of the Primary Endpoint

Incidence Rates of Adverse Events and Adverse Drug Reactions

The analysis will be based on the safety analysis set which includes all enrolled subjects (enrollment is triggered once an eligible, consenting patient receives their first dose of Prolia). The incidence of adverse events will be summarized by classification according to the adverse event coding dictionary. This summary includes all treatment-emergent adverse events recorded from the start of investigational product on this study through the last data collection time point or any worsening of adverse events initially

experienced before initiation of this study. This summary for adverse events will be performed for the following categories:

- All adverse events
- Prolia-related adverse **drug** reactions
- Serious adverse events
- Prolia-related serious adverse reactions
- Adverse events leading to Prolia therapy discontinuation
- Fatal events

The incidence of adverse events of interest will be presented and 95% CI for the incidence estimate using an exact method will be provided.

A descriptive summary of the adverse events observed with frequency (exposure adjusted) will be provided with 95% CI for the incidence estimate. Safety results obtained in this study will be considered in the context of what is known of the overall safety profile from the global postmarketing experience (eg, the patterns observed with regards to the more frequently reported adverse events and serious adverse events).

In addition to the quantitative analysis, medical assessment of the characteristics of individual adverse events and adverse drug reaction will be conducted. If any unusual patterns are observed in the reported adverse events that are suggestive of possible new or unique adverse drug effects in the Chinese patient population, these safety observations will be investigated further and results summarized within the report.

8.7.2.4.2 Analysis of the Secondary Endpoint

The Effectiveness Analysis Set will include all patients with a baseline and at least 1 postbaseline BMD measurement at the lumbar spine and/or total hip and/or femoral neck. The **summary statistics will be provided for** the following:

BMD Changes

- Percent change (%) in BMD from baseline at month 24 (or as close as possible to the last dose of Prolia) at lumbar spine will be analyzed.
- Percent change (%) in BMD from baseline at month 24 (or as close as possible to the last dose of Prolia) at total hip and femoral neck will be analyzed (if available).

Fracture incidence

The cases of **clinical** vertebral, non-vertebral and hip fracture.

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

The primary and secondary endpoints will be analyzed by the following subgroups if appropriate:

- Age at baseline (years) (< 65, $65 \leq$ age < 75, ≥ 75)
- BMI at baseline (< 18.5, 18.5-23.9, 24-27.9, and ≥ 28)
- History of osteoporosis therapy use (prior and/or concomitant bisphosphonate or other treatment use)
- Hepatic impairment (Child-Pugh class A, B, or C) at baseline
- Renal function at baseline (stage of chronic kidney disease based on estimated GFR) (Normal: eGFR > 90, Mild: eGFR 60-90, Moderate: eGFR 30-60, and Severe: eGFR < 30)
- **Any historical osteoporosis** fracture or without **historical osteoporosis** fracture.

These subgroups will be re-examined for appropriateness and may be re-categorized or omitted (due to small sample size, for example, if there are $< 10\%$ of subjects within a subgroup).

8.8 Quality Control

The Amgen representative(s) and regulatory authority inspectors are responsible for inspecting the various records of the study (eg, CRFs and other pertinent data) provided that patient confidentiality is respected.

The Amgen or Clinical Research Organization (CRO) staff is responsible for verifying the CRFs to verify adherence to the protocol, completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of PMC studies.

The investigator agrees to cooperate with Amgen or CRO staff to ensure that any problems detected in the course of the study, including delays in completing CRFs, are resolved.

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees).

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

Limitations in the internal validity may arise from measurement errors that are the result of imprecision of the instrument, measurement procedure, or human investigator. The collection of study data will be consistent with how medicine is practiced at each

participating site, and then some data may be less frequently collected than in a clinical trial, and hence some data may appear "missing". Dual-energy x-ray absorptiometry scans for BMD are covered by insurance and recommended once a year by clinical guideline. As such, inadequate or lack of BMD data could impact the breadth of data necessary to generalize about the source population. Hence, imprecision may occur in the measurement of study endpoints.

8.9.2 External Validity of Study Design

Limitations in the external validity may arise from recruited individuals not being representative of the target population. To assess the potential of bias, Amgen will list potential sites who may prescribe Prolia in the postmarketing setting. Based on the list, Amgen will check interest and willingness of the potential investigator(s) to participate in this study. Based upon the results, sites who participate in this study will be confirmed, and if an investigator does not want to join the study, the reason will be documented.

8.9.3 Limitations Due to Missing Data and/or Incomplete Data

Some patients may drop out of the study, creating missing or incomplete data for the study endpoint assessments. Such dropout may be related or informative to the outcomes. Consequently, there is a risk for bias and lack of robust data to analyze results.

8.10 Other Aspects

8.10.1 Language

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

9. Protection of Human Subjects

This observational study will comply with all relevant ethical and regulatory requirements, and will not be used for the conduct of marketing surveys or other marketing purposes. The study will comply with Amgen adverse event reporting Standard Operating Procedures (SOPs). This study and data collection will be conducted in accordance with the relevant local laws.

The responsible physician is also responsible to submit the following documents to Amgen or its representative for review before study initiation occurs:

- Signed and dated protocol signature page (Responsible Physican's Agreement)
- Copy of the Central Ethics Board approval of the protocol, waiver for requirement of informed consent where applicable

- Subject or subject's legally acceptable representative has provided informed consent (for countries where required per local regulations)
- Up-to-date curriculum vitae of responsible physician and all co/sub-physicians
- Signed confidentiality agreement
- Signed study contact

The responsible physician will be charged with maintaining correct and comprehensive documentation, while the Amgen monitor/designee is tasked to ensure that the responsible physician is following the correct study protocol.

9.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent form is to be prepared in the language of the potential patient population.

Before a patient's participation in the clinical study, the investigator or his/her delegated representative is responsible for obtaining written informed consent from the patient/patient's parent or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.

As an observational study, the decision of treating the patient with Prolia will be made independently of study. The informed consent form and patient's enrollment procedure can be completed within 4 weeks after the initial denosumab prescription; these steps can be completed on the same day, depending on clinic protocol and patient preference.

The acquisition of informed consent and the patient/patient's parent agreement or refusal of his/her notification of the primary care physician is to be documented in the patient's medical records, and the informed consent form is to be signed and personally dated by the patient/patient's parent or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient or legally acceptable representative. If a potential patient/patient's parent is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to

read the informed consent form to the patient/patient's parent and must allow for questions. Thereafter, both the patient/patient's parent and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

9.2 Independent Ethics Committee (IEC)

A copy of the protocol, proposed informed consent form, where applicable, other written patient information, and any proposed advertising material 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 informed consent form, where applicable, must be received by Amgen before study can be executed.

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 event(s) occurring at the site and other adverse event reports received from Amgen, 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 Amgen.

9.3 Patient Confidentiality

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

- Patients are to be identified by a unique patient identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique patient identification number, include the age at time of enrollment.
- For serious adverse events reported to Amgen, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

Authorized representatives of China Amgen Limited, the regulatory agency(s), and the IEC shall have direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, 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 patient 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 subject 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 subject appropriate steps for withdrawal of their consent from the study.

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

Adverse events, product complaints, and other safety findings, such as pregnancy and lactation cases, will be collected and reported in this study. Investigators should also follow appropriate local and postmarketing reporting requirements.

10.1 Definition of Safety 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.

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Appendix D.

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)

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.

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device (ie, prefilled syringe), or adverse events resulting from use error or from intentional misuse of the device.

10.1.2 Serious Adverse Events

A serious adverse event is any adverse event 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, whether accidental or intentional, misuse, **addiction,** or abuse involving an Amgen product,
- Pregnancy and lactation exposure,
- 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 product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Amgen will collect complaints on the following product:

- Prolia 60 mg prefilled syringe

Product complaints may include but are not limited to issues related to:

- Appearance (eg, broken, cracks, color, particles, odor)
- Labeling (eg, missing, torn, smudged)
- Durability (eg, stability issues)
- Open packaging
- Device damage (eg, prefilled syringe with bent needle)
- Inability of customer to understand product labeling
- Inability of customer to deliver the product successfully, including partial or
- incomplete delivery (eg, defective delivery system [syringe])

10.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from healthcare professionals, etc prospectively. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to Prolia will be collected from enrollment. The Investigator is responsible for ensuring that all safety 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 subject's records after the subject ends the study. 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, these safety events must be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness. Non-serious Adverse Events must be reported in an expeditious manner, not to exceed 15 calendars days of Investigator awareness.

If the electronic data capture (EDC) system is unavailable to the site staff, the **reportable events mentioned above** must still be reported to Amgen within **specified reporting timeframes stated**. For EDC studies 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 Worksheets. 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.

Patient's education will be provided at the time of ICF signature. Then **adverse events, serious adverse event and ADRs** will be reported by patients during follow up visits.

10.2.1 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

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 IEC must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IEC 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 IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12. Plans for Disseminating and Communicating Study Results

Interim results are included in periodic safety update reports due to the NMPA, and final results will be included in an application for re-examination.

12.1 Publication Policy

The results of this study will be submitted for publication.

Authorship of any publications 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.

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

China Prolia® Prescribing Information.

National Survey of Osteoporosis, China National Health Commission, 2018: http://k.sina.com.cn/article_2194948720_82d4427002000d5cy.html

Si L, Winzenberg TM, Jiang Q, Chen M, Palmer AJ. Projection of osteoporosis-related fractures and costs in China: 2010-2050. *Osteoporos Int*. 2015 Jul;26(7):1929-1937.

Wang O, Hu Y, Gong S, et al. A survey of outcomes and management of patients post fragility fractures in China. *Osteoporos Int*. 2015 Nov;26(11):2631-2640.

Xia WB, He SL, Xu L, et al. Rapidly increasing rates of hip fracture in Beijing, China. *J Bone Miner Res*. 2012 Jan;27(1):125-129.

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 Real-world, Prospective, Observational Study of Prolia® (Denosumab) in Chinese Women With Postmenopausal Osteoporosis (PMO)

EU PAS Register® number: EUPAS37579
Study reference number (if applicable): 20180401

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]	☒	☐	☐	8.2.1
1.1.2 End of data collection[2]	☒	☐	☐	8.2.1
1.1.3 Progress report(s)	☐	☒	☐	N/A
1.1.4 Interim report(s)	☐	☒	☐	N/A
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Summary Table
1.1.6 Final report of study results.	☒	☐	☐	8.2.1

Comments:

N/A

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6
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)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7.1
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	6.3
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	6.3

Comments:

Primary Objective: To estimate the incidence rates of adverse events, serious adverse events, and adverse drug reactions (ADRs) among PMO patients receiving Prolia according to the China Prescribing Information (PI) in a postmarketing setting

There is no hypothesis to be tested and the study will provide descriptive data on use of Prolia; the incidence of adverse events and ADRs; BMD at the lumbar spine, total hip, and femoral neck; clinical fractures, and patient characteristics in the postmarketing setting.

[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)	☒	☐	☐	4
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)	☒	☐	☐	8.3.1
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)	☒	☐	☐	8.3.2.4

Comments:

This study is a real-world, prospective, single arm, observational multi-center study in postmenopausal women with osteoporosis who are being prescribed Prolia on label (per the China Prolia PI) in a postmarketing setting in Mainland China. No study drug will be provided by Amgen. There will be no control group. Study population and data resource described in Section 4.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	SOA
	4.2.2 Age and sex	☒	☐	☐	Title, 4
	4.2.3 Country of origin	☒	☐	☐	Title, 4
	4.2.4 Disease/indication	☒	☐	☐	Title, 4
	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)	☒	☐	☐	4

Comments:

Schedule of Activities (SOA); Title refers to protocol title.

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)	☒	☐	☐	SOA

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:

This is a prospective study with SOA and so exposure is defined by SOA and completion of study.

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?	☒	☐	☐	8.7.2.4.1 and 8.7.2.4
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.7.4.1 and 8.7.2.4
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:

N/A

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)	☒	☐	☐	8.9.2
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Limitations in the external validity may arise from recruited individuals not being representative of the target population (section 8.9.2). No other bias.

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:

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)	☒	☐	☐	8.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
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)	☒	☐	☐	8.3.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 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:

N/A

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7.2
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	8.7.2.3
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?	☒	☐	☐	8.7.2.2
10.8 Are relevant sensitivity analyses described?	☒	☐	☒	8.7.2.1

Comments:

N/A

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)	☒	☐	☐	8.6, 8.6.1
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12.1

Comments:

Standard Amgen processes for clinical trial and data management will be used in this study.

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?	☒	☐	☐	8.9.1
12.1.2 Information bias?	☒	☐	☐	8.9.2
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:

N/A

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.3

Comments:

N/A

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	11.1

Comments:

N/A

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.1

Comments:

N/A

Name of the main author of the protocol: _____

Date: dd/Month/year: _____

Signature:

Appendix C. Sample Safety Reporting Form(s)

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.

4. **IP Administration including Lot # and Serial # when known / available.**

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.

- 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 # 20180401** **Prolia**	**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

Email To: svc-ags-in-cn@amgen.com

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
						<Prolia>		<drug/device>		<drug/device>		<drug/device>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	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 # 20180401** **Prolia**	**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 #
<<Prolia>>	☐ 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

A **Study # 20180401** **Prolia**	**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

Common Terminology Criteria for Adverse Events (CTCAE) V5.0 will be used for adverse event severity scoring. The CTCAE is available at the following location:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix E. Pregnancy and Lactation Notification Worksheets

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: 20180401

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 Proprietary - Confidential

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: 20180401

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