Title: Prospective Observational Study to Describe Characteristics and Management of Postmenopausal Women With Osteoporosis Treated With Prolia® in France and its use in Routine Clinical Practice

The PILOTE Study

AMG 162 – Prolia® (Denosumab)

Amgen Protocol Number (Denosumab) 20130240

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Original Protocol:	07 July 2014
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Amendment 2:	15 May 2016
Amendment 3:	30 May 2017
Amendment 4:	**16 February 2018**

Investigator's Agreement

I have read the attached protocol entitled Prospective Observational Study to Describe Characteristics and Management of Postmenopausal Women With Osteoporosis Treated With Prolia® in France and its use in Routine Clinical Practice, dated **16 February 2018** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), with the ethical principles described in the Declaration of Helsinki, with the Good Epidemiological Practices (GEP) and with and applicable national or regional regulations/guidelines.

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)

Protocol Synopsis

Title: Prospective Observational Study to Describe Characteristics and Management of Postmenopausal Women With Osteoporosis Treated With Prolia® in France and its use in Routine Clinical Practice

Study Phase: 4 (Observational, non-interventional)

Indication: Treatment of osteoporosis in postmenopausal women at increased risk of fracture

Study Objectives:

- Primary : To evaluate the persistence with Prolia® at 12 months in postmenopausal women with osteoporosis (PMO) in France
- Secondary :
  - To evaluate the persistence with Prolia® at 24 months in PMO women in France
  - To describe, for two successive years, the characteristics of PMO women in France treated with Prolia®, and the history of their previous osteoporosis treatment
  - To describe the use of Prolia® in routine clinical practice during approximately 30 months from **the date of enrollment**.
  - To describe patients reported adverse drug reactions and fractures

Hypotheses: The study is descriptive in nature, and no formal hypothesis will be tested. Point estimate and 95% confidence interval (CI) for persistence with Prolia® treatment at 12 months will be provided.

Baseline Characteristics

- Baseline characteristics related to socio-demographics, osteoporosis related condition, previous osteoporosis treatment of patients and characteristics of physicians will be collected, if available, to describe patients receiving Prolia® in both waves 1 and 2.

Outcomes:

The following outcomes will be collected for wave 1 only, except for the safety outcomes which will be collected for both waves 1 and 2.

- Primary:
  - Patient occurrence of persistence (Yes or No) at 12 months
- Secondary:
  - Patient occurrence of persistence (Yes or No) at 24 months
  - Time to non-persistence at 24 months
  - Occurrence of patients referred to another physician for follow-up on Prolia® treatment (Yes or No)
  - Number of injections received by patient (1, 2, 3, 4, or ≥ 5 injections)
  - Occurrence of patient receiving the first, second, third, fourth and fifth injection
  - Number of times a patient received a Prolia® injection by the prescriber
  - Number of times a patient received a Prolia® injection outside the prescriber's office by a nurse or another health care provider (HCP)
  - Patient occurrence of osteoporosis-related vertebral and non-vertebral fractures reported during study
  - Patient occurrence of ADRs and SADRs as collected in routine clinical practice

Study Design:

This is a multicenter, observational and non-interventional study in PMO patients who receive Prolia® (60 mg subcutaneous [SC]) in France. Patients in the study will be enrolled in 2 waves, each targeting specific aspects of the overall study objectives. The first wave will enroll approximately 500 patients who will be followed for approximately 30 months from the **date of enrollment**. Patients enrolled in this wave will provide descriptive data on persistence to Prolia® as well as a description of the characteristics of patients being prescribed Prolia®, information regarding Prolia® prescription and administration, **and** procedures pertaining to Prolia® and safety. The second wave will enroll approximately 250 patients and will only provide a cross-sectional description of the characteristics of patients being prescribed Prolia®.

Patients will be eligible to enroll within 4 weeks after receiving their first Prolia® prescription. The decision to treat the patient with Prolia® must be made independent of and before study enrollment. However, the writing of the prescription for Prolia®, the first Prolia® injection and/or administration of informed consent may happen at the same visit. It is anticipated that patients will receive their Prolia® injection every 6 months as part of their routine clinical care.

With regard to the first wave, the estimated duration of enrollment is approximately 6 months. Patients will receive Prolia® as part of clinical care. Investigators will offer participation in the study to all patients prescribed Prolia® who meet eligibility criteria during the enrollment period. Enrollment in the study will be stopped when the required number of patients has been enrolled in the 2 respective waves. A log will be maintained that includes all patients eligible for the study but not enrolled, including the age of the patient and the reason for not enrolling. Detailed data regarding the patients past medical history including prior bisphosphonate use will be collected at the initial visit to characterize the patient population. It is anticipated that patients will return to the site to receive their Prolia® prescription and/or injections as per their routine clinical care. After the initial visit, information regarding Prolia® prescription and administration, procedures pertaining to Prolia® administration and osteoporosis, concomitant medication use, ADRs and SADRs, product complaints, other safety findings will be obtained at each clinical visit/contact. Information obtained will be recorded for approximately 30 months after entering the study.

With regard to the second wave, 250 additional patients will be enrolled one year after the initiation of the first wave of enrollment to provide another cross-sectional description of patients' characteristics who are prescribed their first dose of Prolia® in France as part of their routine clinical care. These patients will be enrolled over an approximately 6-month period, and only baseline data and any reports of adverse drug reactions will be collected. Investigators will offer participation in the study to all patients prescribed their first dose of Prolia® at their site during the enrollment period until the required numbers of patients are enrolled in the 2 respective waves of the study. A log will be maintained of all patients eligible for the study but not enrolled, including the age of the patient and the reason for not enrolling.

Site selection:

Around 2000 specialists in rheumatology and 9000 general practitioners will be randomly selected from a list of rheumatologists whether in hospital or private practice nationwide and a list of general practitioners managing patients with osteoporosis.

In all, 300 physicians initially interested to participate are expected, from which about 180 physicians will be qualified to participate. One-hundred and ten physicians will be initiated and the others will be considered as rescue sites (replacing inactive or cancelled sites).

Sample Size:

Approximately 500 patients will be enrolled in the first wave of enrollment and 250 patients in the second wave of enrollment. Since this is an observational study with descriptive objectives, the sample size was based on the level of precision (ie, half-width) of the 95% CI. For the first wave the sample size was based on the primary endpoint of persistence at 12 months overall and in pre-defined subgroups of interest as defined in Section 10.1.3. For the first and second wave, a sample size of approximately 500 and 250 patients will provide a half-width for the 95% CI around

the point estimates of at most 4.9% and 6.2%, respectively. A smaller sample size is proposed for the second wave since these patients will provide only baseline characteristics.

Summary of Patient Eligibility Criteria:

Inclusion criteria:

Patients will meet the following inclusion criteria at enrollment into the study:

- PMO women in whom a decision has been made to treat with Prolia® (60 mg SC)
- Received their first prescription of Prolia® in the last 4 weeks
- Patient has provided informed consent before enrolling in the study

Exclusion criteria:

- Patients participating in ongoing or previous Prolia® clinical trials.

For a full list of eligibility criteria, please refer to Section 4.1.

Investigational Product

Amgen Investigational Product Dosage and Administration: None

Non-Amgen Investigational Product Dosage and Administration: None

Non-investigational Product: None

Procedures: There are no procedures or changes to the routine clinical management of patients participating in the study. Baseline characteristics will be described for patients enrolling in both waves 1 and 2. Patients enrolling in wave 1 will be followed for approximately 30 months from the date of **enrollment** in the study. It is anticipated that patients will return to the site to receive their Prolia® prescription and/or injections as per their routine clinical care. Clinical information obtained for routine clinical practice will be recorded where available, including Prolia® administration, previous and current therapies, medical history (including fracture), ADRs, SADRs, product complaints, other safety findings and co-morbidities.

For a full list of study activities, including the timing of each activity, please refer to Section 7 and the Schedule of Activities (Table 1).

Statistical Considerations:

The study is descriptive in nature, and no formal hypothesis will be tested. In general, data summaries will be presented by wave and by subgroups of interest.

Categorical outcomes will be summarized by the number and percentage of patients in each category, and the corresponding 95% CI. Continuous outcomes will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles and minimum and maximum values.

The primary outcome of this study is patient persistence at 12 months. Patients will be defined as persistent with Prolia® at 12 months if they receive at least 2 injections, and the second injection at 6 months is no later than 6 months + 8 weeks (or 239 days) from the baseline injection. They will be defined as persistent with Prolia® at 24 months if the patient receives at least 4 injections (including the baseline) and the time between any 2 consecutive injections is not more than 6 months + 8 weeks (or 239 days).

Baseline characteristics will be summarized for wave 1 and 2. All post-baseline outcomes other than safety outcomes will be summarized for wave 1 only. Post-baseline safety outcomes will be summarized for both waves 1 and 2.

Interim analyses will be based on the full analysis set (FAS) which includes all enrolled patients (provided informed consent, have a non-missing enrollment date) who received at least one Prolia® prescription.

Final analyses will be performed on the primary analysis set (PS) which consists of all patients in FAS that:

- **received at least one Prolia® injection**
- **have not received Prolia® injections prior to first Prolia® prescription**
- **do not have more than 100 days between first Prolia® prescription and enrollment date.**

The safety analysis set includes all enrolled patients in the FAS who received at least one Prolia® injection. **F**or the persistence outcome, analysis sets will be defined for the 12-month and 24-month persistence outcomes as follows:

12-month persistence analysis set (PAS) consists of all patients in the **PS** that:

- are not referred by the investigator to another physician for treatment follow-up before the second injection**.**
- are referred by the investigator to another physician before the second injection but complete information on second injection (injection yes/no and if yes the full date) is obtained via patient reporting**.**

24-month PAS consists of all patients in the **PS** that:

- are not referred by the investigator to another physician for treatment follow-up before the 4th injection**.**
- are referred by the investigator to another physician before the 4th injection and:
  - the referral occurred after the patients miss a dose or received a dose later than 6 months + 8 weeks relative to the previous dose, or
  - complete information on injection history up to the fourth injection (injections yes/no and if yes the full dates) is obtained via patient reporting**.**

Persistence outcomes

Primary Outcome

Percentages and 95% CIs will be provided for persistence at 12 months, based on the 12-month PAS. Percentages and 95% CIs will be provided for the primary outcome for selected subgroups.

Persistence at 24 months

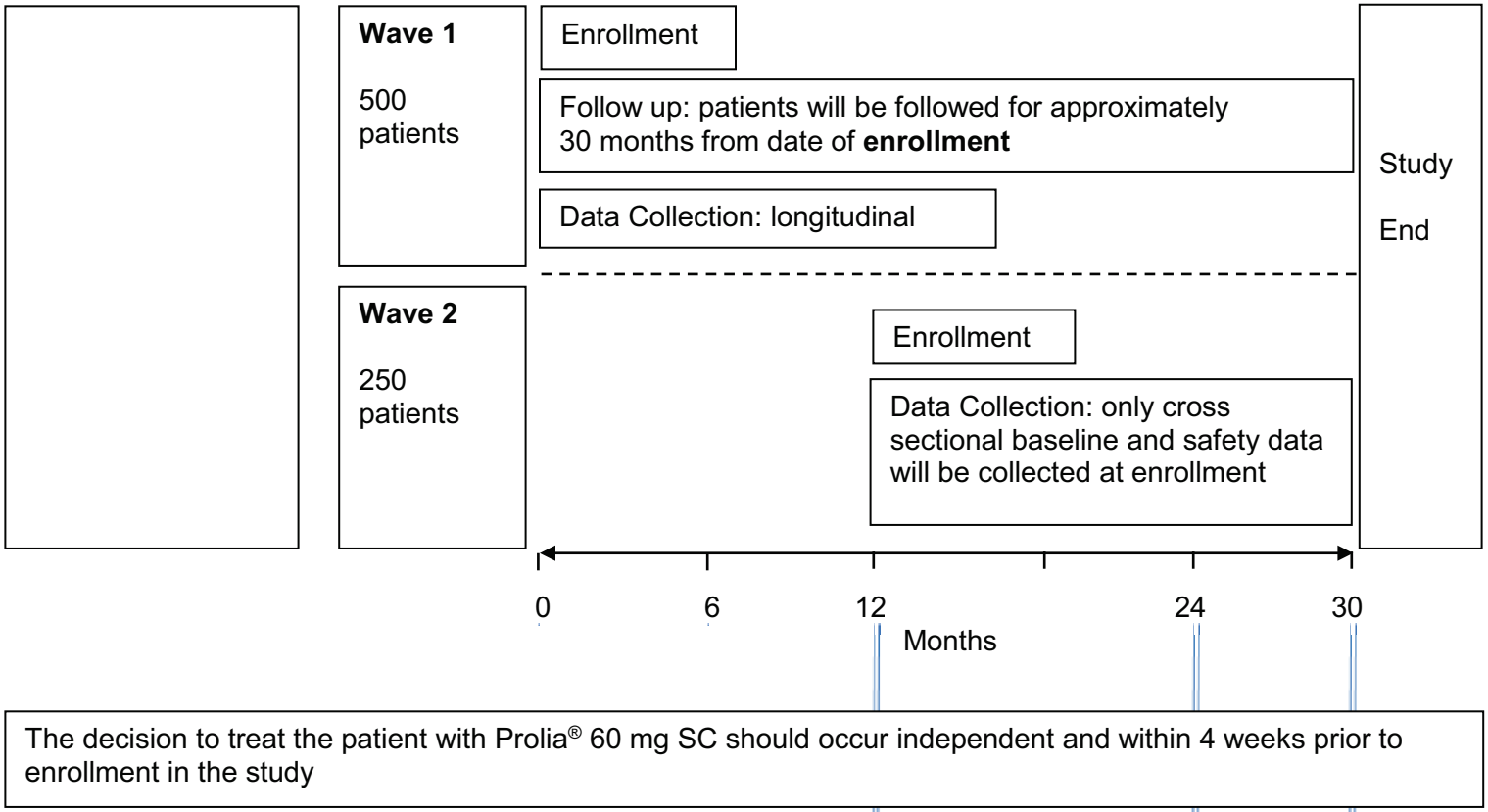
Percentages and 95% CIs will be provided for persistence at 24 months, based on the 24-month PAS.

Kaplan-Meier estimates will be provided for the time to non-persistence based on the **PS**.

For a full description of statistical analysis methods, please refer to Section 10**.**

Study Design and Treatment Schema

20130240: Prospective Observational Study to Describe Characteristics and Management of Postmenopausal Women With Osteoporosis Treated With Prolia® in France and its use in Routine Clinical Practice



Study Glossary

Abbreviation or Term	Definition/Explanation
ADR	adverse drug reaction
BMD	bone mineral density
BMI	body mass index
BP	bisphosphonate
CI	confidence interval
CRA	clinical research associate
CRO	clinical research organisation
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
EDC	electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Follow-up	defined as when the last patient completes the last protocol-specified assessment in the study
End of Study for Individual Patient	defined as the last day that protocol-specified activities are conducted for an individual patient
End of Study (end of trial)	End of study is defined as the date that the last patient enrolled in wave 1 completes approximately 30 months of observation or when the last patient in the study ends their participation in the study
EU	European Union
FAS	full analysis set
HCP	Health Care Provider
ICF	informed consent form
ICH	international committee on harmonization
Q6M	every 6 months
PAS	persistence analysis set
PC	product complaint
PMO	postmenopausal women with osteoporosis
PS	**primary analysis set**
SADR	serious adverse drug reaction
SC	subcutaneous
SmPC	summary of product characteristics

Abbreviation or Term	Definition/Explanation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include patient identification, Randomization identification, and Stratification Value.
Date of Enrollment	defined as the first day that patient signed informed consent form for participating in the study

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1. OBJECTIVES

1.1 Primary

- To evaluate the persistence with Prolia® at 12 months in postmenopausal women with osteoporosis (PMO) in France

1.2 Secondary

- To evaluate the persistence with Prolia® at 24 months in PMO women in France
- To describe, for two successive years, the characteristics of PMO women in France treated with Prolia®, and the history of their previous osteoporosis treatment
- To describe the use of Prolia® in routine clinical practice during approximately 30 months from **the date of enrollment**.
- To describe patients reported adverse drug reactions and fractures

2. BACKGROUND AND RATIONALE

2.1 Disease

Osteoporosis is a common, systemic skeletal disorder characterized by low bone mass and compromised bone strength predisposing individuals to an increased risk of fracture (NIH Consensus Statement (2000). Osteoporosis is a major public health threat: the prevalence of osteoporosis was reported as an estimated 200 million people worldwide (Reginster and Burlet, 2006).

The morbidity and mortality associated with osteoporosis-related fractures result in significant clinical, human, and economic costs (Cree et al, 2003). About 40 to 50% of women are at risk of having an osteoporosis related fracture in their lifetimes (Dennison et al, 2006). In Europe, in 2010, 22 million women and 5.5 million men were estimated to have osteoporosis and 3.5 million new fragility fractures were sustained (Svedbom et al, 2013). In France, in 2010, it was estimated that the number of women aged > 50 years with osteoporosis was 3,480,000 and that approximately 377,000 new fragility fractures were sustained comprising 55,000 hip fractures, 36,000 vertebral fractures, 47,000 forearm fractures, and 118,000 other fractures (Svedbom et al, 2013).

Osteoporosis can be treated effectively with antiresorptive agents, such as bisphosphonates, or by anabolic agents, such as parathyroid hormone analogues (Papapoulos and Makras, 2008). Clinical studies have demonstrated the efficacy of the bisphosphonate class of drugs in reducing the risk of osteoporosis-related fractures (Papapoulos, 2005). However, difficult dosing regimens, lack of patient satisfaction and medication side-effects may limit drug adherence (Sambrook and Cooper, 2006).

2.2 Prolia® Background

Denosumab is a fully human monoclonal antibody that inhibits RANKL, an essential regulator of osteoclast differentiation, activation and survival (Denosumab investigator's brochure, 2017). Administration of denosumab 60 mg subcutaneously (SC) every 6 months (Q6M) (Prolia®) has been shown to decrease bone remodeling with consequent increases in bone mineral density (BMD) and decreased risk for new vertebral, nonvertebral, and hip fractures (Cummings et al, 2009). Additionally, denosumab treatment for up to 8 years has been shown to be associated with persistent reduction of bone turnover, continued increases in BMD, and sustained low fracture incidence with the benefit/risk profile remaining favorable. (Papapoulos et al, 2013).

2.3 Non-Amgen Medicinal Product Background

Not applicable

2.4 Rationale

Denosumab 60 mg SC Q6M (Prolia®) was granted a marketing authorisation in the European Union (EU) on 26 May 2010 via the centralised procedure and is applicable to the European Economic Area territories (ie, EU member states plus Iceland, Liechtenstein and Norway) for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. In France, it was approved for reimbursement on 27 September 2013 for the treatment of PMO in women at increased risk of fracture, as a second line therapy after bisphosphonates (BPs).

The French Health Authorities request a pharmaco-epidemiological study in France with the objective to provide real world impact on morbidity among patients treated with Prolia®, according to the current therapeutic strategy in osteoporosis. This study should be able to provide data on fracture efficacy, compliance and long term efficacy in real clinical practice; to identify the type and duration of previous drugs, particularly bisphosphonates prescribed prior to Prolia® in PMO management and to provide the descriptive results on previous osteoporosis treatment each year during the study.

According to the French Health authorities, patients at increased risk of fracture are defined as women with history of fragility fracture or, in the absence of fractures, women with low BMD (T-score < -3) or a T-score ≤ - 2.5 in association with other risk factors for fractures; "second line therapy after BPs" is defined as having at least 3 consecutive months of BPs in the last year before starting Prolia®.

This study is being conducted in accordance with the French authority guidance. Postmenopausal women will be enrolled in 2 waves, separated by one year. The 2 waves will allow characterizing PMO patients receiving Prolia® in France at 2 different time points. The independent study scientific committee has opined that the follow-up period should be sufficient to respond to the clinical management questions from the French Health Authorities in that it should allow to collect information until the 24-month injection, ie, the fifth injection including the injection at Prolia® initiation. The allowable window for persistence (maximum of 6 months + 8 weeks between consecutive injections), could delay the 24-month visit by a maximum of 6 months. Therefore the follow-up period will be approximately 30 months.

Clinical Hypotheses

The study is descriptive in nature, and no formal hypothesis will be tested. However, for binary outcomes of interest, including persistence at 12 and 24 months, point estimates and 95% CIs will be provided.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multicenter observational study in PMO patients who receive Prolia® (60 mg SC) in France. These sites will reflect, as much as possible, the local prescribing and administration practices of Prolia® in France, with respect to specialty (general practitioners, rheumatologists working at hospital and in private office) and/or geographic location.

The study participants will be enrolled in 2 waves separated by a 1-year interval. Patients enrolling in the first wave will provide the following information: persistence to Prolia® treatment over the observation period; baseline characteristics of patients being prescribed Prolia®, including previous treatment for osteoporosis; Prolia® prescription and administration data; and safety which includes adverse drug reactions (ADRs), serious adverse drug reactions (SADRs), product complaints and other safety findings**.** This first wave will enroll approximately 500 patients who will be followed for approximately 30 months from **the date of enrollment.** Approximately 250 subjects will be enrolled a year later in order to provide descriptive information including previous bisphosphonate therapy on patients being prescribed Prolia® each year during the study. Patients enrolled in the second wave will only provide another cross-sectional description of the baseline characteristics of patients being prescribed Prolia® and information on any ADR, SADR, product complaints and other safety findings. Each site

will enroll patients until either the site specific maximum allowable number is attained or the total patients targeted by the respective study waves is reached (whichever comes first). This observational study will not alter the routine clinical management of patients and will comply with all French local regulations.

Patients will be eligible to enroll within 4 weeks after receiving their first Prolia® prescription. The decision to treat the patient with Prolia® must be made independent of and before study enrollment. However, the writing of the prescription for Prolia®, the first Prolia® injection, and/or administration of informed consent may happen at the same visit. It is anticipated that patients will receive their Prolia® injection every 6 months as part of their routine clinical care.

Patients will be defined as persistent with Prolia® at 12 months if the patient receives at least 2 injections, and the second injection at 6 months is no later than 6 months + 8 weeks (or 239 days) from the baseline injection. They will be defined as persistent with Prolia® at 24 months if the patient receives at least 4 injections (including the baseline) and the time between any 2 consecutive injections is not more than 6 months + 8 weeks (or 239 days).

With regard to the first wave, the estimated duration of enrollment of the 500 patients is approximately 6 months. The protocol will specify that investigators will offer participation in the study to all patients treated with Prolia® who meet eligibility criteria during the enrollment period until the required number of patients have been enrolled in the study. A log will be maintained of all patients eligible for the study but not enrolled, including the age of the patient and the reason for not enrolling. Detailed data including prior bisphosphonate use will be collected at the initial visit to characterize the patient population. It is anticipated that patients will return to the site to receive their Prolia® prescription and/or injections. After the initial visit, information regarding Prolia® prescription for osteoporosis and administration procedures, concomitant medication use, ADRs, SADRs, product complaints and other safety findings will be collected at each clinical visit/contact as per routine clinical practice. Additional information as outlined in Table 1 will be collected during routine clinical visits over a period of approximately 30 months. Given the 6 monthly administration frequency of Prolia®, this observation period is thought appropriate to ascertain persistence with Prolia®, treatment practices employed, and to document ADRs and SADRs.

With regard to the second wave, enrollment will start, for each site, one year after the initiation of the first wave of enrollment in order to provide another cross-sectional

description of characteristics of patients being prescribed Prolia® in France as part of their routine clinical care. These patients will be enrolled over a 6-month period and only data on baseline descriptors and ADRs, SADRs, product complaints and other safety findings will be collected. The protocol will specify that investigators will offer participation in the study to all patients treated with Prolia® who meet eligibility criteria during the enrollment period until the required number of patients have been enrolled in the study. A log will be maintained of all patients eligible for the study but not enrolled, including the age of the patient and the reason for not enrolling. Patient characteristics will be collected at baseline for each of the 2 waves of patients according to the following 3 dimensions:

- Socio-demographic related
- Condition-related (osteoporosis)
- Patient-related (use of prior osteoporosis therapies including bisphosphonate, strontium, contraindications to bisphosphonates, other comorbidities, and health insurance)

Site characteristics will be collected at baseline for each of the 2 waves of patients according to the following two dimensions:

- Physician-related (specialty, age and sex)
- Site related (geographic region and site type)

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study outcomes are defined in Section 10.1.1.

3.2 Number of Sites

The study will be conducted in approximately 110 active sites in France. Sites may be added or removed as deemed necessary to ensure enrollment of the target number of patients.

Sites that do not enroll patients within 2 months after site initiation may be closed and may be replaced.

3.3 Number of Patients

Participants in this observational study shall be referred to as “patients”.

Approximately 750 patients will be enrolled in this study. The justification for the sample size is provided in Section 10.2.

3.4 Replacement of Patients

Patients who are withdrawn or removed from treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Patients

Patients in wave 1 will be enrolled over approximately a 6 month period. All patients in this group will be observed for approximately 30 months from **the date of enrollment**.

Patients in wave 2 also will be enrolled over approximately 6 months. Enrollment in this wave will initiate one year after that for wave 1. Only data on baseline descriptors and ADRs, SADRs, product complaints and other safety findings will be collected at the time of enrollment for patients in this cohort and then the participation of the patients in this study will end.

3.5.2 End of Study

End of study is defined as the date that the last patient enrolled in wave 1 completes approximately 30 months of observation or when the last patient in the study ends their participation in the study.

4. PATIENT ELIGIBILITY

Postmenopausal women with osteoporosis who receive a prescription of Prolia® in France and who meet the eligibility criteria will be eligible to participate in the study.

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of enrolling).

Before any study-specific activity, the appropriate written informed consent must be obtained (see Section 12.1).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101 PMO women in whom a decision has been made to treat with Prolia® (60 mg SC)

102 Received their first prescription of Prolia® in the last 4 weeks.

103 Patient has provided informed consent before enrolling in the study.

4.1.2 Exclusion Criteria

201 Patients participating in ongoing or previous denosumab clinical trials

5. SITE SELECTION AND PATIENT INCLUSION

5.1 Site Selection

Investigators will be randomly selected among around 2600 specialists in rheumatology whether in hospital or private practice nationwide, and around 14,000 general practitioners managing patients with osteoporosis. The initial lists of potential investigators are provided by the independent company CEGEDIM.

Randomly selected potential investigators (approximately 2000 specialists in rheumatology and 9000 general practitioners (GP)) will receive mailings describing the study along with a confidentiality agreement and a reply coupon to send back their response regarding participation in the study. Investigators declining participation in the study will be requested to mention the reason for their decision so as to address issues pertaining to an eventual selection bias if any.

If there is a shortfall in the number of investigators agreeing to participate, reminder mails and/or contact for non-responders can be sent.

Four hundred answers are expected, of which 300 physicians will agree to participate. A qualification call will be performed by a Clinical Research Associate (CRA) for about 250 investigators among those who agreed to participate in the study.

Each investigator will be considered as a site. One hundred and eighty physicians are expected to be qualified as investigators and will be prepared to be initiated. Of these, 110 will be opened and the others will be considered rescue sites. If a site is inactive for a period of 2-months after initiation, it may be replaced by a rescue site. Whenever possible (if enough physicians' agreement were obtained in each area), the distribution of sites will mirror that of the rheumatologists and GPs managing osteoporosis patients in France.

The participating investigator will be trained on the study protocol during on-site training visits performed by a CRA prior to the study commencing.

5.2 Patient Selection

All patients must personally sign and date an appropriate consent form before being enrolled into this study (see Section 12.1).

Enrollment is defined as the date the patient is enrolled in the study by signing an approved informed consent form. Upon obtaining consent each site should immediately register the patient in the electronic data capture (EDC) system in order to generate the patient number. PPD [redacted]

PPD [redacted]

[redacted] This number will be used to identify the patient throughout the observational study and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the entire observational study.

Each site should maintain a confidential patient list that enables site study staff to link an assigned patient identification number to that patient's medical records.

6. TREATMENT PROCEDURES

This study is designed to follow and observe patients who are being prescribed/administered Prolia® in routine clinical practice. Patients will be provided with a diary to note details such as date of administration of Prolia®. No study specific treatment will be provided.

6.1 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary as part of their routine clinical care, including calcium and vitamin D supplementation.

7. STUDY ACTIVITIES

There are no procedures or changes to the routine clinical management of patients participating in the study. However, informed consent date and baseline characteristics related to socio-demographics, osteoporosis related condition, patient and physician will be collected, if available, to describe patient characteristics in both waves 1 and 2.

Patients at increased risk of fracture defined will be identified according to the French Authorities guidelines as defined below:

- Women with history of fragility fracture

OR

- T-score < -3

OR

- T-score ≤ - 2.5 associated with at least 2 of the following risk factors:
  - Age > 60 years old
  - Current or past systemic corticosteroids use: at a dose ≥ 7.5 mg/day of prednisolone (or equivalent doses of other glucocorticoids)
  - Body Mass Index (BMI) < 19 Kg/m²,

- History of a hip fracture in first degree parent (mother or father)
- Menopause before the age of 40

Patients enrolling in wave 1 will be followed for approximately 30 months from the date of their **enrollment**. It is anticipated that patients will return to the site to receive their Prolia® prescription and/or injections as part of their routine clinical care. Clinical information obtained for routine clinical practice will be recorded where available, including Prolia® administration, previous and current therapies, medical history (including fracture), ADRs, SADRs**,** product complaints and other safety findings and co-morbidities (Table 1).

7.1 Schedule of Activities

Table 1. Schedule of Activities

Information to be obtained during routine clinical practice (to be recorded as available)

	Enrollment[a]	Follow-up data[a, b]	End of Study (**approx.** 30 months) or Early Termination[a]
Informed consent	X		
Type of prescribing health care professional (including site type, specialty and physician age and sex)	X		
Patient socio-demographics (age and age group at enrollment),	X		
Menopause history (including type and age at onset)	X		
Postmenopausal osteoporosis and fracture history[c] (including BMD, BMD T-score[d], age of PMO diagnosis, and pharmacologic/surgical treatments)	X		
Medical history (co-morbidities, parent history of fracture,)	X		
Clinical risk factors (height, weight)	X	X	X
History of osteoporosis medications including strontium and bisphosphonate uses	X		
Contraindications to bisphophonates[e]	X		
Data on medical laboratory tests performed including those for treatment of osteoporosis[f]	X	X	X
Behavioral risk factors for osteoporosis (eg, smoking, alcohol consumption)	X		
BMD assessment (yes/no)		X	X
Calcium and Vitamin D supplementation	X	X	X
Current PMO medication use	X	X	X
Prolia® administration	X	X	X
Site management practice of patient[g]	X	X	X
Fractures during study		X	X
ADRs, serious ADRs, product complaints and other safety findings	X	X	X
Switch from Prolia® treatment to another treatment		X	X
Discontinuation and reasons for discontinuation from Prolia®		X	X
End of study/Early termination date			X

Footnote defined on the next page

[a] Both enrollment and follow-up data will be collected in patients enrolled in wave 1. Only cross sectional baseline and safety data will be collected on enrollment for patients enrolled in wave 2.
[b] All data recorded will be collected during routine clinical practice at approximately 6 month intervals, where available.
[c] Only low-energy trauma fractures occurring after 50 year-old.
[d] Only the last BMD assessment before Prolia® initiation will be collected (with results).
[e] See Appendix B.
[f] The following tests will be collected (with the results at enrollment, without the results at the follow-up visits): serum calcium level, serum vitamin D level, creatinine, creatinine clearance, serum CTX test.
[g] Management of the patient receiving Prolia® will include data on referral pattern and type of HCP injecting Prolia®.
BMD = bone mineral density; PMO=postmenopausal women with osteoporosis; ADR= adverse drug reaction.

8. WITHDRAWAL FROM STUDY

Patients' Decision to Withdraw

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

Withdrawal of full consent for a study means that the patient does not wish to or is unable to continue further study participation; patient data up to withdrawal of consent will be included in the analysis of the study. Any patient may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the patient appropriate procedures for withdrawal from the study.

Should a patient request or decide to withdraw from the study, all efforts (including phone calls to patient as allowed by local laws) will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable electronic Case Report Form (eCRFs).

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Definition of Adverse Events and Adverse Drug Reactions

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

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

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

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 drug reaction is an adverse event that is considered related to the medicinal product. The investigator is responsible for ensuring that any adverse drug reactions observed by the investigator or reported by the patient will be recorded in the patient's medical record.

9.1.2 Definition of Serious Adverse Events and Serious Adverse Drug Reactions

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 significant medical hazard” 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 significant medical hazards” 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.

A serious adverse drug reaction is a serious adverse event that is considered related to the medicinal product.

9.1.3 Other Safety Findings

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

- Medication errors, overdose, whether accidental or intentional, misuse, 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,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

9.1.4 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) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product. Product Complaints need to be reported for any complaints related to Prolia® to Amgen Safety department within 1 business day on the ADR form provided by Amgen.

9.2 Safety Reporting Requirements

The investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) observed by the investigator or reported by the patient that occur after signing of the informed consent form through the final study contact are recorded in the patient's appropriate study documentation. Safety events must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of investigator awareness.

See Appendix A for sample Safety Report Form(s), Appendix C for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix D for sample Pregnancy Notification Worksheets and Appendix E for sample 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 on study Case Report Forms (CRFs) where safety data may also be recorded (eg, Event CRF).

The investigator is responsible for ensuring that all ADR and SADR events, other safety findings and product complaints for the drug being studied (Prolia) and which occurred after the first dose administration observed by the investigator or reported by the patient through the end of the study are reported using the applicable eCRF and Amgen is notified using the paper ADR forms within 1 business day.

The investigator must assign the following ADR attributes:

- Adverse drug reaction event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity,

- Assessment of relatedness to Prolia®, and
- Action taken
- ADR outcome.

The severity of the ADR will be graded using the following scale:

- Mild: Aware of sign or symptom, but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity
- Severe: Incapacitating with inability to work or do usual activity
- Life-Threatening: Refers to an event in which the patient was, in the view of the investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.)
- Fatal

The definition of the 5 severity levels refers to the Common Terminology Criteria for Adverse Events (CTCAE, V4).

The investigator must assess whether the adverse drug reaction event is possibly related to Prolia®. This relationship will be indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the Prolia®? The investigator is expected to follow reported serious adverse drug reactions until stabilization or resolution.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor patients for serious adverse drug reactions. However, if the investigator becomes aware of a serious adverse drug reaction after this protocol-required reporting period, the investigator will report the event to Amgen within 1 business day following the investigator's knowledge of the event. Serious adverse drug reactions reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting. All events related to other drugs need to be reported via the non-clinical trial route.

9.2.1 Protocol Exempt Safety Language

Prolia® has an established safety profile with extensive post marketing experience. In this observational study, it is considered appropriate to collect only adverse drug reactions (ie, adverse events considered by the investigator to be related to Prolia®), and serious adverse drug reaction (SADR) together with other safety findings (eg, pregnancy, medication errors, overdose; see Section 9.1.3) and product complaints (see Section 9.1.4)

If any of the exempted events have a fatal outcome, they should still be reported individually within 1 business day of investigator awareness.

All safety information that is not specified in this section, including all fatal events, are to be collected and submitted to Amgen within the specified time frame.

10. STATISTICAL CONSIDERATIONS

10.1 Study Outcomes, Analysis Sets, and Covariates

10.1.1 Wave 1 Study Outcomes

Primary Outcome

- Patient occurrence of persistence (Yes or No) at 12 months

Patients will be defined as persistent with Prolia® at 12 months if the patient receives at least 2 injections, and the second injection at 6 months is no later than 6 months + 8 weeks (or 239 days) from the baseline injection.

Secondary Outcomes

Administration of Prolia®

- Persistence at 24 months
  - Patient occurrence of persistence (Yes or No) at 24 months
  - Time to non-persistence at 24 months

Patient will be defined as persistent with Prolia® at 24 months if the patient receives at least 4 injections (including the baseline) and the time between any 2 consecutive injections is not more than 6 months + 8 weeks (or 239 days).

- Occurrence of patient referred to another physician for follow-up on Prolia® treatment (Yes or No)
- Number of injections received by patient (1, 2, 3, 4, or ≥ 5 injections)
- Occurrence of patient receiving the first, second, third, fourth and fifth injection
- Number of times a patient received a Prolia® injection by the prescriber
- Number of times a patient received a Prolia® injection outside the prescriber's office by nurse or another health care provider

Fracture

- Patient occurrence of osteoporosis-related vertebral and non-vertebral fractures during the study.

Osteoporosis-related fractures are defined as all fractures excluding skull, facial bones, mandible, metacarpus, finger phalanges, toe phalanges and cervical vertebrae and not associated with known high trauma severity (fall from higher than the height of a stool,

chair, first rung on a ladder or equivalent (> 20 inches) or severe trauma other than a fall) or pathological fractures.

Safety outcomes

- Patient occurrence of ADRs and SADRs as collected in routine clinical practice,

10.1.2 Analysis Sets

Full analysis set

For each wave, the full analysis set (FAS) includes all patients enrolled into the study (provided informed consent and have a non-missing enrollment date) who received at least one Prolia® prescription.

Primary analysis set

The primary analysis set (PS) includes all patients in FAS that:

- **received at least one Prolia® injection**
- **have not received Prolia® injections prior to first Prolia® prescription**
- **do not have more than 100 days between first Prolia® prescription and enrollment date**

Persistence analysis sets

For the first wave only, persistence analysis sets (PAS) at 12 months and 24 months will be defined as follows:

12-month PAS consists of all patients in the **PS** that:

- are not referred by the investigator to another physician for treatment follow-up before the second injection**.**
- are referred by the investigator to another physician before the second injection but complete information on second injection (injection yes/no and if yes the full date) is obtained via patient reporting.

24-month PAS consists of all patients in the **PS** that:

- are not referred by the investigator to another physician for treatment follow-up before the fourth injection**.**
- are referred by the investigator to another physician before the fourth injection and:
  - the referral occurred after the patients missed a dose or received a dose later than 6 months + 8 weeks relative to the previous dose**, or**
  - or complete information on injection history up to the fourth injection (injections yes/no and if yes the full dates) is obtained via patient reporting**.**

Safety analysis set

Safety analysis set includes all patients in the FAS who received at least one Prolia® injection.

10.1.3 Subgroups

The following subgroups will be used to describe persistence at 12 and 24 months:

- Age group (< 65; 65 - <75, ≥ 75)
- BMD T-score (< -3.0, -3.0 to ≤ -2.5, > -2.5)
- History of osteoporosis related fracture (yes vs no)
- Prior treatment with osteoporosis therapies including bisphosphonates (yes vs no)
- Prior treatment with bisphosphonates (yes vs no)

10.2 Sample Size Considerations

Approximately 500 patients will be enrolled in the first wave of enrollment and 250 patients in the second wave of enrollment. Since this is an observational study with descriptive objectives, the sample size was based on the level of precision (ie, half-width) of the 95% confidence interval (CI) around the point estimates of binary outcomes.

The first wave sample size was based on the primary outcome of persistence at 12 months. The patients that are referred to another physician may be excluded from the 12-month persistence analysis sets, as defined in Section 10.1.2. If 20% of the patients in the first wave are referred to another physician before the second injection, a sample size of approximately 500 patients is proposed to provide a 12-month persistence analysis set of approximately 400 patients. All lost to follow-up patients that have not been referred to another physician will be included in the persistence analysis set. Therefore, lost to follow-up patients should not have an impact on the sample size nor on the half-width of the CIs around the point estimate.

According to previous publications (Silverman et al, 2013), the expected persistence to Prolia® at 12 months was estimated at 81.9%. Considering this 12-month persistence estimate, and excluding 20% of the patients from the 12-month persistence analysis set due to referral, a sample size of approximately 400 patients will provide a half-width of the 95% CI around the 12-month persistence estimate of 3.8%. Sensitivity analysis shows that if the point estimate is different from 81.9%, the half-width of the 95% CI around the 12-month persistence estimate will be at most 4.9% assuming a point estimate of 50%, where the 95% CI is the widest (Table 2).

For the second wave, all patients are expected to be included in the full analysis set. The sample size was based on the level of precision (ie, half-width) of the 95% CI around the percentage of baseline characteristics as defined in Section 10.1.3. A sample size of approximately 250 patients will provide a half-width for the 95% CI around the point estimates of at most 6.2%, based again on a point estimate of 50%, where the 95% CI is the widest.

Table 2. Half-width of the 95% Confidence Interval for Subgroups

Number of patients	Half-width of the 95% CI (%)
25	19.6
30	17.9
35	16.6
40	15.5
45	14.6
50	13.9
100	9.8
150	8.0
250	6.2
300	5.7
350	5.2
400	4.9
450	4.6
500	4.4

Half-widths were calculated assuming that the percent of the point estimate is 50% to be conservative.

10.3 Planned Analyses

The planned analyses are to be performed for each wave separately. The study is completed when all patients in the first wave have been followed up for approximately 30 months and all patients in the second wave have the chance to complete baseline assessments.

10.3.1 Interim Analyses for the First and Second Wave Baseline Characteristics

Two interim analyses are planned to describe patients that are being prescribed Prolia® in France.

The first one will be performed after enrollment for wave 1 is completed. The second analysis will be performed for wave 2 after enrolment for wave 2 is completed and all baseline data has been cleaned and validated. The objective of these analyses is to characterize these patients to inform the French authorities.

10.3.2 Primary Analysis for the First Wave

The primary analysis will be performed **at the time of the final analysis. Data may be summarised before the final analysis to support regulatory filings.**

10.3.3 Final Analysis for the First Wave

The final analysis for the study, including the analysis of the primary endpoint for the first wave will occur after all enrolled patients are given the opportunity to complete the follow-up period.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

All **interim analyses will be based on the FAS**, except for safety summaries. **All primary and final analyses, except for safety and persistence summaries, will be based on the PS**.

Analyses are descriptive. In general, data summaries will be presented by wave (ie, wave 1 and 2 will not be combined) and subgroups of interest. Categorical outcomes will be summarized by the number and percentage of patients in each category. Continuous outcomes will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles, and minimum and maximum values.

10.4.1.1 Wave 1 and Wave 2 Baseline Characteristics

The baseline characteristics will be summarized for wave 1 and wave 2. Baseline characteristics include all available baseline data on socio-demographics, osteoporosis related condition, patient and physician characteristics, and the combined characteristics based on the French authority guidance as defined in Section 7.

Moreover, in each wave, the following baseline subgroups, based on the French authority guidance will be described:

- Patients at increased risk of fracture (as defined in Section 2.4,)
- Patients at increased risk of fracture receiving Prolia® as a second-line therapy (any prior PMO therapy)
- Patients at increased risk of fracture receiving Prolia® after BPs
- Patients at increased risk of fracture receiving Prolia® as a second-line therapy after receiving BP
- Patients at increased risk of fracture receiving Prolia® after receiving BP for < 3 consecutive months in the last year
- Patients at increased risk of fracture receiving Prolia® after receiving BP for < 3 consecutive months in the last year, and for whom BPs are contra-indicated
- Patients receiving Prolia® as a second-line therapy (any prior PMO treatment)
- Patients receiving Prolia® after BPs
- Patients receiving Prolia® as a second-line therapy after receiving BP

- Patients receiving Prolia® after receiving BP for < 3 consecutive months in the last year
- Patients receiving Prolia® after receiving BP for < 3 consecutive months in the last year, and for whom BPs are contra-indicated
- Patients receiving Prolia® for whom BPs are contra-indicated. Contraindications to BPs are defined in Appendix B.

10.4.2 Wave 1 Outcome Analyses

All outcomes below will be summarized for wave 1 only, except when otherwise specified.

10.4.2.1 Primary Outcome

Percentages and 95% CIs will be provided for persistence at 12 months, based on the 12-month PAS.

Patients in the PAS that miss an injection or receive it later than 6 months + 8 weeks relative to the baseline injection, for any reason, independent of a referral, will be classified as non-persistent.

Percentages and 95% CIs will be provided for the primary outcome for selected subgroups (see Section 10.1.3).

10.4.2.2 Secondary Outcomes Related to Administration of Prolia®

Patient occurrence of persistence at 24 months

Percentages and 95% CIs will be provided for persistence at 24 months, based on the 24-month PAS.

Patients in the PAS that miss an injection or receive it later than 6 months + 8 weeks relative to the previous injection, and prior to 24 months for any reason, independent of a referral will be classified as non-persistent.

Time to Non-persistence

Kaplan-Meier estimates will be provided for the time to non-persistence based on the **PS**. If patients are referred to another physician or are lost to follow-up and are considered persistent by that time, they will be censored at the date corresponding to their last recorded date of Prolia® prescription/injection plus 6 months, date of referral or date of lost to follow-up, whichever occurs first. Percentage estimates of persistent patients and respective 95% CI will be provided.

Other Outcomes

For all other outcomes related to Prolia® administration, summary statistics will be provided based on the **PS**, overall, and by referral to another physician (yes/no) as applicable.

10.4.2.3 Fracture Outcome

The number, percentage and rates of patients reporting fractures based on the **PS** will be provided, overall and by fracture location.

The following information will be collected for each fracture: date of fracture, location, trauma severity, and fracture category (severe/not severe). The osteoporosis-related fracture will be categorized as severe or not according to the 2012 French societies guidelines for the pharmacological treatment of postmenopausal osteoporosis: a severe osteoporosis related fracture is associated with a significant increase in mortality. It includes proximal femoral fractures, proximal humeral fractures, vertebral fracture, pelvic fractures, distal femoral fractures, 3 simultaneous rib fractures, and proximal tibia fractures (Briot et al, 2012).

10.4.2.4 Safety Outcomes

Patient incidence (number, percentage and rates) of ADRs and serious ADRs based on the safety analysis set will be tabulated by system organ class and preferred term. Patient incidence of deaths and adverse events leading to discontinuation of Prolia® also will be reported.

Safety outcomes are expected to be reported mainly for wave 1. However, any ADR or SADR reported by patients in wave 2 will be summarized as well.

11. STUDY LIMITATIONS

The general practitioners (GP) will be randomly selected from a list of GPs managing osteoporosis and may lead to physicians' selection bias. However, it will allow targeting the physicians already involved in osteoporosis management and able to actively enroll patients, thus limiting a very low response rate. Moreover, the list from which sites will be selected at random is quite large, and should be representative of all GPs therefore, limiting the bias. The rheumatologists will be randomly selected from the national list of all rheumatologists whether working at hospital or in private practice.

To limit patient selection bias, it is planned that the physician proposes the study participation to all patients fulfilling the eligibility criteria. A screening log of the patients refusing to participate will be maintained, including the reason for not enrolling.

Prolia® injections will be administered most probably by a nurse outside of the prescriber's office, which is typical in routine clinical practice in France. In these cases, wherever possible, the data collection on treatment administration will be done retrospectively (eg, when patient returns to the prescriber's office for her next visit or injection). A diary to note the date of the injection will be provided to the patient and may therefore interfere with the usual practice. However, this diary will not be a reminder tool to remind the patient to be injected but a tool to collect the actual date the injection was performed. According to the definition of persistence, the accurate date of the injection is required.

Some of the patients who enroll in the study may be lost to follow up due to reasons such as the patient going to another physician for treatment or other natural processes of attrition. Among patients being referred to another physician, the most frequent case expected in routine care in France should be referral by a rheumatologist who initiates Prolia® and with the patient being followed-up by her GP. This situation may lead to a lack of information on the follow-up visits, and these patients may differ from those not referred. To limit lost to follow-up patients, phone calls to all the patients after the allowable window of the Prolia® injection used to calculate persistence are planned.

12. REGULATORY OBLIGATIONS

12.1 Informed Consent

This observational study will comply with all relevant national requirements. The following section is applicable per local governing law and/or regulations.

Before a patient's participation in the observational study, the investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative after adequate explanation of the aims and methods. The signature of the informed consent form by the patient will also authorize the investigator to collect patient's nominative data.

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.

The acquisition of informed consent should be documented in the patient's medical records, and the informed consent form should be signed and personally dated by the patient or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form should be

retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the patient or legally acceptable representative.

If a potential patient 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 and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

Patients' nominative data provided by the patient after obtaining her consent will be sent to an independent CRA of the clinical research organization (CRO) by the investigator in a sealed envelope. These patients' data will be kept in a secure area and will not be collected on a CRF. If a patient is lost to follow-up, and after the investigator has done all he/she can to have the patient's data, the independent CRA may contact the patient directly in order to try to complete the follow-up status and, if appropriate, the date of Prolia® injection and the type of HCP injecting Prolia®. At the end of the study, the contact details of patients will be destroyed.

12.2 National Commission for the Protection of Private Data and Rights

In order to meet the study objectives, the patients will be subjected to the collection of medical data, clinical data, biological data and concomitant treatments.

Before being enrolled in the study the patients will have to be informed clearly by their doctor about the nature and the objective of the study. They will also have been informed about their right to oppose to, to access to and to rectify their own data via their medical doctor.

Consequently, the present protocol has been submitted for opinion to the CCTIRS (French Consultancy Committee for the Processing of Data related to Research in the field of Health), followed by a request for authorization from the CNIL (French National Commission for the protection of private data and rights) (Law n° 2004-801 of August 6th 2004 related to the protection of physical individuals concerning processed private data and amending Law n° 78-17 of January 6th 1978 related to information, files and rights and Law n° 94-548 of July 1st 1994).

12.3 CNOM (French National Medical Order)

The protocol and the financial agreements used within the scope of this study will be submitted for opinion to the French National Medical Order (CNOM) (section L.4113-6 of the Public Health Code).

In accordance with section L4113-9 of the Public Health code, the participating physicians will have to communicate these agreements to the relevant County Medical Order within a month of concluding the agreement.

Moreover, according to the law No2011-2012 dated 29th of December 2011, related to the French sunshine act, the sponsor or his representative have to publish on the French unique website, the signature of these financial agreements.

12.4 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 eCRF demographics page, in addition to the unique patient identification number, include the age at time of enrollment.
- For Serious Adverse Drug Reactions 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.

The participating physician will have to make sure that the patient's confidentiality is preserved. Only the patient's identification number related to the study must be used to identify the forms or other documents whether they are submitted to Amgen France or not.

The physician will make sure not to use for any other purpose than the conduct of the study all the information and all the documents he/she will have knowledge of directly or indirectly and namely the study protocol and personal or not personal data.

- In compliance with applicable regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the French authorities 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 her study-related records, including personal information, without violating the confidentiality.

12.5 Investigator Signatory Obligations

Each clinical study report is to be signed by the Scientific Committee**.**

The Scientific Committee comprises four members validated by the Haute Autorité de Santé: one hospital rheumatologist, one private office rheumatologist, one general practitioner and one epidemiologist.

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Study Termination

Where applicable by local law and governance, if Amgen amends the protocol, agreement from the Investigator must be obtained. The French Authorities must be informed of all amendments and give approval.

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 study contract.

13.2 Study Documentation and Archive

The participating physician is responsible for forwarding the following documents to Amgen before the initiation of the study:

- signed and dated protocol page (participating physician's agreement),
- signed and dated financial agreement with attached appendices depending on the type of agreement chosen.

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

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

eCRF entries may be considered source data if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data).

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 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 regulatory authority and Amgen

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

13.3 Study Monitoring and Data Collection

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

The Amgen or CRO clinical monitor is responsible for verifying the eCRF at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The clinical monitor is to have access to patient medical records and other study-related records needed to verify the entries on the eCRF.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Around thirty site visits are planned for quality check, in order to control the quality of the patients' data. The analysis of on-site controlled data will define for each parameter the proportion of consistent data, discordant data (with analysis of the reasons for discordance), and data absent from the source documents.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRF must be maintained and readily available.
- Updates to eCRFs will be automatically documented through the software's "audit trail.To ensure the quality of clinical data across all patients and sites, a clinical data management review is performed on patient data received at Amgen or CRO. During this review, patient data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen or CRO reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study. This signature indicates that the investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self-Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

13.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements of data collection as stipulated in the protocol for each patient in the study. For patients who withdraw prior to completion of the study and are unable or unwilling to continue the study (Table 1), the investigator can search publically available records (where permitted) to ascertain survival status if allowed by local law. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

13.5 Language

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

13.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The

committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- 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 review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

13.7 Compensation

Any arrangements for compensation to patients for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

14. REFERENCES

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15. APPENDICES

Appendix A. Sample Adverse Drug Reaction Report Form

Project ID: 20130240	A	**Safety Reporting Form** Primary Data Collection	Date of Report:
		Fax reports to: Amgen Local Office **France Fax number: 0805 540 386**	

1. Indicate event type: ☐ AE/Other safety finding ☐ AE/Other safety finding with Product Complaint ☐ Product Complaint only

2. Vendor Contact Details

name	phone	fax
address		
city	state/province	
postal code	country	

3. Reporter ID

name or ID	phone	fax
address		
city	state/province	
postal code	country	

4. HCP Contact Details (if other than reporter)

name		
country		
address		
city	state/province	postal code
phone	fax	

5. Patient

Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
	☐ F ☐ M		☐ Yes ☐ No

Weight	Height	Race	Is patient also reporter?
☐ lbs ☐ kg	☐ in ☐ cm		☐ Yes ☐ No

6. Medical History (include primary diagnosis)

7. Suspect Product Information (include dosing details)

Product: _____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Freq

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial size

8. AE, other safety finding, or product complaint information — HCP ONLY

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (if patient died, list date of death) Cause of Death: (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Hospitalization Prolonged? ☐ Yes ☐ No; Admitting dx (provide discharge summary); Date Admitted (day month year); Date Discharged (day month year)	Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=Drug rechallenge (state outcome); 6=resolving	Outcome: 1=resolved; 2=resolved w/ sequelae; 3=resolving	Severity: 1=mild; 2=moderate; 3=severe	Relationship to Product/ Device: Is there a reasonable possibility that this event may have been caused by the Product / Device?	
								Product	Device
								Y N	Y N
								Y N	Y N
								Y N	Y N

9. Description: chronological summary of symptoms or product complaint from above (signs, diagnosis, treatment, concomitant medications including those used to treat event.)

Reporter Signature: _____ Page 1 of ____

DONNEES PERSONNELLES--Les Informations que vous communiquez à Amgen SAS seront traitées dans le cadre de la pharmacovigilance et la surveillance de la tolérance des médicaments ainsi que la gestion des contacts pour le suivi des effets indésirables déclarés. Merci de ne transmettre que les informations demandées dans ce formulaire. Ces données peuvent être transmises à des organismes publics nationaux, communautaires ou étrangers en charge de la pharmacovigilance. Ces informations pourront être transférées dans le but d'être analysées et conservées par les personnes habilitées au sein du Groupe Amgen, notamment aux Etats-Unis à Amgen Inc, la société mère, ainsi que par des sociétés travaillant pour son compte, notamment en Inde et aux Philippines. Les transferts sont réalisés en conformité avec les réglementations applicables relatives à la protection des données. Les transferts de données au sein des entités du groupe Amgen sont réalisés en conformité avec les législations applicables ainsi que nos règles contraignantes d'entreprise (BCR). Pour en savoir plus sur nos BCR, notamment sur votre capacité à soumettre une plainte concernant un traitement qui contreviendrait aux BCR, merci de consulter http://www.amgen.com/bcr/ Amgen prend toutes les précautions techniques, juridiques et administratives pour garantir la bonne exécution de ces transferts. Conformément à la loi « Informatique et Libertés » du 6 janvier 1978 modifiée, vous bénéficiez d'un droit d'accès et de rectification des informations vous concernant, que vous pouvez exercer en écrivant au Correspondant Informatique et Libertés d'Amgen SAS, 18-20 Quai du Point du Jour 92100 Boulogne Billancourt ou par email à cilamgen@amgen.com. Vous pouvez également, pour des motifs légitimes, vous opposer au traitement des données vous concernant.

FORM-067756 Ver. #: 3.0 Effective date: 07-Jul-2014 Page 1 of 1 *ADR Form Created: 25-MAY-2016*

Appendix B. Situations Allowing Initiating Prolia® After Less Than 3 Months of BP in the Previous Year

1. Situations related to BP contraindications as per SmPC :

- Common to all commercialized BPs in France - Alendronate (Fosamax®, Fosavance®), Risédronate (Actonel®, Adrovance®), Zoledronate (Aclasta®):
    - Hypersensibility to this medication or one of its components
    - Hypocalcemia
    - Chronic renal insufficiency :
        - Creatinine clearance < 35 ml/min (for alendronate and zoledronate)
        - Creatinine clearance < 30 ml/min (for risedronate).
    - Pregnancy/lactation

- Specific to Alendronate (Fosamax®)
    - Esophageal abnormalities delaying esophageal emptying, as stenosis or achalasia
    - Inability to remain upright for at least 30 minutes

2. Other clinically relevant situations allowing a BPs prescription of less than 3 months in the last year before starting Prolia® (according to the Scientific Committee):
    - Side effects incompatible with the continuation or re-introduction of BPs (eg, digestive disorders, musculoskeletal disorders) according to the patient
    - Previous failure to BPs (fracture, bone loss) as defined by the prescriber
    - Impaired renal function with a creatinine clearance ranging from 30 and 44 ml/min in patients with comorbidities (eg, high blood pressure, diabetes)

Appendix C. Additional Safety Reporting Information

Adverse Event Severity Scoring System

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

Appendix D. Pregnancy Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

0 805 540 386

1. Case Administrative Information

Protocol/Study Number: Prolia French observational Study 20130240

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 DOB:** mm_____/ dd_____/ yyyy_____

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 LMP mm_____/ dd_____/ yyyy_____ ☐ Unknown

Estimated date of delivery mm_____/ dd_____/ yyyy_____ ☐ Unknown ☐ N/A

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:** _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011

Page 1 of 1

Appendix E. Lactation Notification Worksheet

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# 0 805 540 386

1. Case Administrative Information

Protocol/Study Number: Prolia French observational Study 20130240

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 Date of Birth:** mm_____ / dd_____/ yyyy_____

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:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

Amendment 4

Protocol Title: Title: Prospective Observational Study to Describe Characteristics and Management of Postmenopausal Women With Osteoporosis Treated With Prolia® in France and its use in Routine Clinical Practice

Amgen Protocol Number Prolia® *20130240*

Amendment Date: *16 Feb 2018*

Rationale:

The statistical section of the protocol is being updated to clarify the patient population set that will be reviewed in both the primary and final analysis set.

Administration, typographical and formatting changes were made throughout the protocol.

Description of Changes:

Section: Global

Change: Corrected typographical and formatting errors throughout protocol.

Section: Global

Change: Corrected document date from 30 May 2017 to 16 Feb 2018

Section: Title Page

Add:

Amendment 4: 16 Feb 2018

Section: Title Page: Key Sponsor Contact

Replace:

PPD
Amgen Limited, 1 Uxbridge Business Park
Sanderson Road, Uxbridge, Middlesex
UB8 1DH, United Kingdom
PPD

With:

PPD
Amgen Limited, 1 Uxbridge Business Park
Sanderson Road, Uxbridge, Middlesex
UB8 1DH, United Kingdom
PPD

Section: Global

Replace:

Patients enrolling in wave 1 will be followed for approximately 30 months from the date of **first injection** in the study

With:

Patients enrolling in wave 1 will be followed for approximately 30 months from the date of **enrollment** in the study

Section: Glossary

Add:

CRO	clinical research organisation
CTCAE	Common Terminology Criteria for Adverse Events
EU	European Union
HCP	Health Care Provider
PS	Primary Analysis Set

Section: Glossary

Replace:

End of Study (end of trial)	**as when the last patient is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts**
Study Day 1	defined as the first day that patient signed informed consent form for participating in the study

With:

End of Study (end of trial)	**End of study is defined as the date that the last patient enrolled in wave 1 completes approximately 30 months of observation or when the last patient in the study ends their participation in the study**
Date of Enrollment	defined as the first day that patient signed informed consent form for participating in the study

Section: 10.1.2 Analysis Sets

Add:

Full analysis set

For each wave, the full analysis set (FAS) includes all patients enrolled into the study (provided informed consent and have a non-missing enroll**l**ment date) who received at least one Prolia® prescription.

Primary analysis set

The primary analysis set (PS) includes all patients in FAS that:

- **received at least one Prolia® injection**
- **have not received Prolia® injections prior to first Prolia® prescription**
- **do not have more than 100 days between first Prolia® prescription and enrollment date**

Section: 10.1.2 Analysis Sets. Persistence Analysis Set

Replace:

Persistence analysis sets

For the first wave only, persistence analysis sets (PAS) at 12 months and 24 months will be defined as follows:

12-month PAS consists of all patients in the **FAS that**:

- are not referred by the investigator to another physician for treatment follow-up before the second injection**.**
- are referred by the investigator to another physician before the second injection but complete information on second injection (injection yes/no and if yes the full date) is obtained via patient reporting.

24-month PAS consists of all patients in the **FAS that**:

- are not referred by the investigator to another physician for treatment follow-up before the fourth injection**.**
- are referred by the investigator to another physician before the fourth injection and:
  - the referral occurred after the patients missed a dose or received a dose later than 6 months + 8 weeks relative to the previous dose, or
  - or complete information on injection history up to the fourth injection (injections yes/no and if yes the full dates) is obtained via patient reporting**.**

With:

Persistence analysis sets

For the first wave only, persistence analysis sets (PAS) at 12 months and 24 months will be defined as follows:

12-month PAS consists of all patients in the **PS** that:

- are not referred by the investigator to another physician for treatment follow-up before the second injection**.**
- are referred by the investigator to another physician before the second injection but complete information on second injection (injection yes/no and if yes the full date) is obtained via patient reporting.

24-month PAS consists of all patients in the **PS** that:

- are not referred by the investigator to another physician for treatment follow-up before the fourth injection**.**
- are referred by the investigator to another physician before the fourth injection and:
  - the referral occurred after the patients missed a dose or received a dose later than 6 months + 8 weeks relative to the previous dose, or
  - or complete information on injection history up to the fourth injection (injections yes/no and if yes the full dates) is obtained via patient reporting**.**

Section 10.3.2: Primary Analysis for the First Wave

Add:

The primary analysis will be performed at the time of the final analysis. **Data may be summarised before the final analysis to support regulatory filings.**

Section: 10.4. Planned Methods of Analysis. 10.4.1 General considerations

Replace:

All analyses, except for persistence and safety summaries, will be based on the FAS.

With:

All **interim analyses will be based on the FAS**, except for safety summaries. **All primary and final analyses, except for safety and persistence summaries, will be based on the PS**

Section 10.4.2.2 Secondary Outcomes Related to Administration of Prolia®

Patient occurrence of persistence at 24 months
Replace:

Time to Non-persistence
Kaplan-Meier estimates will be provided for the time to non-persistence based on the **FAS.** If patients are referred to another physician or are lost to follow-up and are considered persistent by that time, they will be censored at the date corresponding to their last recorded date of Prolia® prescription/injection plus 6 months, date of referral or date of lost to follow-up, whichever occurs first. Percentage estimates of persistent patients and respective 95% CI will be provided.

Other Outcomes

For all other outcomes related to Prolia® administration, summary statistics will be provided based on the **FAS**, overall, and by referral to another physician (yes/no) as applicable.

With:

Time to Non-persistence

Kaplan-Meier estimates will be provided for the time to non-persistence based on the **PS**. If patients are referred to another physician or are lost to follow-up and are considered persistent by that time, they will be censored at the date corresponding to their last recorded date of Prolia® prescription/injection plus 6 months, date of referral or date of lost to follow-up, whichever occurs first. Percentage estimates of persistent patients and respective 95% CI will be provided.

Other Outcomes

For all other outcomes related to Prolia® administration, summary statistics will be provided based on the **PS**, overall, and by referral to another physician (yes/no) as applicable.

Section: 10.4.2.3 Fracture Outcome

Replace:

The number, percentage and rates of patients reporting fractures based on the **FAS** will be provided, overall and by fracture location.

With:

The number, percentage and rates of patients reporting fractures based on the **PS** will be provided, overall and by fracture location

Section 14: References

Replace:

Denosumab (Prolia®) Investigator's Brochure (Ed **4.1**) **2016**. Thousand Oaks, CA. Amgen Inc

With:

Denosumab (Prolia®) Investigator's Brochure (Ed **6**) **2017**. Thousand Oaks, CA. Amgen Inc